

Clinical Applications and Use of Medicinal Cannabis

David Zammit Dimech

Supervisor: Professor Anthony Serracino Inglott

Co-Supervisor: Dr. Louise Grech

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Abstract

Over the years, cannabis has been utilized for its medicinal properties to address a myriad of complaints including muscular spasms, insomnia, depression, pain and nausea. The dopamine-mediated euphoric effect, which was later attributed to the ability of the tetrahydrocannabinol component of cannabis to activate the CB1 receptor in the human body, has led Western countries to criminalize use of cannabis in the first half of the twentieth century. In recent years, numerous studies have heightened awareness about cannabis's potential medicinal benefits, demonstrating its efficacy in such clinical contexts as chemotherapy-induced nausea, epilepsy and multiple sclerosis spasticity. In Malta, the 2014 Drugs Dependence (Treatment Not Imprisonment) Act was amended in 2018 to allow for clinical use of authorized medicinal cannabis products. This was followed shortly after by the enactment of the Production of Cannabis for Medicinal And Research Purposes Act which delivers a legal framework for the possibility of producing cannabis in Malta for medicinal and research purposes. The developing potential of medicinal cannabis in patient care demarcates a shift in attitude towards cannabis from a legislative perspective that will however also require a clear and measurable change in perception by healthcare professionals in order to translate into benefits in delivery of medical care to patients. This research aimed to explore the therapeutic potential of medicinal cannabis by analyzing current international literature on its indications, contraindications, and administration modalities. This data was also intended to assist in proposing a simplified stepwise framework for clinical trials in this field. Through dissemination of a 25-item questionnaire that was validated by an expert panel ahead of distribution., the study also assessed the perceptions and concerns of the Maltese healthcare professionals on the use of medicinal cannabis, extracting pertinent considerations and uncertainties, and noting attitudes to help evaluate critical issues that ought to be addressed when reviewing the potential clinical use of medicinal cannabis within the Maltese healthcare context. Statistical analyses identified a weak positive correlation between the age of doctors

and their propensity to favour prescribing medicinal cannabis ($r= 0.20$, $p= 0.040$), mostly among males ($r= 0.34$, $p= 0.009$). Both pharmacists ($r=0.41$, $p<0.001$) and doctors ($r= 0.57$, $p< 0.001$) who had higher knowledge of medicinal cannabis evidenced a more favourable approach to its clinical use, believing that patients could derive benefit from medicinal cannabis and feeling more comfortable in discussing its integration as potential therapy with patients. In doctors this proved to be a stronger predictor of prescription attitude than knowledge and education categories assessed in a hierarchical regression analysis ($\beta= 0.71$, $p< 0.001$, $t=6.84$). Comparison of results reflected similar statistical patterns for both doctors and pharmacists in terms of attitudes, beliefs and knowledge of medicinal cannabis. A systematic review was conducted following PRISMA guidelines. Searches were performed in PubMed, Ovid, Web of Science, and Cochrane databases using predefined terms related to medicinal cannabis and its clinical applications for a variety of conditions. Eligible studies mostly included randomized controlled trials, cohort studies, and case-control studies evaluating the therapeutic efficacy of medicinal cannabis across various conditions. Data on clinical outcomes, administration modalities, and adverse effects were extracted and analyzed. The clinical trials and studies assessed were also considered in the clinical trial framework proposition, ensuring its compliance with current compliance regulations for clinical trials in the European Union. Questionnaire dissemination to Maltese doctors and pharmacists returned 200 responses, which were utilized for the development of a series of educational initiatives including a lecture series and a patient information brochure. These were validated via feedback from an expert panel. Survey results were in line with those recorded in multiple other regions and, in general, suggested acknowledgment of potential benefits for patients but also hesitancy in engaging with clinical use of medicinal cannabis. The main concerns expressed by healthcare professionals were poor formal education on the subject, unclear evidence-based clinical guidelines and limited training opportunities. It transpires that there is need for vigorous interventions in order to prepare a workforce of healthcare professionals in dealing effectively with discussing with and dispensing medicinal cannabis to eligible patients. Requirements include a significant investment of time and resources, as well as a willingness

on the part of healthcare professionals to engage with the latest research and to learn about the various ways in which cannabis can be used as a therapeutic alternative in some clinical contexts.

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Appendix 2. Healthcare professionals' questionnaire on use of medicinal cannabis

Appendix 3. Validation form: questionnaire

Appendix 4. Educational lecture series and validation form

Appendix 5. Lecture series assessment quiz

Appendix 6. Patient information brochure and validation form

Appendix 7. Validation form: clinical trial framework

Appendix 8. Current publications and research

Abbreviations

Δ 8-THC: Δ 8-tetrahydrocannabinol

Δ 9-THC: Δ 9-tetrahydrocannabinol

Δ 9-THCA: Δ 9-tetrahydrocannabinolic acid

2-AG: 2-arachidonoylglycerol

5HT: 5-hydroxytryptamine

ACPA: arachidonoyl cyclopropamide

AD: Alzheimer's Disease

AEA: anandamide (N-arachidonoyl ethanolamine)

AED: antiepileptic drug

AIDS: acquired immunodeficiency syndrome

ALS: amyotrophic lateral sclerosis

AMPK: adenosine monophosphate activated kinase

AMP: adenosine monophosphate

ATP: adenosine triphosphate

BMI: body mass index

CBC: cannabichromene

CBD: cannabidiol

CBDA: cannabidiolic acid

CBDV: cannabidivarin

CBG: cannabigerol

CBGA: cannabigerolic acid

CBN: cannabinol

CBND: cannabinodiol

CBs: cannabinoids

CNCP: chronic non-cancer pain

COX-2: cyclooxygenase-2

BDT: dialectical behaviour therapy

ECS: endogenous / endocannabinoid system

EGF: epidermal growth factor

EGFR: epidermal growth factor receptor

EMA: European Medicines Agency

ERK1/2: extracellular signal regulated kinase1/2

FAAH: fatty acid amide hydrolase

FAK: focal adhesion kinase

FDA: Food and Drug Administration

GABA: gamma-aminobutyric acid

GAD: generalized anxiety disorder

GPCR: G protein-coupled receptor

GPR55: G protein-coupled receptor 55

HPA: hypothalamic-pituitary-adrenal

LGS: Lennox-Gastaut syndrome

MAGL: monoacylglycerol lipase

MDD: major depressive disorder

MMPs: matrix metalloproteinases

mPFC: medial prefrontal cortex

MS: multiple sclerosis

NMDA: N-methyl-D-aspartate

OEA: oleoylethanolamide

OD: opioid use disorder

PAI-1: plasminogen activator inhibitor-1

PD: Parkinson's Disease

PI3K: phosphatidylinositol-3-kinase

PPAR- α : peroxisome proliferator- activated receptor alpha

PPAR- γ : peroxisome proliferator-activated receptor gamma

PTSD: post-traumatic stress disorder

ROS: reactive oxygen species

SAD: social anxiety disorder

SNRIs: serotonin-norepinephrine reuptake inhibitors

SSRIs: selective serotonin reuptake inhibitors

SUDs: substance use disorders

THCV: tetrahydrocannabivarin

TRPV1: transient receptor potential vanilloid type 1

TRPV2: transient receptor potential vanilloid type 2

VEGF: vascular endothelial growth factor

WHO: World Health Organization

Chapter 1 - Introduction

1.1 Historical perspective into the use of cannabis in medicine

Over the centuries, mankind has farmed the cannabis plant for its multivariate uses, including its benefits as a reliable source of textile fibre. This permitted its elaboration into useful material such as ropes, baskets and fishing nets. It was also extensively used as a source of food, oil, in decorations and also in religious rituals (Piluzza et al., 2013). Its recreational use by different civilizations after what Clarke and Merlin (2013) describe as a likely coincidental discovery of the psychoactive properties of the plant, is also postulated. Its ability to adapt, survive and grow in a variety of climactic conditions, even when these were unfavourable, has further ensured its presence over thousands of years (Crocq, 2020).

Taxonomically, the plant is classified into three species. The two major ones are *Cannabis sativa* and *Cannabis indica*, with *Cannabis indica* being less fibrous, having more psychoactive properties and is shorter than *Cannabis sativa*. The wild species *Cannabis ruderalis* is only present in the wild (Walsh et al., 2021).

Cannabis sativa may be considered as one of the most controversial plants in our society due to its toxicity caused by the psychotropic effects of the most well-known component, THC or -trans-9-tetrahydrocannabinol, which was first isolated in 1964 by Raphael Mechoulam (Russo, 2007; Mariotti et al., 2016). Cannabidiol (CBD) has several pharmacological properties but it does not exhibit the psychotropic qualities of THC. In particular, it has been associated with analgesics, antioxidants and anti-inflammatory effects, which also appear to reduce the side effects of THC (Russo, 2011).

With more liberal policies being enacted in a growing number of countries around the globe, the concept of medicinal cannabis playing a major role in public health is becoming increasingly relevant (Urits et al., 2021). A historical perspective dwelling on the use of cannabis and its medicinal properties across the globe and within cultures is given in the next section of the dissertation.

1.1.1 Cultivation of cannabis and its use over time

The etymology of the name of the plant itself can contribute to retracing its origin and movement from one continent to another. “can” or “kan” means to describe its hollow, woody stem, while “bis” identifies its pleasant scent. This linguistic backdrop corroborates the early Asian origin and its movement to Europe and Africa. With its expansion to Middle Eastern and European territories the pronunciation preserves the common roots with Arabs referring to the plant as quannob, quanneb in Hebrew, kannabas in Greek and the Latin version kannabis (Odieka, 2022).

The most likely geographical domestication beginnings of *Cannabis sativa* are owed to South-East Asia or Central Asia, with evidence of its use as a fibre in the production of baskets dating to the early paleolithic age unearthed in the Moravian regions in the Czech Republic, proving its presence among ancient human settlements in Europe (Bonini et al., 2018).

A number of academics speculate an origin for the plant dating back to Pleistocene epoch (Bonini et al., 2018). That would mean going back millions of years. Scholars are more certain of the presence of *Cannabis* around 12,000 years ago in the Holocene epoch in a general area situated in present-day Kazakhstan, Siberia and



Figure 1.1. Origin and distribution of cannabis around the globe. The arrows indicate the movement of the plant across countries and continents over the centuries, since its likely origin in Central Asia around 12,000 BCE. Adapted from Warf (2014).

Mongolia close to the Altai mountains in Central Asia, as well as the nearby mountain range of the Hindu Kush and the Himalayas in South-East Asia. It is from there that it reached the rest of Asia, Europe and Africa, migrating with people such as the nomadic Arabs and Iranian Scythians before being taken to the new world by Europeans and African slaves. Archaeological records and fossil retrievals of the Cannabis plant exist in both seed, fruit and fibre form as well as microfossils such as phytoliths and pollen, retrieved on Japanese territory and estimated to be from the Mesolithic era, but considered to have reached Japan from mainland Asian regions. These too demonstrate the movement from Asia to Europe, with the former being the critical point of origin of the plant (Pisanti & Bifulco, 2018).

Early uses of cannabis were associated more to its effectiveness as a textile fibre, with remnants from Neolithic times in modern day Taiwan suggesting it has been around for at least 12,000 years (Cherney & Small, 2016). Appreciation of cannabis for its potential medicinal advantages dates back to approximately 2700 BC with Chinese Emperor Shen Nung considered a habitual user of the plant as a medicine and regarded as the father of Chinese medicine (Russo, 2004). The Emperor instructed his people in cultivation of both crops and hemp, which already carried tradition in Chinese culture for multivariate uses, but he specifically accentuated the medicinal value of cannabis. Use of cannabis for its medicinal properties is also recorded in Japanese history, most probably due to direct influence from ancient Chinese medicine tradition (Turgeman & Bar-Sela, 2019; Ahn et al., 2020).

A review on the history of the use of cannabis for its medicinal properties, is given by Kalant in his article "Medicinal use of cannabis: history and current status" published in 2001. Basing their articles on literature findings, Kalant (2001) and Russo (2004) indicate that the use of medicinal cannabis started in Central Asia, in the regions of

present-day China and India, with neighbouring South-East Asia being another potential region where its use might have originated (Stevens et al., 2016). At the historical Chinese Yanghai tombs a grave dating back to 700 BC contained *Cannabis sativa* that had been buried alongside the remains of a man (Jiang et al., 2006). The use of cannabis in the Indian and Tibetan territories gained in popularity initially due to its psychoactive properties and the association with spiritual rituals around 1000 BC. Initially referred to as bhang, it assisted in meditation and other religious practices but in Ayurvedic medicine it soon picked up as a medicinal remedy for a number of ailments, including as a stimulant for appetite, pain relief, to assist diuresis, to control convulsions and spasms, as an aphrodisiac, an anaesthetic, to treat parasitic infections, as an antitussive, and as an energy booster (Crocq, 2020).

Evidence dating back to as early as the fourth century depicts use of cannabis for medicinal properties in the Middle East with remains of a 14-year-old girl who had died while giving birth, showing remains of burnt cannabis plants over her abdomen (Pain, 2015). Distribution of cannabis to Arab territories is attributed to a different migratory route than that which carried the plant to European territory with nomadic Arabs and traders who engaged in seafaring activities between Arab lands and India. With Arab medical tradition being more developed than that of early European countries, the use of cannabis to treat a variety of ailments is documented well before a more considerable utility of medicinal cannabis was noticed in Europe. It was used to assist in childbirth, as an anti-inflammatory and an analgesic, to treat headaches, fever, convulsions, dysentery, poisoned animal bites, nausea and malaria. The plant was also known to the Jewish people even before their migration out of Egyptian land and in Egyptian historical manuscripts and ancient tombs, including that of Ramses II,

there is evidence of use of cannabis for both religious purposes as well as medicinal ones (Leal-Galicia, 2018).

The introduction of cannabis to Europe is attributed to Iranian Scythians via migratory routes from Central Asia and through the vast Russian territories around 1500 BC. The Persians' main uses for the plant was in religious rites and as a multipurpose, reliable fibre but it is also documented how it was utilized within the medical field as an antidepressant, to induce abortion, to treat renal calculi symptoms, as an aphrodisiac, to alleviate pain from arthritis and bruising (Crocq, 2020). Within Europe, however, there was no specific emphasis on its medicinal properties over the years but rather as a fibre with which to produce clothing, bows, ropes and sails, and at times as food among some wealthier circles. Its cultivation for use in manufacturing on a large scale would later be carried out in Italy in medieval years, where various wealthy port cities engaged in trade and commerce embraced its potential in this regard. Before that however, with respect to the Middle East and Asia, it was only around 2000 years ago that it was discovered in Europe as an effective antiparasitic, analgesic and a useful medication for alleviating arthritis pain and burned skin. It was also noted by famous physicians from the Greek and Roman periods that it could cause impotence as well as infertility (Leal-Galicia, 2018). This trend never picked up in Europe however, and although for centuries it was still used as a fibre for the production of useful materials, especially in the seafaring trade, there was a decline in its promotion as a medicament followed by denigration of the plant as a drug of inebriation that should be ostracized. This culminated in the Roman Catholic church declaring it unholy under papal decree penned by Pope Innocent VIII in the late 15th century and associated it with satanic rituals. Despite the ban cannabis was consumed by some and exploited for its medicinal qualities even in monasteries, especially in parts of

England, Germany and Eastern Europe, given credibility by physicians and botanists of the time (Bonini et al., 2018).

Dutch and British intercontinental travels and conquests in the East brought to a rediscovery of cannabis, especially with colonization of India, and its medicinal properties featured more prominently as the colonizers got acquainted with medical practices in India that to a degree had captivated some in the West and would later see a resurgence in modern history. In the meantime, from Europe and Africa, cultivation and use of the plant had spread more widely to the Americas, predominantly by the early British settlers who appreciated its textile qualities (Ko et al., 2016; Bonini et al., 2018).

From the early nineteenth century use of cannabis had been advocated for by a number of physicians, with Irishman Dr. William Brooke O'Shaughnessy exposing its wonders to the West after encountering it in prevalent use in India, having pursued studies in Calcutta. He had proposed its use as a muscle relaxant and an analgesic, while London-based Dr. Clendinning and Dr. Greene were among the first to suggest its use for treatment of migraines (Ko et al., 2016; Leal-Galicia, 2018; Bodine & Kemp, 2022). Multiple other exponents in the field of medicine had attested to the use of Cannabis in alleviating headaches and neuralgia up to the early twentieth century in the West. French linguist Antoine Isaac Silvestre de Sacy, who had a special interest in the Orient, also contributed extensively to the circulation of knowledge about cannabis and its uses in medicine when translating ancient books in Arabic about the subject (Crocq, 2020). In mid-19th century Italian pharmacist Erba produced galenic formulations and marketed the cannabis-based medicine for the treatment of arthritis, nausea and migraine. There was popular demand as physicians on the peninsula

promoted its use in different territories and Europe as well as the United States incremented use of medicinal cannabis in the decades to follow. Pharmaceutical companies on both sides of the Atlantic embarked on manufacturing and marketing a variety of cannabis formulations (Leal-Galicia, 2018; Turgeman & Bar-Sela, 2019).

The withdrawal of Cannabis for medicinal use, in no small part due to industrial and political interference connected to handling of competition in the synthetic fibres business, was met with disapproval and protest from the medical community in the West (Baron, 2015). Cannabis was listed in the British Pharmacopoeia and the United States (US) Pharmacopoeia for its sedative and anticonvulsant properties before being removed in 1932 from the British Pharmacopoeia and 1941 from the United States Pharmacopoeia (Kalant, 2001; Aggrawal et al, 2009; Bridgeman & Abazia 2017). By 1996 California legalized medicinal cannabis, followed by multiple other states in the US (Levinsohn and Hill, 2020). Nowadays, a total of 38 US states have legalized the use of cannabis for medicinal purposes (New York Post, 2024).

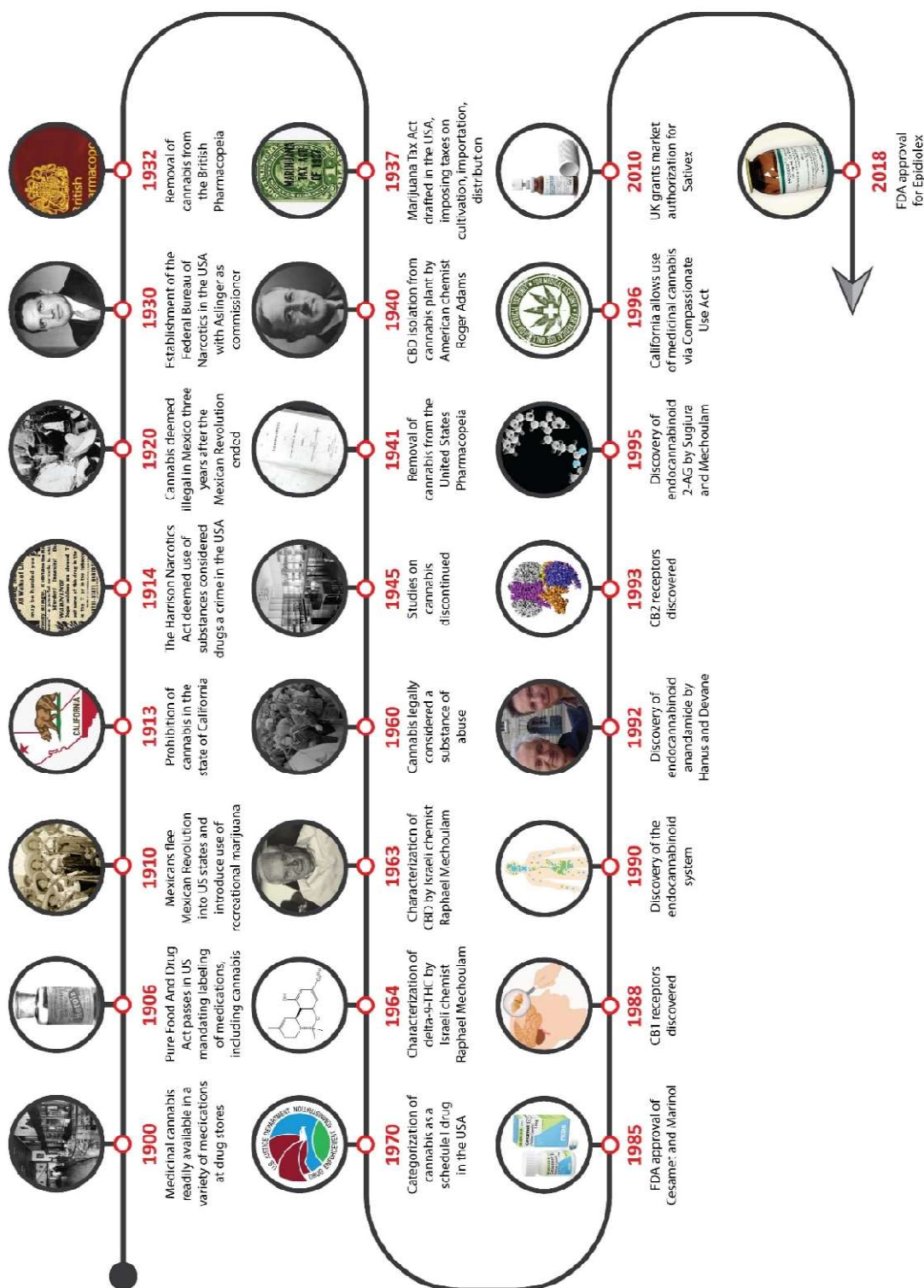


Figure 1.3. *Historical timeline of cannabis use. Landmarks events from 1900 to 2018. Based on data from Pisanti & Bifulco (2017), Crocq 2020) and Charitos et al. (2021).*

1.2 Cannabinoids and the endocannabinoid system

This section describes the effect of *cannabis sativa* on the endocannabinoid system which serves as the basis for understanding of the origin of therapeutic and nontherapeutic effects of cannabis in the medical field.

1.2.1 Cannabinoids

Cannabis sativa, is a herbaceous annual dioecious plant forming part of the Cannabaceae family producing around 565 compounds, of which 120 are cannabinoids (Atakan 2012; Andre et al, 2016; Hanus et al, 2016; Carcieri et al., 2017, Choi et al., 2020; Breijyeh et al., 2021). Among the many chemically active compounds it contains, such as flavonoids, alkaloids and terpenoids, it is the cannabinoids that are the most active and are primarily located in the female flowers (Brenneisen, 2007; Bonini et al., 2018; Pantoja-Ruiz et al., 2022). *Cannabis sativa* continuously garnered more and more interest after the discovery of a unique group of terpenophenolic compounds that present the typical C₂₁ terpenophenolic skeleton - the phytocannabinoids. This term encompasses compounds that originate from the Cannabis plant. Since the early 1940s, 90 cannabinoids have been isolated from cannabis and characterized (Russo, 2004; Citti et al., 2018).

Among the cannabinoids found in the *Cannabis sativa* plant - cannabigerol, beta-caryophyllene, cannabinol and other endocannabinoids - the two major cannabinoids which have been studied in literature are delta-9-tetrahydrocannabinol (D-9-THC) and CBD, found in female flowers and located mostly in their trichome cavity (Pertwee, 2008; Pertwee et al, 2010; Skraper and Di Marzo; 2012; Schrot and Hubbard, 2016).

THC is considered the most potent cannabinoid and the one primarily responsible for the psychoactive properties attributed to the cannabis plant (Gaoni, 1964; Adams and Martin 1996; Pertwee, 2004; Borgelt et al, 2013; Bonini et al., 2018). CBD lacks psychoactive properties and has been implicated as a potential therapeutic agent for a myriad of conditions such as (but not limited to) neurological disorders, psychiatric conditions, oncology and chronic pain (Scuderi et al, 2009; Massi et al, 2012; Iseger and Bossong, 2013; Birdsall et al, 2016; O'Connell et al, 2017; Pisanti et al, 2017; Zaki et al, 2017; Gatson and Szaflarski, 2018; Mirelman et al, 2019; Ghabrash et al, 2020; Laux et al, 2020; Pane and Sacca, 2020; Schoevers et al, 2020). In the human body, unlike what can happen in some animals, CBD is not converted to D-9-THC (Crippa et al., 2020).

The delta-9-tetrahydrocannabinol acid (THCA) is the carboxylic acid precursor of THC which, when heated, undergoes decarboxylation becoming THC. It is plausible that THCA has no psychoactive effects, possibly because it has a weak affinity for the CB1 receptor, reducing binding to it. This is in contrast to its byproduct of decarboxylation, THC (Breijyeh et al., 2021). THCA's targets include transient receptor potential channel signaling, the metabolism of prostaglandins and phospholipids, 2-arachidonoylglycerol and anandamide (Moreno-Sanz, 2016). Its efficacy to alleviate vomiting and nausea would be more significant than the possibilities granted by THC itself, showing peripheral activity, no side effects on the subjects' motor activity and not inducing any hypothermia in clinical trials. It is postulated that it will be a preferable option to THC given these apparent advantages over its byproduct (Rock et al., 2013).

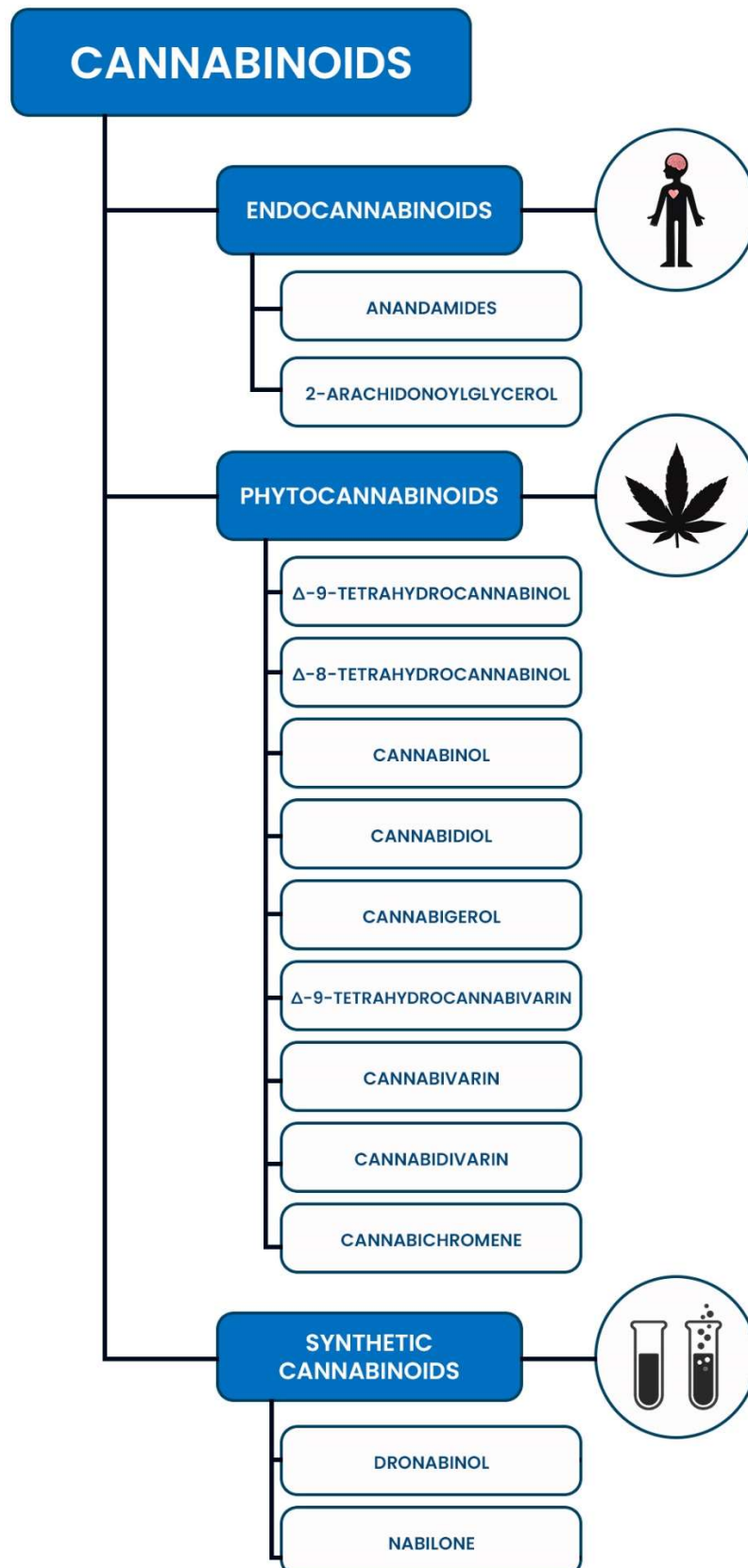


Figure 1.4. *Cannabinoid classification. Major cannabinoids in the three main sources of origin of cannabinoids: endogenous, plant-derived and synthetic laboratory-manufactured. Based on data from Lu & Mackie (2016), Morales et al. (2017) and Schurman et al. (2020).*

Tetrahydrocannabivarin (THCV), at the CB1 receptor, functions as a neutral antagonist affecting intake of food and thus effective in weight management therapies when taken at low doses. Higher doses demonstrate catalepsy symptoms on a similar level as with THC. At such doses it does not induce anxiety and neither does it induce nausea but reduces it. Nonetheless its useful therapeutic purpose is in weight loss management (Pacher et al., 2017; Lowe et al., 2021).

Apart from the main components in the cannabis plant inflorescence, tetrahydrocannabinolic acid (THCA) and cannabidiolic acid (CBDA), other cannabinoids which considered minor yet worth taking note of, are cannabinolic acid (CBNA), cannabichromenic acid (CBCA), and cannabigerolicacid (CBGA), all of which producing neutral species on decarboxylation. Cannabigerolicacid (CBGA) produces cannabigerol (CBG), exhibiting antifungal, antibacterial and analgesic properties. From cannabichromenic acid (CBCA), cannabichromene (CBC) is derived. It also presents antifungal and antibacterial properties, as well as anti-inflammatory activity. Cannabinol (CBN) is a strong sedative and results from long term storage and oxidation of tetrahydrocannabinol (THC) (McPartland & Russo, 2001; Morales et al., 2017; Corroon & Felice, 2019).

1.2.2 Terpenes and terpenoids

Terpenes and terpenoids represent a highly diverse group of volatile organic compounds prominently responsible for the distinctive aroma and flavour characteristics of cannabis and many other plant species (McPartland & Russo, 2001). While cannabinoids receive significant research attention due to their bioactive properties, terpenes and terpenoids crucially contribute to the sensory qualities of

cannabis through their strong aromatic profiles (Russo, 2001). Terpenes are simple hydrocarbons, whereas terpenoids represent their oxygenated derivatives, encompassing a wide array of structurally related molecules such as limonene, myrcene, and pinene (McPartland & Russo, 2001). In cannabis, terpenoids occur abundantly within glandular trichomes alongside cannabinoids, providing not only distinctive scents and flavours but also synergistic pharmacological effects, a phenomenon referred to as the "entourage effect" (Russo & McPartland, 2003). These compounds interact pharmacologically with cannabinoids to modulate receptor activity, influencing cannabis's psychoactive and therapeutic outcomes (McPartland & Russo, 2001). For instance, the terpene myrcene contributes sedative effects, while limonene demonstrates anxiolytic and antidepressant properties (Russo, 2001).

From an evolutionary perspective, terpenoids serve critical ecological roles, including protection against herbivory and microbial infection, as well as attraction of pollinators, thus influencing plant reproductive success and survival (McPartland & Russo, 2001). Consequently, cannabis terpenoid profiles have likely evolved under selective pressures associated with ecological interactions, possibly influenced by prolonged human cultivation selecting for favourable aromatic and pharmacological traits (Russo & McPartland, 2003). Moreover, the therapeutic potential of terpenoids extends beyond aroma and taste. Their medicinal properties include antimicrobial, anti-inflammatory, analgesic, antioxidant, and anxiolytic effects, underscoring their substantial relevance in phytotherapy and holistic medicine (Russo, 2001).

1.2.3 The endocannabinoid system

The endocannabinoid system is a naturally occurring lipid-based physiological system, usually in association with neuronal tissue. It is composed of agonists and cannabinoid receptors (CBRs) and is present in all the animal species except the insects. The endocannabinoid system evolved to regulate potential stressors that could damage the organism, playing a role in helping the body maintain a state of balance and well-being in response to disruptive internal and external stressors. The endocannabinoid system exerts influence on functions such as memory, metabolism, mood, bone metabolism, regulation of immunity and pain sensation. It is regulated via physiological functions such as sleep, nutrition, stress and physical activity, as well as other modulators, as would be phytocannabinoid exposure. These elements assist in downregulating and upregulating it, as it maintains direct communication with multiple systems in the body (Di Marzo & Piscitelli, 2015; Bruggren et al., 2019; Zagzoog et al., 2020; Abu-Amna et al., 2021; de Melo Reis et al., 2021).

In the brain, endocannabinoid system signalling is largely coupled with cannabinoid receptor 1 (CB1), which is linked to Go and Gi proteins, hence the correlation between the endocannabinoid system and cannabis for medicinal use. When this coupling occurs, cAMP-dependent protein kinase cyclic adenosine monophosphate (cAMP) activity decreases, leading to the activation of A-type potassium channels and the inhibition of voltage-gated calcium channels (Martinez-Orgado et al., 2007). This can affect the release of neurotransmitters such as dopamine, glutamate and gamma aminobutyric acid (GABA). The inhibition of enzymes such as monoacylglycerol lipase (MAGL) and fatty acid amide hydrolase (FAAH) can prolong the activity of endocannabinoid ligands and modulate endocannabinoid signalling in the brain (Adel

& Alexander, 2021). The most well-known endocannabinoids are anandamide, characterized in 1992, and 2-arachidonoylglycerol which was identified three years later (Citti et al., 2018; Breijyeh et al., 2021; Lal et al., 2021; Rock & Parker, 2021; Walsh et al., 2021; Legare et al., 2022).

Phytocannabinoids, which are derived from the cannabis plant, can interact with the body's cannabinoid receptors and produce a range of psychoactive and therapeutic effects. In addition, phytocannabinoids can also affect a specific subset of transient receptor potential channels, which are involved in the sensations of pressure, temperature, and smell. Endocannabinoids also bind to other G protein-coupled receptors, such as GPR18, GPR55, and GPR119, and can regulate signals related to cell proliferation and migration (Corroon & Felice, 2019; Sexton et al., 2021).

Deficiencies in the endocannabinoid anandamide has been linked to anxiety and depression, while an overactive endocannabinoid system can lead to increased appetite and weight gain (Corroon & Felice, 2019). Endocannabinoid Deficiency Syndrome proposes that certain clinical disorders may stem from deficiencies in endogenous cannabinoid signaling, either due to reduced ligand availability, receptor dysfunction, or genetic variation (Russo, 2016). Some studies have also suggested that a disturbance in the endocannabinoid system may be involved in the development of Alzheimer's and Parkinson's (Inglet et al, 2020; Ortiz et al., 2022). Other conditions potentially linked to Endocannabinoid Deficiency Syndrome include neuropsychiatric disorders such as schizophrenia, where mutations in cannabinoid receptors, particularly CB1, have been implicated (Kucerova et al., 2014; Leweke et al., 2014; Seillier, 2021).

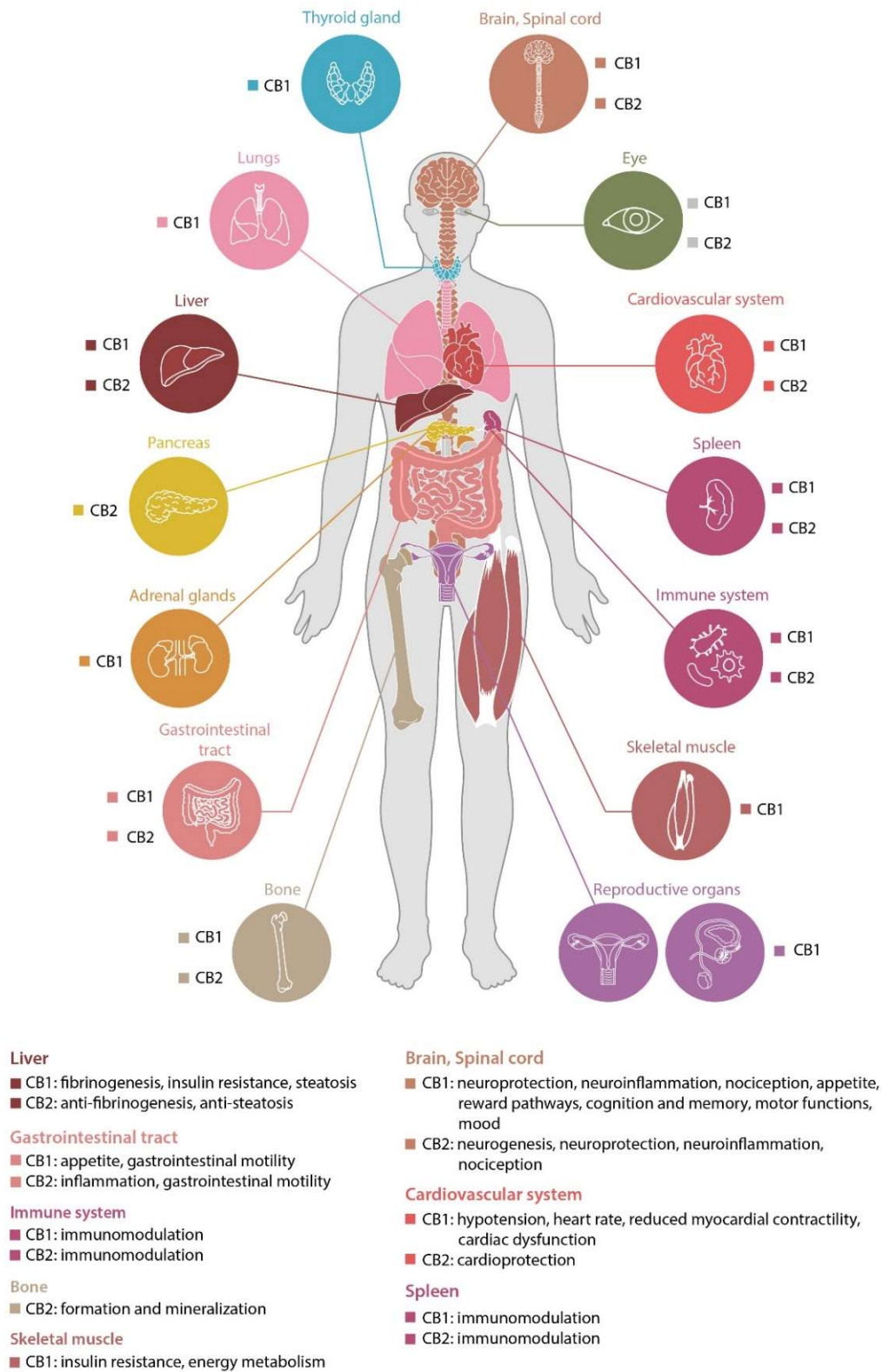


Figure 1.5. Generalized view of CB1 and CB2 distribution and functions in the human body; the presence of the receptors is not exclusive to the organ systems indicated but represents the one most prevalent when there is a clear imbalance towards one receptor over another. Based on data from Scott et al., (2022), An et al., (2020) and Haspula & Clark (2020).

Individuals with such mutations might experience impaired endocannabinoid signaling, manifesting as neurotransmitter imbalances and behavioural disturbances. Therapeutically, exogenous phytocannabinoids like THC and CBD have the potential to compensate for diminished endogenous cannabinoid activity (McPartland & Russo, 2001). THC administration increases the release of anandamide (Burstein & Hunter, 1995), whereas, although modestly, CBD inhibits FAAH, responsible for breaking down anandamide, thus enhancing endocannabinoid tone (Bisogno et al., 2001; Mlost et al., 2020). Endocannabinoid Deficiency Syndrome might provide a rationale for the medicinal use of cannabis and underscores the intricate physiological role of cannabinoid signaling in maintaining neurological and psychological homeostasis (McPartland & Russo, 2001).

1.2.4 Cannabinoid receptors

Cannabinoid receptors are a type of G protein-coupled receptor (GPCR) that are activated by the body's endocannabinoids and by plant-derived cannabinoids such as THC and CBD. These receptors are found throughout the body and are involved in a wide range of physiological processes, including pain sensation, mood, memory, and appetite (Zagzoog et al., 2020). When activated, cannabinoid receptors can cause a variety of effects, including the modulation of neurotransmitter release and the activation of intracellular signaling pathways. These effects can lead to the therapeutic benefits associated with cannabis use (Rice & Cameron, 2018; Legare et al., 2022).

Both cannabinoid receptors have been investigated as antinociceptive receptors. The cannabinoid receptor CB2 was defined in 1993. Two years earlier it had been the cannabinoid receptor CB1 that was characterized through scientific evidence. The two

are present in cells within differing primary regions, with the former present more readily in the immune system and therefore CB2 agonists being involved in inflammatory mechanisms and the regulation of the immune system. It is also detected in systems such as the gastrointestinal, reproductive, respiratory and cardiovascular systems (Adel & Alexander, 2021; Urits et al., 2021). It is also observed in the brain, particularly in areas involved in inflammation or pathology, including the thalamic nuclei, the brainstem, amygdala, cerebral cortex, hippocampus, striatum and the cerebellum. Studies have suggested that increased endocannabinoid production or upregulation of cannabinoid receptor activity may be able to modulate inflammatory responses (Gaston & Szaflarski, 2018; Abu-Amna et al., 2021; Urits et al., 2021; Walsh et al., 2021). The CB1 receptor is a more constant presence within the central nervous system in such areas as the cerebral cortex, cerebellum, hippocampus, basal ganglia and the amygdala (Rice & Cameron, 2018; Turgeman & Bar-Sela, 2019; Adel & Alexander, 2021). Essentially exhibiting particularly high concentrations in brain regions associated with cognitive functions, emotional responses, and motor coordination (Sexton et al., 2021). They are found on the peripheral endings and central terminals of primary afferent neurons, as well as in the dorsal root ganglion. Its agonists are therefore associated with synaptic neurotransmitter release (Bruggren et al., 2019; Breijyeh et al., 2021).

However, for those cannabinoids acting at the CB1 receptors the usefulness may be limited by side effects and the patient demonstrating tolerance for the drug over time. The affinities of phytocannabinoids relative to the CB1 and CB2 receptors vary (Amin & Ali, 2019). This refers to how strongly a phytocannabinoid binds to a cannabinoid receptor, and it has implications for the potential therapeutic effects. THC, for example, has a high affinity for CB1 receptors, which is thought to be responsible for its

psychoactive effects (Zagzoog et al., 2020). In contrast, CBD has a low affinity for CB1 receptors and is thought to produce its therapeutic effects through other mechanisms. Research is ongoing to better understand the relationship between the affinities of different phytocannabinoids for CB1 and CB2 receptors and their potential therapeutic effects (Joshi & Onaivi, 2021).

Intriguingly, genomic analyses reveal that cannabinoid receptors possess ancient evolutionary origins, traceable to early metazoans, suggesting these receptors emerged long before cannabis plants synthesized cannabinoid ligands. Proto-cannabinoid receptors, considered evolutionary precursors to modern CB receptors, are hypothesized to have originated in primitive multicellular organisms, with their emergence estimated at over one billion years ago (McPartland et al., 2006). Subsequent evolutionary differentiation led to the development of distinct CB receptor subtypes, such as CB2 receptors, which phylogenetic evidence suggests first appeared around 600 million years ago, correlating approximately with the divergence of vertebrate lineages. This implies that cannabinoid receptors significantly predate mammalian evolution, underscoring their conserved physiological importance throughout evolutionary history. The relatively later emergence of specialized CB₁ receptors within vertebrates reflects an evolutionary adaptation to increasing complexity in neural signaling mechanisms and receptor specialization within advanced organisms. The presence of homologous CB-like receptors across diverse animal taxa, ranging from primitive marine organisms to mammals, underscores their fundamental biological significance, implying their role initially involved binding to endogenous cannabinoid-like ligands rather than plant-derived cannabinoids (Elphick & Egertová, 2001).

Anandamide interacts significantly with CB receptors and indicates the ancestral receptor-ligand pair predates divergence among animals and plants, providing insight into receptor evolution (Devane et al., 1992). This evolutionary dynamic is shaped by processes such as gene duplication, mutation, and natural selection, allowing receptor subtypes to either acquire novel physiological functions or become vestigial due to reduced ligand exposure over evolutionary timescales (McPartland et al., 2006). Cannabinoid receptors exhibit constitutive activity, maintaining a baseline level of signaling even in the absence of external ligands, an intrinsic property critical to preserving physiological homeostasis (Pertwee, 1997; Howlett et al., 2002). This constitutive signaling capacity positions CB receptors uniquely as regulatory elements that modulate cellular function through subtle shifts in receptor activation, rather than causing intense physiological responses typical of full agonist binding (McPartland & Russo, 2001). Consequently, phytocannabinoids function predominantly as partial agonists at CB receptors, prompting modest receptor activation sufficient to restore or enhance endogenous cannabinoid signaling without precipitating the receptor desensitization commonly seen with continuous activation by full agonists (Pertwee, 1997).

Interactions between cannabinoids and their receptors are markedly complex and cannot be simplified into conventional lock-and-key models, due to the nuanced way cannabinoids modulate multiple signaling pathways through CB1 receptor interactions (Kenakin, 2002). Evidence demonstrates that a single cannabinoid can differentially activate distinct intracellular pathways, a phenomenon known as functional selectivity or biased agonism, reflecting the sophisticated nature of CB receptor pharmacodynamics (Pertwee, 1997; Kenakin, 2002). Additionally, cannabinoids exhibit interactions with a variety of non-CB receptors, including neurotransmitter

receptors and ion channels, thereby expanding their physiological relevance beyond traditional cannabinoid receptor activation and encompassing broader therapeutic potentials such as neuroprotection and anti-inflammatory effects (Russo & McPartland, 2003). This multifunctionality highlights the therapeutic complexity and potential of cannabinoids, necessitating further exploration into their diverse molecular mechanisms and pharmacological profiles (Kenakin, 2002; Russo & McPartland, 2003). CB receptors may also act as vestigial receptors, reflecting evolutionary remnants whose current physiological significance stems primarily from the nuanced regulation of endogenous ligand systems, underscoring their adaptability and continued relevance in mammalian physiology (McPartland & Glass, 2001). Thus, cannabinoid receptors serve essential roles far beyond interactions with plant cannabinoids, significantly contributing to the intricate balance of physiological systems throughout evolutionary history (Elphick & Egertová, 2001).

1.2.5. Coevolution theory

The coevolution theory concerning Cannabis and cannabinoid receptors proposes that a dynamic evolutionary relationship emerged from intricate interactions between plant-produced cannabinoids and animal cannabinoid receptors, particularly in humans. One of the foundational questions within this theory addresses why animals possess receptors responsive to plant-derived ligands. One explanatory hypothesis is "surreptitious mimicry," where phytocannabinoids from Cannabis mimic structurally analogous endogenous molecules produced by animals themselves, subsequently binding to receptors originally evolved for internal physiological regulation (McPartland et al., 2006). This theory is further enriched by the idea of ligand-receptor coevolution,

characterized by reciprocal selective pressures. Receptor mutations potentially induce ligand specificity changes, concurrently influencing ligand biosynthesis pathways within plants. Such reciprocal adaptation highlights the evolutionary plasticity in both receptor affinity and cannabinoid ligand chemistry, each refining the biological functions of the other across extensive evolutionary timescales (Elphick & Egertová, 2001).

Human evolution may particularly illustrate cannabinoid receptor adaptations due to extended interactions with phytocannabinoids. Enhanced sensory acuity and cognitive capacities, potentially conferred by cannabinoid-induced modulation of neural circuits, might have offered adaptive advantages, enhancing evolutionary fitness and reproductive success (McPartland et al., 2006). Moreover, it is hypothesized that cannabinoids significantly contributed to critical cognitive advancements in humans, potentially influencing the development of complex language, sophisticated tool-making abilities, rhythmic perception, and even the emergence of artistic expression (McPartland et al., 2006). Such cognitive evolutionary hypotheses extend to the FOXP2 gene, which is closely associated with the neurogenetic basis of human speech and language abilities. It has been suggested that epigenetic or genetic modifications related to cannabinoid exposure could have influenced FOXP2 gene expression or function, thereby shaping language capabilities and cognitive development in ancestral human populations (McPartland et al., 2006).

Significantly, comparative physiological studies reveal species-specific differences in cannabinoid receptor densities and distribution, particularly between rodents and humans. The relatively higher sensitivity to THC observed in humans could indicate a selective evolutionary pressure that favoured receptor affinity enhancements to

phytocannabinoids, evidencing the coevolutionary hypothesis (McPartland et al., 2006). Over evolutionary history, such receptor affinity modifications could have been selectively advantageous, potentiating survival and successful reproduction within cannabis-exposed populations. Coevolution is equally reflected in Cannabis phytochemical evolution. Humans exerted significant selective pressures on Cannabis cultivars, consciously or unconsciously influencing cannabinoid profiles that best matched human physiological demands (Russo, 2001). Consequently, Cannabis evolved a diverse repertoire of phytocannabinoids, each characterized by specific receptor affinities and nuanced physiological interactions, optimized through millennia of reciprocal evolutionary interactions with humans (Russo & McPartland, 2003).

The therapeutic efficacy observed in contemporary cannabinoid-based medicines is often explained by the principle of coevolution. Complex mixtures of cannabinoids, naturally optimized to human receptor profiles over thousands of years, often surpass synthetic analogs in therapeutic utility, reinforcing coevolution as a guiding concept in medicinal plant pharmacology (Russo, 2001; Russo & McPartland, 2003). The validity of this principle extends beyond cannabinoids, seen also in diverse biological phenomena like leaf-cutting ants cultivating antibiotic-producing fungi or vertebrates consuming specific alkaloid-rich plants to ameliorate neurotransmitter deficits, further underscoring coevolutionary medicinal relationships across diverse taxa (McPartland et al., 2006).

1.2.6. Synthetic cannabinoids

Synthetic cannabinoids are chemicals that are designed to mimic the effects of the active compounds in cannabis, such as THC and CBD. These chemicals are often

used as research tools to study the effects of cannabinoids in the body, or as pharmaceutical drugs to treat various medical conditions (Pacher et al., 2017; dos Santos et al., 2021).

Nabilone and dronabinol are two synthetic THC analogs that have been approved by the Food and Drug Administration (FDA) in the United States for the alleviation of nausea and vomiting induced by chemotherapy treatment. The former has been around since the late 1970s being tested in clinical trials. They demonstrated its efficacy and safety for the indicated use and has been part of therapy for a number of cancer patients over the years (Bonini et al., 2018; Breijeyh et al., 2021; Walsh et al., 2021). Dronabinol has also been investigated for its potential use as an analgesic to assist in alleviating chronic pain in those individuals in whom opiates alone are not enough, as well as in cancer patients with metastases to their bones. Apart from preventing nausea and vomiting in people undergoing chemotherapy it also treats their loss of appetite and associated weight loss (Ciccone et al., 2016; Ebbert et al., 2018; Rice & Cameron, 2018; dos Santos et al., 2021; Lal et al., 2021).

Levonantradol, which has been studied as a potential treatment for chronic pain, and HU-210 ((6aR)-trans-3-(1,1-dimethylheptyl)-6a,7,10,10a-tetrahydro-1-hydroxy-6,6-dimethyl-6H-dibenzo[b,d]pyran-9-methanol), a highly potent synthetic cannabinoid that is used as a research tool to study the effects of cannabinoids in the body (Breijeyh et al., 2021). Rimonabant, which was known as Zimulti and Acomplia when it was approved for use in Europe as an anti-obesity drug in 2006 is not available anymore, having been withdrawn from the market two years later due to severe psychiatric side effects and associated safety concerns (Pacher et al., 2017; Breijeyh et al., 2021). JWH-018 (1-pentyl-3-(1-naphthoyl)indole) was first developed by Dr. John W.

Huffman in the 1990s as a research tool for studying the endocannabinoid system. It is one of the most commonly found synthetic cannabinoids in herbal incense products (Amin & Ali, 2019). AM-2201 is similar to JWH-018, and also found in many herbal incense products, but is a more potent alternative and has a longer duration of action. Due to its qualities it has been often sold as a "legal" alternative to natural cannabis (Jang et al., 2014).

It is postulated that synthetic cannabinoids can be clinically useful in certain medical situations, such as when the use of natural cannabis is not feasible or when specific doses of active compounds are needed. However, the safety and effectiveness of synthetic cannabinoids has not been extensively studied. They are designed to mimic the effects of natural cannabinoids but can be more potent and have more unpredictable effects, resulting in a compromised risk benefit ratio (Morales & Reggio, 2021).

1.2.7. Pharmacokinetics of cannabinoids

The pharmacokinetics of cannabinoids has been the subject of research in recent years and can be considered a complex process, dependent on the method with which cannabis is delivered. Cannabinoid pharmacokinetics can be affected by a number of factors other than the method of administration. The dose and potency of the product, drug interactions, metabolism, elimination methods, as well as the specific physiological characteristics of the individual exert a relevant role. Understanding the pharmacokinetics of cannabinoids can help inform its safe and effective use (Devinsky et al., 2014). Out of all pharmacokinetic processes, the extent to which absorption occurs can vary greatly depending on a variety of factors, including the bioavailability

and lipophilicity of the product, and also the unique characteristics of the organ tissue it is being absorbed by (MacCallum & Russo, 2018).

Cannabinoids generally belong to the C₂₁ terpenophenolic compounds derived from *Cannabis sativa* L. and characterized structurally by a dibenzopyran nucleus (Turner et al., 1980). The pharmacological activity of cannabinoids depends heavily on structural elements such as side-chain length and hydroxylation patterns. For example, classical cannabinoids typically have a pentyl sidechain, whereas THCV possesses a shorter propyl sidechain, influencing its potency. Δ -Tetrahydrocannabinol (Δ 8-THC), though structurally similar to Δ 9-THC, is less abundant but pharmacologically comparable (Mechoulam et al., 1999). THC is highly fat-soluble and tends to accumulate in fatty tissue and the spleen, which can act as long-term storage sites for the compound. Therefore, because cannabinoids are highly lipophilic and have low water solubility, they are most effectively absorbed through the skin or orally when in the presence of fats, oils, or polar solvents such as ethanol. Due to this low water solubility, absorption via the gastrointestinal tract can be unpredictable and can result in varying pharmacokinetic effects (Amin & Ali, 2019).

Metabolism of cannabinoids primarily occurs in the liver via cytochrome P450 enzyme systems. Major metabolites of Δ 9-THC include the psychoactive metabolite 11-hydroxy- Δ 9-THC (11-OH-THC) and the inactive metabolite 11-nor-9-carboxy- Δ 9-THC (THCCOOH), excreted predominantly as glucuronide conjugates in urine (Harvey et al., 1978; Agurell et al., 1986; Harvey, 1992). CYP2C9, CYP2C19, and CYP3A4 enzymes notably catalyze these oxidative pathways, with CYP3A4 particularly implicated in further oxidation steps (Bornheim et al., 1993).

The bioavailability of orally delivered cannabinoids is often low, with estimates of around 6% due to the extensive metabolism that occurs in the liver before the substance reaches the rest of the body. This is known as first-pass metabolism and can significantly reduce the amount of the cannabinoids that is available for the body to use. The oral-mucosal or sublingual route of administration, which involves delivering substances through sprays or lozenges placed under the tongue, has a similar level of bioavailability to the oral route but with less variability. Most of the research on this method has focused on the use of nabiximols, a spray containing a 1:1 ratio of THC and CBD. One dose of nabiximols containing 10 mg of each compound can produce a peak serum concentration of CBD of 3.0 ± 3.1 µg/L within 2.8 ± 1.3 hours (Devinsky et al., 2014).

The route of cannabinoid administration therefore profoundly influences their bioavailability. Smoking cannabis rapidly delivers Δ^9 -THC to the bloodstream, with peak plasma concentrations occurring within minutes and bioavailability ranging between 10% and 27% (Perez-Reyes et al., 1983). Rectal and sublingual routes offer alternative methods to bypass significant first-pass metabolism, substantially enhancing cannabinoid bioavailability. For instance, rectal administration via THC hemisuccinate ester in suppositories demonstrated bioavailability of up to 67% (ElSohly et al., 1991). Intravenous administration achieves the highest bioavailability, rapidly reaching peak plasma concentrations; however, it is less practical therapeutically (Lucas et al., 2018).

Although structurally similar to Δ^9 -THC, CBD exhibits different pharmacokinetics and lacks significant psychoactive effects. It undergoes extensive hepatic metabolism, primarily forming hydroxylated metabolites with low systemic bioavailability after oral

administration, approximately 6%, due to pronounced first-pass metabolism (Samara et al., 1988). CBD's ability to inhibit or induce certain CYP enzymes, such as CYP3A4 and CYP2C, can modify the metabolism of co-administered drugs, potentially altering therapeutic outcomes (Bornheim et al., 1993; Bornheim & Grillo, 1998). Studies have shown that inhaled CBD can reach peak plasma concentrations within 10 minutes and has a bioavailability of around 31%, although this method requires specialized equipment and patient cooperation (Millar et al., 2018). Researchers have also explored the potential of using transdermal methods to deliver CBD to the body, but the compound's high fat solubility has posed challenges. In order to prevent accumulation of the drug in the skin, special ethosomal delivery systems are required, which are currently impractical and expensive to use. As a result, transdermal CBD delivery remains a largely unexplored area of research but with increasing scientific interest to exploit the several advantages that transdermal delivery has to offer with regards to cannabis administration (Tijani et al., 2021; Mahmoudinoodezh et al., 2022). The concentration of CBD in the body is influenced by its high fat solubility, with an estimated distribution volume of around 32 litres per kilogram. It is quickly distributed throughout the brain, fat tissue, and other organs. A significant portion of CBD is also bound to proteins in the blood, including up to 10% that is bound to red blood cells. Because of its preferential distribution to fatty tissue, there is a potential for accumulation of the compound in the body when used long-term, particularly in individuals with a high body fat percentage (Devinsky et al., 2014). CBD, like many other cannabinoids, is metabolized by the liver through hydroxylation by P450 enzymes, primarily those belonging to the CYP2C and CYP3A isoenzyme families. The resulting metabolite undergoes further processing in the liver before being excreted in the faeces and, to a lesser extent, in the urine. The estimated elimination

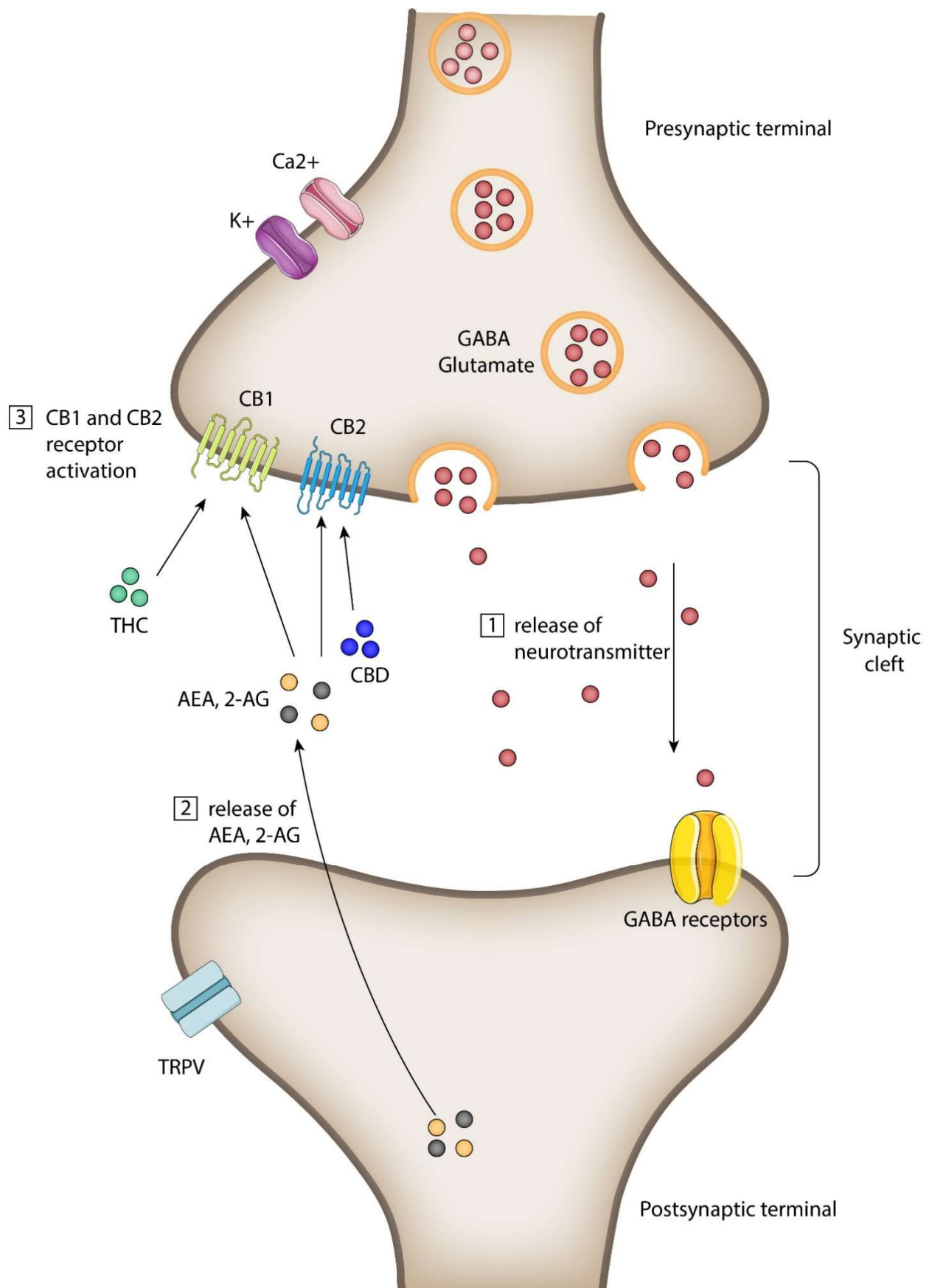


Figure 1.6. Synapse in the endocannabinoid system. Phytocannabinoid and endocannabinoid activity at the presynaptic terminal, modulating endocannabinoid system processes. Based on data from Niaz et al. (2017) and Kolesarova et al., (2023).

half-life of CBD in humans is between 18 and 32 hours, and in chronic cannabis users, clearance was observed to be between 960 and 1560 millilitres per minute following a single dose (Devinsky et al., 2014; White, 2019).

1.2.8. Pharmacodynamics of cannabinoids

The pharmacodynamics of cannabis involves insight on how active constituents of the cannabis plant interact with biological systems, particularly through cannabinoid receptors (Pertwee, 1997). Cannabinoid receptors are primarily coupled to Gi / Go proteins, leading to inhibition of adenylate cyclase and a reduction in cyclic AMP levels (Pertwee & Ross, 2002). In neurons, activation of CB1 receptors also modulates ion channels, including inhibition of N-, P/Q-, and L-type calcium channels and activation of inwardly rectifying potassium channels, leading to decreased neurotransmitter release (Mackie et al., 1995). Figure 1.6 illustrates activity at the synapse. Anandamide and 2-AG are synthesized on demand from membrane phospholipids and act retrogradely to suppress presynaptic release of neurotransmitters like glutamate and GABA (Ohno-Shosaku & Kano, 2001). This feedback inhibition is vital for maintaining synaptic balance, particularly in the hippocampus and cerebellum (Wilson & Nicoll, 2001). Anandamide is mainly degraded by FAAH, while 2-AG is metabolized by monoacylglycerol lipase (Cravatt et al., 1996). Inhibition of these enzymes enhances endocannabinoid tone and has therapeutic potential in pain and inflammation (Beltramo et al., 1997). AM404 and VDM-11 are inhibitors of endocannabinoid uptake, which potentiate synaptic effects of endogenous cannabinoids (De Petrocellis et al., 2000). Irreversible FAAH inhibitors such as AM374 and AM381 show higher potency than earlier agents like PMSF and also exhibit

behavioural effects consistent with enhanced cannabinoid signaling (Boger et al., 1999).

Despite the debate about THC and CBD is often central to considerations about medicinal cannabis neither of the molecules is biosynthesized inside the plant. The *Cannabis sativa* plant instead produces THCA and CBDA, of which not much is known yet with regards to their biochemical activity. Most relevant is that, mediated by heat, there is decarboxylation of THCA and CBDA to get the neutral variant species and bioactive substances, CBD and THC (Ligresti et al., 2006; Lucas et al., 2018). THC is a partial agonist at CB1 receptors and mediates most of the psychoactive effects of cannabis. By contrast, CBD exhibits low affinity for both CB1 and CB2 but can antagonize receptor activity and modulate endocannabinoid tone indirectly (Bisogno et al., 2001). There is limited information on the potential for drug interactions involving CBD in humans, but some theories suggest that it could impact its use in people with epilepsy. In vitro and animal studies have shown that CBD is a potent inhibitor of P450 isozymes, particularly CYP2C and CYP3A, which are involved in the metabolism of many medications. However, these effects have not typically been observed at the concentrations used in human studies. In animal studies, repeated administration of CBD has been shown to induce CYP2B isozymes (CYP2B1/6), which could have implications for people with epilepsy, as antiepileptic drugs such as valproate and clobazam are metabolized by these isozymes. Additionally, because a significant portion of CBD is metabolized by CYP3A4, it is possible that enzyme-inducing antiepileptic drugs such as phenytoin and carbamazepine could decrease CBD levels in the blood (Harvey, 1999).

1.2.9. Administration modalities

Various methods of administration including smoking or vaporizing, consuming it orally in the form of edibles or capsules, and applying it topically as a cream or oil are presented. Each mode of administration has its own unique benefits and drawbacks (Lucas et al., 2018; Vinette et al., 2022). Smoking or vaporizing provides the quickest onset of effects but may have negative effects on the respiratory system. Oral consumption has a slower onset but allows for more accurate dosing. Topical application is the slowest to take effect but provides targeted relief without affecting the entire body (Poyatos et al., 2020).

While there are several ways to administer CBD, the most common method is inhalation, either through smoking marijuana for recreational or medicinal purposes or through the use of specialized devices that aerosolize or vaporize the compound. Combustion at high temperatures (600-900 degrees Celsius) produces toxic by-products such as carbon monoxide, tar, ammonia and polycyclic aromatic hydrocarbons (MacCallum & Russo, 2018). In the long-term there will be an association with respiratory symptoms such as coughing, bronchitis and phlegm production, but not with lung cancer or chronic obstructive pulmonary disease unless mixed with tobacco, which could consequently increase the risk of respiratory problems and cancer. This method is therefore not suitable for medicinal purposes due to the potential harmful effects of smoking, but it does demonstrate the lungs' ability to quickly and efficiently deliver drugs to the bloodstream (Meenah-Atrash & Rahman, 2021).

Cannabis can be vaporized by heating it at 160-230 degrees Celsius. This method reduces the amount of carbon monoxide produced but does not completely eliminate

the production of polycyclic aromatic hydrocarbons. Vaporization produces fewer harmful by-products than smoking and has been associated with fewer respiratory symptoms (MacCallum & Russo, 2018).

Oils, capsules, and other oral routes are becoming increasingly popular due to their convenience and ability to accurately dose. Edibles such as brownies and cookies may be harder to dose consistently. Juicing and cannabis teas do not allow for adequate decarboxylation of raw cannabis plant material. nabiximols, an oromucosal spray, is currently the only cannabis-based prescription medication that delivers a standardized dose of CBD and THC in a 1:1 ratio and has been extensively researched. Lozenges and tinctures have intermediate onset times and limited research (MacCallum & Russo, 2018).

Topical administration of cannabis is ideal for treating localized symptoms such as dermatological conditions and arthritis, although there is limited research evidence to support its use. Cannabinoids are highly lipophilic, which can cause difficulties with diffusion and accumulation on the skin following poor absorption across membranes. Transdermal application bypasses first-pass metabolism, but absorption is very slow. A steady state concentration is reached within 24 hours for CBD and 17 hours for THC when using a transdermal patch. The effects remain effective for up to 72 hours for CBD and 14 hours for THC. The absorption of cannabinoids through the skin can be affected by blood flow and skin permeability at the site of application (Mahmoudinoodezh et al., 2022).

Delivery can be sublingual by putting or spraying it under the tongue. This can be done with sprays that are mostly made of THC and CBD mixed with alcohol. Sublingual delivery leads to rapid absorption through the mucosa because the drug goes directly

into the bloodstream and there is less first pass metabolism (Stella et al., 2021). The effects of sublingual administration present rapidly, with higher levels of the drug in the blood than via the oral route. Within 15 minutes to 1-hour peak levels in the blood will be registered. Psychoactive presentations are noted in 45 minutes with THC preparations in propylene glycol and ethanol, and the maximum effect was recorded after 180 minutes. The amount of drug that the body absorbs through the sublingual route is similar to the oral route, but there is less variation (MacCallum & Russo, 2018).

There has been a limited number of studies which have investigated the use of cannabinoids in suppository form. Ester formulations of cannabinoids can be applied rectally using suppositories, which may be suitable for certain populations such as those with cancer, gastrointestinal symptoms, or the elderly (Damsky Dell & Stein, 2021). THC-hemisuccinate may offer the best absorption, although research in this area has not been extensive. Rectal administration allows for fast absorption of cannabinoids into the bloodstream, bypassing first-pass metabolism. Peak plasma concentration is typically reached within 2 to 8 hours, and the bioavailability of rectally administered cannabinoids is 13.5%. This is twice as high as with oral administration and can vary depending on the specific formulation (ElSohly et al., 2018).

1.3. Clinical Applications

It is plausible that in the past, in ancient India, use of cannabis was recommended to address sleep disturbances (Choi et al., 2020). Studies conducted over recent years have focused on potential benefits of the plant for the treatment of sleep disorders, including insomnia (Cousens and DiMascio, 1973; Ware et al., 2010; Tringale and Jensen, 2011; Shannon and Opila-Lehman, 2016; Walsh et al., 2021) and sleep

apnoea (Jumpertz et al., 2010; Prasad et al., 2013; Calik et al., 2014; Farabi et al., 2014). A number of disorders can be at the origin of sleep disturbance issues and these have also been found to be alleviated by use of medicinal cannabis. Literature indicates that medicinal cannabis can be used for post-traumatic stress disorder (Fraser et al., 2009; Roitman et al., 2014), fibromyalgia (Walitt et al., 2016), Parkinson's Disease (Chagas et al., 2014), chronic pain of cancerous origin (Portenoy et al., 2012) chronic non-cancer pain (Notcutt et al., 2004; Narang et al., 2008) such as rheumatoid pain (Blake et al., 2006) and neuropathic pain (Ware et al., 2010; Toth et al., 2012; Mücke et al., 2018), and neuropathic pain which could also be HIV-associated (Bedi et al., 2010; Aly and Masocha, 2021). Studies have shown improvement in addressing the associated peripheral symptoms of sleep disruptions, incidence of REM sleep behaviour disorders and nightmares that often accompany some or all of the aforementioned conditions, as well as increased sleep quality of the patient (Black et al., 2019).

Benefits have also been reported in alleviating symptoms of fibromyalgia (Walitt et al., 2016), ulcerative colitis (Kafil et al., 2018), Crohn's Disease (Kafil et al., 2018), neuropathic pain (Ware et al., 2010; Toth et al., 2012; Mücke et al., 2018; Aly and Masocha, 2021), epilepsy (Koppel et al., 2014; Carter, 2020) and multiple sclerosis (Nielsen et al., 2018; Rice, 2018). This section presents a literature-based exploration of medical indications for cannabis, contemplating on the postulated interaction between the effect of cannabis on the endocannabinoid human system and its receptors leading to therapeutic and non-therapeutic effects.

1.3.1 Epilepsy

According to the World Health Organization (WHO), epilepsy is one of the most common neurological disorders, affecting an estimated 50 million people worldwide, representing about 1% of the global population (World Health Organization, 2024). The prevalence of epilepsy varies by region, with higher rates seen in developing countries. The WHO also estimates that 80% of people with epilepsy live in low- and middle-income countries (Fiest et al., 2017). A significant proportion of these individuals experience seizures that are refractory to traditional antiepileptic drugs (Franco & Perucca, 2019; Navarro, 2023).

Recent studies and clinical trials have demonstrated the efficacy of CBD in reducing seizure frequency and improving quality of life for patients with various forms of epilepsy (Navarro, 2023; Reddy, 2023). These findings are supported by historical evidence dating back to the 19th century, where cannabis extracts were used to treat convulsive disorders (Reddy, 2023). Despite the initial decline in its medical use due to legal restrictions, the resurgence of interest in cannabis-based therapies has led to a better understanding of its mechanisms and potential benefits (Lazarini-Lopes et al., 2020).

1.3.1.1 Pathophysiology of epilepsy and the endocannabinoid system

Epilepsy results from abnormal neuronal activity in the brain, leading to seizures. These seizures can vary in type and severity, from focal seizures affecting a specific part of the brain to generalized seizures that involve the entire brain (Talwar et al., 2023). The pathophysiology of epilepsy involves a complex interplay of genetic,

structural, metabolic, immune, and infectious factors that disrupt the normal balance between excitatory and inhibitory signals in the brain (Lazarini-Lopes et al., 2020; Reddy, 2023). At the cellular level, epilepsy is associated with alterations in neurotransmitter systems, ion channel function, and synaptic connectivity. These changes can result in hyperexcitability and hypersynchrony of neuronal networks, which are hallmarks of epileptic activity (Talwar et al., 2023; Fátima Dos Santos et al., 2024). Specific genetic mutations have been identified in various forms of epilepsy, such as mutations in the SCN1A gene in Dravet syndrome and mutations in the CDKL5 gene in CDKL5 deficiency disorder (Lattanzi et al., 2021).

The endocannabinoid system plays a crucial role in modulating neuronal excitability and maintaining homeostasis in the central nervous system, with its cannabinoid receptors CB1 and CB2, endogenous ligands, and enzymes involved in their synthesis and degradation. CBD interacts with the endocannabinoid system and other receptor systems, such as transient receptor potential vanilloid (TRPV) channels, G protein-coupled receptor 55 (GPR55), and serotonin receptors, to exert its anticonvulsant effects (Lattanzi et al., 2021). Studies have shown that CBD can reduce neuronal hyperexcitability by modulating calcium and potassium channels, enhancing the inhibitory effects of GABA, and reducing the release of pro-inflammatory cytokines (Franco & Perucca, 2019). These mechanisms contribute to its ability to prevent seizure propagation and reduce the frequency and severity of seizures in patients with epilepsy (Gray & Whalley, 2020).

1.3.1.2 Traditional therapeutic strategies: efficacy and limitations

Epilepsy management has traditionally relied on antiseizure medications (ASMs), which aim to control seizures by modulating neuronal excitability. These medications include various classes such as sodium channel blockers, GABA enhancers, and glutamate blockers. Despite the availability of over 30 ASMs, approximately 30% of epilepsy patients suffer from drug-resistant epilepsy (DRE), characterized by seizures that are not adequately controlled by existing treatments (Lazarini-Lopes et al., 2020). For these patients, polypharmacy, which involves the use of multiple ASMs, is a common strategy. While this approach can enhance seizure control, it often leads to increased side effects and drug interactions, making management more complex (Talwar et al., 2023). In addition to traditional ASMs, surgical interventions, including resective surgery and neurostimulation techniques like vagus nerve stimulation (VNS) and responsive neurostimulation (RNS), are employed for patients with focal epilepsy (Reddy, 2023).

Despite advancements in epilepsy treatment, significant limitations remain, particularly in the management of drug-resistant epilepsy (DRE). One of the primary challenges is the limited efficacy of current antiseizure medications (ASMs) in a substantial subset of patients. Approximately one-third of epilepsy patients do not achieve adequate seizure control with existing medications, necessitating the exploration of alternative treatments (Murillo-Rodriguez et al., 2020). The use of polypharmacy, which involves the combination of multiple ASMs, is a common strategy to enhance seizure control. However, this approach often leads to increased side effects such as sedation, cognitive impairment, and behavioural changes, which can significantly impact patients' quality of life and complicate long-term treatment adherence (Reddy, 2023).

Additionally, the potential for drug-drug interactions with polypharmacy further complicates the therapeutic regimen, requiring careful monitoring and dose adjustments (Mitelpunkt et al., 2019). However, these procedures are invasive and not suitable for all patients. The success rates of surgical interventions vary, and some patients may still experience seizures post-surgery. Furthermore, access to these specialized treatments may be limited due to geographical, financial, or institutional constraints (Gaston & Szaflarski, 2018).

Another major limitation is the variability in patients' responses to ASMs. Factors such as genetic differences, the presence of comorbid conditions, and variations in individual pharmacokinetics and pharmacodynamics can influence treatment outcomes. This variability underscores the need for personalized medicine approaches that tailor treatments to the unique genetic and physiological profiles of patients (Navarro, 2023). Moreover, long-term use of ASMs can lead to tolerance, where the effectiveness of the medication diminishes over time. Chronic exposure to certain ASMs may also contribute to adverse effects on bone density, hormonal balance, and overall metabolic health. These long-term complications necessitate regular monitoring and potential adjustments to treatment regimens (Chen et al., 2019). The lack of comprehensive therapeutic guidelines for some newer ASMs presents another challenge. Variability in formulations, dosages, and treatment protocols can lead to inconsistent therapeutic outcomes. This highlights the need for continued research and the development of standardized treatment protocols to optimize epilepsy management (Knupp et al., 2019).

1.3.1.3 Therapeutic effects of cannabinoids in epilepsy

There has been significant scientific endeavour in the use of cannabinoid-based drugs for treating epilepsy, particularly treatment-resistant epilepsy and paediatric-onset drug-resistant epilepsy (de Carvalho Reis et al., 2020). Phytocannabinoids such as CBD, CBG, CBDV, and D9-THCV have been found to have anti-convulsant properties and could potentially be developed into safer alternatives or adjuncts to traditional antiepileptic drugs (AEDs). Among these cannabinoids, D9-THC and CBD have received the most attention for their anti-convulsant effects. It is believed that THC's anticonvulsant activity is due to its ability to stimulate CB1R receptors. Preclinical evidence suggests that the endogenous cannabinoid system may play a role in regulating seizure frequency (Inglet et al., 2020). However, more research has been focused on CBD due to its good tolerability and lack of psychoactive effects. CBD's anticonvulsant effects are thought to be due to its properties as a 5-HT agonist, its actions on voltage-gated sodium ion channels, and its ability to modulate intracellular calcium storage. CBD, in combination with a prescription antiepileptic drug regimen, may be able to reduce seizure frequency in patients with refractory epilepsy and other severe seizure disorders (Gaston & Szaflarski, 2018).

The FDA approved the use of a CBD-based oil solution for treating Lennox-Gastaut syndrome and Dravet syndrome, two severe forms of epilepsy that affect children, on June 25, 2018 (Koo et al., 2020; Golub & Reddy, 2021). The oral solution, called Epidiolex®, was found to significantly reduce the frequency and duration of epileptic seizures in as many as 71% of children and 89.5% of adults with treatment-resistant epilepsy and Dravet syndrome. Furthermore, long-term studies have shown that CBD

is well-tolerated and can improve patient quality of life when used as part of a long-term treatment plan (Abu-Sawwa et al., 2020).

Clinical studies on the use of medicinal cannabis for epilepsy have increasingly demonstrated the potential efficacy of CBD as a treatment for drug-resistant epilepsy. A notable example is the use of Epidiolex®, a pharmaceutical-grade CBD, which has been evaluated in several randomized, double-blind, placebo-controlled trials. These studies have primarily focused on paediatric populations with severe forms of epilepsy such as Dravet syndrome and Lennox-Gastaut syndrome (LGS). In a study by Devinsky et al. (2018), involving 120 children and young adults with Dravet syndrome, participants were randomized to receive either 20 mg/kg/day of CBD or a placebo. The results showed a significant reduction in median monthly seizure frequency in the CBD group (from 12.4 to 5.9 seizures) compared to the placebo group (from 14.9 to 14.1 seizures), with a median reduction difference of 22.8 percentage points ($P = 0.01$) (Gaston & Szaflarski, 2018). Additionally, a higher percentage of patients in the CBD group achieved a 50% reduction in seizure frequency compared to the placebo group (43% vs. 27%, respectively). Another pivotal trial assessed the efficacy of CBD in patients with LGS, demonstrating a similar trend. In this study, 225 patients were randomized to receive either CBD or a placebo, and the CBD group experienced a median reduction in atonic seizures of 41.9% compared to 17.2% in the placebo group. These studies underscore the potential of CBD to significantly reduce seizure frequency in patients with treatment-resistant epilepsy. A systematic review by Lattanzi et al. (2021) further supports these findings. The review, which included data from various clinical trials, indicated that CBD was effective in reducing seizure frequency and had a favourable safety profile, with serious adverse events being infrequent. Long-term studies also suggest sustained efficacy and safety of CBD. For

instance, a long-term open-label extension study of CBD in patients with LGS showed continued reduction in seizure frequency and good tolerability over an extended period (Lattanzi et al., 2021).

Preclinical studies have provided insights into the mechanisms by which cannabinoids exert their anticonvulsant effects. CBD has been shown to have multiple mechanisms of action that contribute to its efficacy in reducing seizures. These include modulation of intracellular calcium levels, inhibition of adenosine reuptake, and agonism at serotonin receptors. Additionally, CBD has been found to have neuroprotective properties, which may contribute to its overall therapeutic effects in epilepsy. Studies using animal models of epilepsy have demonstrated that CBD can reduce the frequency and severity of seizures. For instance, Izquierdo et al. (1973) showed that CBD significantly reduced seizure discharges in a hippocampal seizure model in rats. Further, Consroe and Wolkin (1977) found that CBD was effective in reducing seizure activity in various experimentally induced seizure models. These preclinical findings support the clinical observations and suggest a robust anticonvulsant potential of CBD (Consroe & Wolkin, 1977).

Moreover, recent studies have explored the role of other cannabinoids, such as cannabidivarin (CBDV), which have also shown promise in preclinical models. The diverse mechanisms and the broad-spectrum efficacy of cannabinoids underscore their potential as therapeutic agents for epilepsy. The evidence from both clinical studies and preclinical models strongly supports the potential of medicinal cannabis, particularly CBD, in the treatment of epilepsy, especially in cases where conventional antiepileptic drugs have failed. Clinical trials have consistently demonstrated significant reductions in seizure frequency and favourable safety profiles for CBD.

Preclinical studies further elucidate the mechanisms by which cannabinoids exert their effects, highlighting their role in modulating key pathways involved in seizure generation and propagation. Continued research is essential to fully understand the long-term efficacy and safety of these treatments, as well as to optimize dosing regimens and identify which patient populations are most likely to benefit from cannabinoid therapy (Huntsman et al., 2020).

1.3.1.4 Potential mechanisms and therapeutic strategies

The exact mechanisms by which CBD exerts its anticonvulsant effects are not fully understood, but several pathways have been proposed. CBD interacts with a variety of molecular targets in the brain, including cannabinoid receptors (CB1 and CB2), serotonin receptors (5-HT1A), transient receptor potential vanilloid (TRPV) channels, and G protein-coupled receptor 55 (GPR55) (Navarro, 2023). Unlike THC, CBD has a low affinity for the CB1 receptor, which is primarily responsible for the psychoactive effects of cannabis. Instead, CBD acts as a negative allosteric modulator of CB1, which may contribute to its anticonvulsant properties (Inglet et al., 2020). One key mechanism involves the modulation of intracellular calcium levels. CBD has been shown to inhibit the release of calcium from intracellular stores, which can help reduce neuronal excitability and prevent seizures (Navarro, 2023). Additionally, CBD enhances adenosine signaling, which plays a crucial role in reducing neuronal excitability and inflammation. By increasing adenosine levels, CBD can contribute to the stabilization of neuronal activity and the reduction of seizures (Gray & Whalley, 2020).

Another important mechanism is the inhibition of the equilibrative nucleoside transporter (ENT), which increases extracellular adenosine levels and thereby exerts anticonvulsant effects. CBD also modulates the activity of various ion channels, including TRPV1, which are involved in the regulation of synaptic transmission and neuronal excitability. Additionally, CBD's interaction with GABAergic receptors enhances inhibitory neurotransmission, further contributing to its anticonvulsant effects (Gray & Whalley, 2020). Therapeutically, CBD is used in several formulations, with Epidiolex® being the most notable. Epidiolex® is a highly purified form of CBD that has been approved by the FDA for the treatment of seizures associated with LGS, DS, and TSC. This approval has paved the way for broader acceptance and use of CBD in clinical practice (Navarro, 2023).

1.3.2 Huntington's Disease

Huntington's disease is a rare, autosomal dominant neurodegenerative disorder that manifests symptoms when reaching adulthood, around the 30s or 40s, and progresses over time, leading to a decline in physical and cognitive abilities. Symptoms may include uncontrolled involuntary movements referred to as chorea, difficulty with coordination and balance, cognitive decline, and psychiatric problems. Difficulties with walking, swallowing and speaking ensue. There is currently no cure for Huntington's disease with the typical lifespan of a patient being around 20 years from the onset of symptoms (Ajitkumar & De Jesus, 2023).

The pathological hallmark of Huntington's disease involves extensive neuronal loss, particularly in the striatum, and the presence of intranuclear inclusions within neurons. It is due to a mutation in the HTT gene, which provides instructions for making a protein

called huntingtin. This protein is involved in the development and function of nerve cells in the brain. In people with Huntington's disease the HTT gene contains a repeating CAG sequence. The HTT gene mutation is associated with changes in the expression of several proteins involved in the endocannabinoid system. These changes include a decrease in the expression of the CB1 and GPR55 receptors and the NAPE-PLD enzyme, which is involved in the synthesis of endocannabinoids, and an increase in the expression of the FAAH enzyme, which breaks down endocannabinoids (Lapraire et al., 2015; Gaston & Szaflarski, 2018).

Huntington's disease pathophysiology is complex, involving not only the direct effects of mutant huntingtin protein accumulation but also secondary effects such as impaired mitochondrial function, excitotoxicity, and oxidative stress. The disease predominantly affects the striatum, leading to the degeneration of medium spiny neurons that are crucial for motor control. This neuronal loss underlies the characteristic chorea and motor disturbances associated with the disease (Murillo-Rodriguez et al., 2020; Akinyemi et al., 2020).

1.3.2.1 Traditional therapeutic strategies: efficacy and limitations

Current therapeutic approaches for Huntington's disease primarily aim to manage symptoms rather than cure the underlying genetic disorder. Tetrabenazine, a vesicular monoamine transporter 2 (VMAT2) inhibitor, is the only FDA-approved medication specifically indicated for the treatment of chorea associated with Huntington's disease. Its mechanism involves depleting presynaptic dopamine, which can mitigate the hyperkinetic movements characteristic of Huntington's disease. While tetrabenazine reduces chorea, its effectiveness is limited by significant side effects such as

depression and parkinsonism, reflecting the challenge of managing Huntington's disease symptoms without exacerbating others (Aymerich et al., 2018).

Other symptomatic treatments include antipsychotic drugs, which are used off-label to manage psychiatric symptoms and motor disturbances but can have problematic side effects like cognitive dulling and increased risk of metabolic syndrome. Additionally, medications like selective serotonin reuptake inhibitors (SSRIs) and benzodiazepines are prescribed for psychiatric and mood disorders associated with Huntington's disease but do not address the disease's neurodegenerative aspects (Curtis et al., 2009). Recent pilot studies have explored the use of cannabinoids like nabilone, a synthetic analogue of delta-9-tetrahydrocannabinol, which has shown promise in reducing chorea and improving neuropsychiatric symptoms in Huntington's disease patients. This reflects a growing interest in targeting the endocannabinoid system to provide symptom relief and potentially exert neuroprotective effects due to its modulation of neuroinflammatory pathways (Akinyemi et al., 2020).

The primary limitations of existing therapies for Huntington's disease stem from their focus on symptom management rather than disease modification. Tetrabenazine, while effective in reducing chorea, does not slow the progression of the disease and is associated with side effects that can significantly impair quality of life, such as sedation and increased risk of depression. Antipsychotics and other psychiatric medications often used in Huntington's disease can manage behavioural symptoms but do not address the underlying neurodegeneration and may contribute to further cognitive decline due to their sedative properties. This reflects a broader issue with current Huntington's disease treatments, which often require balancing symptom

management against side effects, complicating long-term care strategies (Moreno et al., 2016).

Another significant limitation is the non-specific nature of most treatments, which often manage psychiatric or movement symptoms without targeting the molecular or cellular abnormalities specific to Huntington's disease. This includes the use of antipsychotics and antidepressants that, while helpful for managing psychiatric symptoms, do not address the progressive loss of neuronal function and may introduce side effects such as cognitive blunting or metabolic issues. Moreover, the existing therapeutic options do not address the complex interaction of multiple pathogenic mechanisms involved in Huntington's disease, such as excitotoxicity, mitochondrial dysfunction, and transcriptional dysregulation caused by the accumulation of mutant huntingtin protein. This gap highlights the need for multi-targeted therapeutic approaches that can more comprehensively address the multifaceted nature of the disease (Saft et al., 2018).

1.3.2.2 Therapeutic effects of cannabinoids in Huntington's Disease

Research into the endocannabinoid system has uncovered potential benefits of cannabinoids in Huntington's disease, largely due to their modulation of neuroinflammatory and neurodegenerative pathways. Cannabinoids such as CBD and THC have been shown to offer neuroprotective effects in preclinical models of Huntington's disease. These effects are mediated through mechanisms including the reduction of excitotoxicity, the modulation of neuroinflammation, and the protection against mitochondrial dysfunction (Moreno et al., 2016). Clinical studies have reported that cannabinoids can improve motor symptoms such as chorea and dystonia, as well as psychiatric symptoms including irritability and apathy, thereby enhancing the quality

of life for Huntington's disease patients. For example, nabilone has shown promise in reducing chorea and improving neuropsychiatric symptoms in pilot studies (Curtis & Rickards, 2006; Saft et al., 2018). Moreover, cannabinoids are being explored for their potential disease-modifying effects. While definitive clinical evidence is still pending, the neuroprotective properties observed in animal models suggest that cannabinoids could delay the progression of Huntington's disease by protecting striatal neurons from degeneration. However, achieving clinically meaningful outcomes will require overcoming current limitations, such as the variability in response and the side effects associated with cannabinoid therapy, which can include sedation and altered mental status (Akinyemi et al., 2020).

A seminal case report by Curtis & Rickards (2006) detailed the administration of nabilone to a patient with severe chorea and irritability associated with Huntington's disease. The intervention began with non-quantified doses of smoked cannabis, which yielded noticeable symptomatic improvements. This led to a formal treatment regimen involving 1 mg of nabilone daily, which sustained the initial benefits, indicating the potential of cannabinoids to manage specific symptoms of Huntington's disease, such as chorea and mood stabilization. However, this being a single case study, calls for further investigation to generalize findings (Curtis & Rickards, 2006). Expanding upon this, Curtis et al. (2009) conducted a randomized, double-blind, placebo-controlled, cross-over pilot study to evaluate nabilone's effects on chorea and neuropsychiatric symptoms in a larger Huntington's disease cohort. The study found that nabilone was well-tolerated and showed potential in reducing chorea and improving psychiatric symptoms, supported by changes in the Unified Huntington's Disease Rating Scale and the Neuropsychiatric Inventory. These findings suggest nabilone's utility in symptom management in Huntington's disease, and the feasibility of a larger trial to

explore these outcomes more conclusively (Curtis et al., 2009). Furthering the exploration of cannabinoid formulations, Saft et al. (2018) used a variety of cannabinoids, including Sativex® (a combination of THC and CBD), dronabinol, and nabilone, to treat severe dystonia in early-onset Huntington's disease patients. This observational study documented improvements in dystonia and motor symptoms, suggesting that cannabinoids might offer therapeutic benefits for Huntington's disease-related motor impairments. Despite the promising results, the small scale and observational nature of the study limit its generalizability, highlighting the need for controlled clinical trials (Saft et al., 2018). López-Sendón Moreno et al. (2016) conducted a double-blind, randomized, cross-over, placebo-controlled pilot trial using Sativex® in Huntington's disease. This study primarily assessed the safety of Sativex®, confirming its tolerability in Huntington's disease patients, though it failed to show significant improvements in clinical symptoms over the trial period. This underscores the complex nature of cannabinoid effects in Huntington's disease, suggesting that longer treatment durations or different dosing strategies might be required to discern meaningful clinical benefits (Moreno et al., 2016).

Preclinical models have also provided valuable insights. These studies often utilize transgenic animal models to investigate the neuroprotective effects of cannabinoids, noting improvements in neuroinflammatory markers and reductions in neuronal degeneration when cannabinoid receptors are activated. Such models have underscored potential mechanisms by which cannabinoids might modulate disease progression through neuroprotective pathways, although translating these findings to clinical applications remains challenging. Preclinical studies using genetically modified mice that model Huntington's disease have shown decreases in the expression of CB1 receptor mRNA in the hippocampus, striatum and cortex during the early stages of the

disease (Dowie et al., 2019). In post-mortem brain tissue from Huntington's disease patients, quantitative autoradiography revealed a significant loss of CB1 receptor protein in the globus pallidus and substantia nigra. These reductions in CB1 receptor expression were accompanied by increased expression of CB2 receptor in astrocytes and microglia in pharmacological rat models of Huntington's disease (Basavarajappa et al., 2017).

In a rat model of Huntington's disease, THC was found to produce neuroprotective effects, which suggests that it may have therapeutic potential in treating the condition. This adds to the evidence that dysfunction of cannabinoid receptors may play a role in the development of Huntington's disease. A small pilot study has also indicated that the drug nabilone may be able to improve motor skills and cognitive function in Huntington's disease patients. These findings suggest that further research is needed to fully understand the potential therapeutic benefits of cannabinoid-based drugs for treating Huntington's disease (Curtis et al., 2009). One case report has described the use of medicinal cannabis and the drug nabilone to improve motor function and cognitive behaviour in a patient with Huntington's disease, although no quantitative measurements were taken and the reports were anecdotal (Curtis & Rickards, 2006). In clinical trials, nabiximols and CBD alone did not have any effect on symptom control in Huntington's disease patients. Treatment with nabiximols was found to increase the expression of CB2 receptors in the periphery but did not affect the expression of other proteins in the endocannabinoid system. These findings suggest that further research is needed to understand the potential therapeutic benefits of cannabinoid-based drugs for treating Huntington's disease (Moreno et al., 2016).

In contrast to the findings of clinical trials of nabiximols, a double-blind trial using the drug nabilone found it to be effective in reducing the involuntary movements associated with Huntington's disease, as well as neuropsychiatric and behavioural outcomes. These findings suggest that nabilone may have potential as a treatment for Huntington's disease, although more research is needed to fully understand its therapeutic effects (Curtis et al., 2009). In a double-blind crossover study with patients presenting spinal cord injuries it was noted that nabilone significantly improved spasticity related to the injury when compared to placebo. Another trial showed that nabilone was effective in relieving pain due to spasticity, although it did not find a significant reduction in overall spasticity (Wissel et al., 2006).

1.3.2.3 Potential mechanisms and therapeutic strategies

The potential mechanisms underlying the therapeutic effects of cannabinoids in Huntington's disease involve a multifaceted interplay between cannabinoid pharmacology and the neurodegenerative pathways associated with Huntington's disease. Several studies have delved into this relationship, aiming to elucidate the exact roles cannabinoids may play in modifying or ameliorating Huntington's disease symptoms and progression.

Preclinical studies have demonstrated that activation of CB1 receptors can mitigate motor deficits and protect neural structures in animal models of Huntington's disease. This protective role is attributed to the ability of cannabinoid receptor activation to modulate glutamatergic release and thus reduce excitotoxicity, a key component of Huntington's disease pathology. Additionally, cannabinoids have shown antioxidant, anti-inflammatory, and neuroprotective effects in various models, suggesting they

might also support neuronal survival and mitigate inflammatory responses in the brain (Basavarajappa et al., 2017).

Clinical studies have further explored these mechanisms. A study involving the administration of Sativex®, a combination of THC and CBD, to Huntington's disease patients highlighted the symptomatic benefits, particularly in reducing spasticity and improving motor functions, though without significant effects on disease progression. This aligns with the proposed modulatory effects of cannabinoids on the central nervous system, which might improve motor symptoms and overall quality of life for Huntington's disease patients (Murillo-Rodriguez et al., 2020).

Furthermore, cannabinoids are also being investigated for their potential to alleviate other Huntington's disease symptoms such as chorea, dystonia, and neuropsychiatric issues like irritability and apathy. For instance, cannabinoids have been observed to improve dystonia in Huntington's disease patients, a prevalent and often debilitating symptom (Curtis et al., 2009). The administration of nabilone and other cannabinoid formulations has led to clinical improvements in dystonia scores and motor function, underscoring the therapeutic potential of targeting the endocannabinoid system in Huntington's disease. The combination of these therapeutic strategies highlights a dual approach: managing symptoms and exploring the potential disease-modifying effects of cannabinoids. Despite these promising results, the exact molecular mechanisms by which cannabinoids exert their effects in Huntington's disease are not fully understood, and further research is necessary to delineate their roles comprehensively (Saft et al., 2018; Murillo-Rodriguez et al., 2020).

1.3.3 Parkinson's Disease

Parkinson's Disease is the second most prevalent neurodegenerative disorder, affecting approximately 1-2% of the population over the age of 65. It is a slowly progressive neurodegenerative disorder resulting in loss of dopamine-producing cells from the substantia nigra pars compacta in the midbrain. The disease is characterized by tremors, bradykinesia, stiffness, an inexpressive mask-like facial expression, postural instability, and difficulty with movement and coordination. Although solid evidence from the current body of studies is not available for the treatment of Parkinson's Disease with the use of medicinal cannabis there does seem to be data suggesting benefits for alleviating tremor symptoms (de Farina et al., 2020). The non-motor features of the disease comprise depression, pain, cognitive impairment, anxiety, sleep disturbance and muscle cramps, and are also debilitating for the patient. There have been reported benefits of cannabinoid treatment for a few of these symptoms (Leehey et al., 2020; Feeney et al., 2021; Yenilmez et al., 2021).

1.3.3.1 Pathophysiology of Parkinson's disease and the endocannabinoid system

The pathophysiology of Parkinson's Disease is deeply rooted in the degeneration of dopaminergic neurons within the substantia nigra pars compacta (SNpc), leading to significant disruptions in the functionality of the basal ganglia. The basal ganglia, which include structures such as the SNpc, striatum, and globus pallidus, play a pivotal role in the modulation of movement through their complex interconnections and neurotransmitter systems (Antonazzo et al., 2019; de Barros Viana et al., 2022). The loss of dopaminergic neurons results in a diminished dopaminergic input to the

striatum, disrupting the delicate balance of movement regulation and resulting in the hallmark motor symptoms of Parkinson's Disease (Fernandez-Ruiz et al., 2015; Bhunia et al., 2022). Compounding this neuronal loss is the accumulation of α -synuclein aggregates in the form of Lewy bodies, contributing to cellular dysfunction and death. Furthermore, neuroinflammation, excitotoxicity, and mitochondrial dysfunction exacerbate neuronal damage, creating a cycle of degeneration that advances the disease. These pathological processes underscore the urgent need for therapies that not only alleviate symptoms but also target these underlying mechanisms to potentially modify the disease course (Bhunia et al., 2022).

The involvement of the endocannabinoid system in Parkinson's Disease introduces a novel therapeutic avenue. The ECS, particularly prevalent in the basal ganglia, regulates neurotransmission through cannabinoid receptors located on presynaptic terminals. These receptors modulate the release of neurotransmitters such as GABA and glutamate, influencing motor control and possibly compensating for dopaminergic deficits. Dysregulation of the ECS in Parkinson's Disease, including changes in cannabinoid receptor expression and endocannabinoid levels, further supports the potential of cannabinoid-based therapies to modulate the neurodegenerative and symptomatic aspects of the disease (Aymerich et al., 2018). Given the complex interaction between the ECS and the dopaminergic systems within the basal ganglia, cannabinoids could offer symptomatic relief and potentially exert neuroprotective effects through anti-inflammatory, antioxidant, and anti-excitotoxic mechanisms. These characteristics position cannabinoids as promising candidates for addressing both the motor and non-motor symptoms of Parkinson's Disease, warranting further clinical and preclinical exploration to fully harness their therapeutic potential (de Barros Viana et al., 2022).

1.3.3.2 Traditional therapeutic strategies: efficacy and limitations

Parkinson's disease remains a challenging neurodegenerative disorder to manage due to its complex pathology and the progressive loss of dopaminergic neurons in the substantia nigra. The mainstay of current treatment revolves around pharmacological management aimed at alleviating symptoms rather than curing the disease. Levodopa, in combination with carbidopa, continues to be the cornerstone of Parkinson's disease treatment, effectively managing motor symptoms for many patients. Levodopa acts as a dopamine precursor, temporarily replenishing dopamine levels in the brain. However, its effectiveness tends to wane over time, and long-term use is often associated with motor fluctuations and dyskinesias (Leehey et al., 2020; Ferreira-Junior et al., 2020).

Dopamine agonists, such as pramipexole and ropinirole, mimic dopamine's action in the brain and are used either in conjunction with levodopa or as monotherapy to manage early Parkinson's disease symptoms. Monoamine oxidase B (MAO-B) inhibitors like selegiline and rasagiline help prevent dopamine breakdown, thereby extending the effectiveness of naturally occurring and externally supplied dopamine (Patricio et al., 2020; Sousa & DiFrancisco-Donoghue, 2023).

In addition to drugs, non-pharmacological strategies, including physical therapy, occupational therapy, and speech therapy, play vital roles in managing Parkinson's disease. These therapies help improve mobility, function, and communication, and are often recommended in conjunction with medical treatments. For advanced Parkinson's disease, options like deep brain stimulation (DBS) and infusion therapies are available. DBS involves surgical implantation of electrodes in specific brain areas to reduce motor symptoms and medication dosages. Infusion therapies involve continuous

delivery of medication via a pump to provide a steady dose, helping manage symptoms effectively with fewer fluctuations (Cooray et al., 2020).

The pipeline for new therapies includes several promising directions, such as gene therapy with investigational treatments aimed at modifying disease progression at a genetic level, cell-based therapies such as the transplantation of dopaminergic neurons to replace those lost to the disease, and novel drug targets including treatments targeting LRRK2 gene mutations, which are a common genetic cause of Parkinson's disease, and therapies aiming to reduce the accumulation of harmful proteins like alpha-synuclein. Despite these advances, there remains no cure for Parkinson's disease, and the treatments primarily focus on symptom management and improving quality of life. Ongoing research continues to explore more effective and sustainable therapeutic strategies, highlighting the need for continued innovation in this field (Mendivil-Perez et al., 2023).

The current therapeutic strategies for Parkinson's disease predominantly focus on symptom management, primarily through pharmacological means such as levodopa, dopamine agonists, and MAO-B inhibitors. However, these therapies carry significant limitations. Levodopa, while initially effective, leads to diminished efficacy over time and can cause motor complications such as dyskinesias after long-term use. Dopamine agonists and other medications often have side effects that can include psychiatric and cognitive disturbances, orthostatic hypotension, and impulse control disorders (Sousa & DiFrancisco-Donoghue, 2023). Additionally, while surgical interventions like deep brain stimulation provide substantial benefits for some patients, they involve invasive procedures with their own risks and complications, including infections, hardware complications, and the need for periodic adjustments or battery

replacements. Furthermore, most current treatments do not halt the progression of the disease but rather aim to alleviate symptoms, leaving a significant need for truly disease-modifying therapies (Cooray et al., 2020).

1.3.3.3 Therapeutic effects of cannabinoids in Parkinson's Disease

Cannabinoids are increasingly being recognized for their potential neuroprotective and symptomatic benefits in neurodegenerative diseases, including Parkinson's disease. Research suggests that cannabinoids may offer anti-inflammatory, antioxidant, and neuroprotective effects, which are particularly relevant given the pathophysiological mechanisms of Parkinson's disease, such as oxidative stress and chronic inflammation. Clinical evidence, though still emerging, points to potential benefits in symptom management, including reductions in tremors, improvements in sleep, and alleviation of pain and rigidity. Some studies have indicated that cannabinoids might improve overall quality of life for Parkinson's disease patients by addressing both motor and non-motor symptoms. Moreover, the neuroprotective properties of cannabinoids suggest they could play a role in slowing the progression of Parkinson's disease, a potential that is under active investigation but has yet to be fully realized in clinical practice (Singh et al., 2023). These therapeutic potentials position cannabinoids as a promising complement to traditional Parkinson's disease therapies, offering a potentially multi-faceted approach to both symptomatic treatment and disease modification. However, further research and clinical trials are necessary to fully understand the efficacy, safety, and mechanisms of cannabinoids in Parkinson's disease treatment (Voicu et al., 2023).

Clinical and preclinical models provide a range of insights into the potential of cannabinoids for treating Parkinson's disease. These studies have explored various aspects of cannabinoid application, including symptomatic relief and potential neuroprotective effects. Consroe et al. (1986) conducted an open-label pilot study with five patients suffering from dystonic disorders, including two with Parkinsonian features. The study observed a dose-related improvement in dystonia with oral administration of CBD, although higher doses exacerbated Parkinsonian symptoms such as hypokinesia and tremor. Despite its limitations, such as its open-label design and small sample size, this study highlights the nuanced effects of cannabinoids and suggests the need for careful dosing. Finseth et al. (2015), through a cross-sectional survey of 207 PD patients, noted that a small percentage used cannabis, which they found effective for managing non-motor symptoms such as mood and sleep improvements. This study underscores the potential of cannabis in improving the quality of life for PD patients, though it relied heavily on self-reported data. Shohet et al. (2017) observed in an observational study that cannabis consumption (smoked or vaporized) led to immediate improvements in motor symptoms and pain in 20 PD patients. This study suggests both peripheral and central pain pathways may be affected by cannabinoid use, though its uncontrolled nature may affect the generalizability of the findings (Shohet et al., 2017).

A randomized, double-blind, placebo-controlled design was conducted to evaluate the effectiveness of nabilone in reducing non-motor symptoms associated with Parkinson's disease. The study found that patients who received nabilone at doses up to 1 mg experienced positive results, with good tolerability and no significant adverse effects. Data indicated that those who received nabilone experienced improvements in non-motor symptoms, while those in the placebo group reported an increase in non-

motor symptoms. Overall, the results suggest that nabilone may be effective in improving non-motor symptoms in patients with Parkinson's disease (Peball et al., 2020).

Preclinical studies using animal models of Parkinson's disease have shown that cannabinoids can exert neuroprotective effects. Models often utilize neurotoxins like 6-hydroxydopamine to induce Parkinsonian symptoms and examine the therapeutic potential of cannabinoids. Cannabinoids have been found to offer neuroprotection in several preclinical studies by reducing neuronal inflammation and cell death. For example, cannabinoid treatment has been shown to reduce the loss of dopaminergic neurons in models that simulate the pathophysiology of Parkinson's disease (Martinez-Pinilla et al., 2019). In animal models, cannabinoids have been shown to improve motor symptoms such as bradykinesia and tremor, which are hallmark symptoms of Parkinson's disease. These effects are believed to be mediated through both CB1 and CB2 receptors, suggesting a complex interaction with the endocannabinoid system that modulates both motor and non-motor symptoms (Mendivil-Perez et al., 2023). The combined findings from clinical trials and preclinical models underscore the potential of cannabinoids in managing both motor and non-motor symptoms of Parkinson's disease. However, clinical studies often report variable efficacy, highlighting the need for more standardized research protocols, larger sample sizes, and longer study durations to better understand the therapeutic potential and safety profile of cannabinoids in Parkinson's disease treatment (Simeï et al., 2024; Hassan et al., 2024).

1.3.3.4 Potential mechanisms and therapeutic strategies

Many individuals with Parkinson's disease encounter stigma due to their condition. Stigma can significantly impact their quality of life. One reason for this is the shame that often results from a dependence on others for help with daily activities, as well as changes in physical appearance. It's worth mentioning that the inability to perform daily tasks is also linked to a higher perception of stigma. CBD may help to improve the ability to complete daily activities, which could in turn reduce feelings of stigma (Angulo et al., 2019).

Research indicates that cannabinoids may impact Parkinson's disease through multiple pathways. The primary mechanisms suggested involve neuroprotection, modulation of the neuroinflammatory response, and mitigation of oxidative stress within the basal ganglia, a brain area significantly affected in Parkinson's disease. Cannabinoids, particularly CBD, may help prevent neuronal death by interacting with the ECS to reduce oxidative stress and apoptosis in dopaminergic neurons. This action is critical since oxidative stress and mitochondrial dysfunction are prominent features in the pathophysiology of Parkinson's disease, contributing to the progressive loss of dopaminergic neurons in the SNpc (Han et al., 2020).

CBD and THC have been shown to modulate the ECS, which is extensively involved in regulating motor functions and neuroprotection. CB1 receptors, predominantly located in the central nervous system, particularly in motor regions, can modulate neurotransmitter release and reduce excitotoxicity, a key factor in neuronal injury. CB2 receptors, while less concentrated in the nervous system, are thought to play a role in modulating the immune response and are upregulated in response to inflammation,

which is another contributing factor in Parkinson's disease pathology (Voicu et al., 2023).

The neuroprotective properties of cannabinoids suggest they can potentially slow Parkinson's disease progression rather than merely treating symptoms. Cannabinoids may protect neurons by enhancing endogenous antioxidative mechanisms and reducing inflammatory cytokine release within the brain (de Barros Viana et al., 2022). Various clinical and preclinical studies have shown that cannabinoids might help manage both motor and non-motor symptoms of Parkinson's disease. For instance, CBD has been observed to improve quality of life by alleviating symptoms such as pain, sleep disturbances, and rigidity without the psychoactive effects associated with THC. Long-term use of levodopa, the current standard treatment for Parkinson's disease, leads to dyskinesias. Cannabinoids have been proposed to have antidyskinetic effects, potentially mediated by the downregulation of CB1 receptors in the basal ganglia involved in movement control (de Fátima Dos Santos Sampaio, 2024). The literature suggests that while there is promising evidence supporting the potential benefits of cannabinoids in Parkinson's disease, further research is needed to conclusively determine their effectiveness and safety. Future studies should aim to clarify the optimal dosages, long-term impacts, and mechanistic pathways of cannabinoids in Parkinson's disease treatment to fully harness their therapeutic potential (Hafida et al., 2024).

1.3.4 Multiple Sclerosis

Multiple sclerosis (MS) is an immune-mediated neurological disease caused by a malfunction of the immune system which destroys axons and myelin sheets within the

central nervous system. With a worldwide prevalence that accounts for almost two and a half million people, it is the most frequent neurological disease in young adults, mostly presenting between the ages of 20 and 40, leading to prolonged and progressive cognitive, physical and psychological disability. It typically has a higher prevalence in women and individuals of European descent (Patti et al., 2020). MS is classified into several types based on the course of the disease: relapsing-remitting MS (RRMS), which is the most common form, characterized by episodes of neurological dysfunction followed by periods of remission; secondary progressive MS (SPMS), which initially follows a relapsing-remitting course before progressing steadily; and primary progressive MS (PPMS), marked by a continuous decline in function from disease onset without initial relapses. These classifications are crucial for determining appropriate treatment strategies and predicting disease progression (Furguele et al., 2021).

The etiology remains unclear but it is believed that both genetic and environmental factors contribute to its development and progression. Chronic central neuropathic pain and spasticity are pronounced symptoms in multiple sclerosis patients. Bladder dysfunction, spasms, ataxia, tremors, sensory alterations, dysphagia, ataxia, tremor, optic neuritis, weakness and fatigue are accompanying symptoms (Breijyeh et al., 2021).

1.3.4.1 Pathophysiology of Multiple Sclerosis

MS is characterized by neuroinflammation, demyelination, and neurodegeneration within the central nervous system (CNS). The pathological hallmark of MS is the formation of demyelinated plaques, predominantly in the white matter of the brain and

spinal cord. These plaques result from the immune-mediated destruction of myelin, the protective sheath surrounding nerve fibres, which is essential for efficient nerve conduction. The pathogenesis of MS involves a complex interplay between genetic, environmental, and immunological factors. It is widely accepted that MS is initiated by the activation of autoreactive T cells, which recognize myelin antigens as foreign and cross the blood-brain barrier (BBB). This process is facilitated by a variety of environmental triggers, such as viral infections and vitamin D deficiency, which interact with genetic predispositions to activate the immune system against CNS components (Al-Ghezi et al., 2019).

Once inside the CNS, these autoreactive T cells secrete pro-inflammatory cytokines such as interferon-gamma (IFN- γ) and interleukin-17 (IL-17), which recruit and activate other immune cells, including macrophages and microglia. These cells contribute to the demyelination and axonal damage observed in MS by releasing additional pro-inflammatory cytokines, reactive oxygen species, and proteolytic enzymes. This inflammatory cascade not only leads to the degradation of myelin but also causes significant axonal damage, which is a major determinant of the permanent neurological disability seen in MS patients (Al-Ghezi et al., 2019). The role of B cells and antibodies has also been increasingly recognized in MS pathophysiology. B cells within the CNS can differentiate into plasma cells and produce antibodies that target myelin. These antibodies form immune complexes that further activate the complement system, exacerbating inflammation and tissue damage. Additionally, B cells act as antigen-presenting cells, further stimulating autoreactive T cells and perpetuating the inflammatory response (Furgieuele et al., 2021).

Neuroinflammation in MS is associated with the upregulation of various microRNAs (miRNAs), which regulate gene expression at the post-transcriptional level. For instance, miR-155 and miR-21 are significantly upregulated in MS and are involved in promoting inflammatory responses by targeting anti-inflammatory pathways. Conversely, miRNAs such as miR-146a and miR-7116 are downregulated in MS, contributing to the dysregulation of immune responses and promoting neuroinflammation (Furguele et al., 2021). The disruption of the BBB is a critical event in the pathogenesis of MS. The BBB normally functions to protect the CNS from peripheral immune cell infiltration. However, in MS, the integrity of the BBB is compromised, allowing the entry of autoreactive lymphocytes and other immune cells into the CNS. This breach is mediated by pro-inflammatory cytokines and matrix metalloproteinases (MMPs) that degrade the extracellular matrix components of the BBB (Patti et al., 2020; Al-Ghezi et al., 2019).

1.3.4.2 Traditional therapeutic strategies: efficacy and limitations

The primary goal of current therapeutic strategies is to slow disease progression, reduce relapse rates, and manage symptoms effectively. The cornerstone of MS treatment involves disease-modifying therapies (DMTs) that modulate the immune response to prevent further neurological damage. These treatments include immunomodulatory and immunosuppressive agents such as interferon-beta (IFN- β), glatiramer acetate, dimethyl fumarate, mitoxantrone, teriflunomide, cladribine, and sphingosine-1-phosphate (S1P) receptor agonists like fingolimod, siponimod, and ozanimod (Furguele et al., 2021). Interferon-beta and glatiramer acetate are among the first-line treatments for relapsing-remitting MS (RRMS). These agents work by

modulating the immune system, thereby reducing the frequency and severity of relapses. Studies have shown that these medications can significantly reduce the annual relapse rate and delay the progression of disability. Dimethyl fumarate, another oral DMT, has been demonstrated to provide neuroprotective effects by activating the Nrf2 pathway, which reduces oxidative stress and inflammation (Abd-Nikfarjam et al., 2023).

More recently, monoclonal antibodies have become a vital component of MS treatment. Natalizumab, a monoclonal antibody against the cell adhesion molecule $\alpha 4$ -integrin, prevents immune cells from crossing the blood-brain barrier, thereby reducing CNS inflammation. Clinical trials have shown that natalizumab can significantly decrease the relapse rate and slow the progression of disability in patients with RRMS. Ocrelizumab, a monoclonal antibody targeting CD20 on B cells, is effective in both RRMS and primary progressive MS (PPMS). It has been shown to reduce the risk of disability progression and lower the number of new brain lesions on MRI (Furgieuele et al., 2021). Symptomatic treatments are also crucial in managing MS-related symptoms such as spasticity, pain, fatigue, and bladder dysfunction. Baclofen and tizanidine are commonly used to treat spasticity, while gabapentin and pregabalin are prescribed for neuropathic pain. Physical therapy, occupational therapy, and lifestyle modifications are essential components of a comprehensive treatment plan aimed at improving the quality of life for MS patients (Hansen et al., 2021).

Despite the advancements in MS treatment, there are significant limitations associated with current therapeutic strategies. One of the primary challenges is the suboptimal efficacy of disease-modifying therapies (DMTs) in a substantial subset of patients. Approximately 30-40% of MS patients do not respond adequately to first-line DMTs,

and many experience breakthrough disease activity, including relapses and the formation of new lesions on MRI. This underscores the need for more effective treatments that can halt disease progression and prevent long-term disability (Gustavsen et al., 2021).

Another major limitation is the side effect profile of existing treatments. Immunosuppressive agents like mitoxantrone and monoclonal antibodies such as natalizumab and alemtuzumab are associated with severe adverse effects, including increased risks of infections, malignancies, and autoimmune disorders (Furigiuele et al., 2021). For instance, natalizumab has been linked to progressive multifocal leukoencephalopathy (PML), a rare but often fatal brain infection caused by the JC virus. These risks necessitate careful monitoring and limit the long-term use of some of the most potent therapies (Abd-Nikfarjam et al., 2023).

The management of MS-related symptoms also presents challenges. Treatments for spasticity, pain, and other symptoms often provide only partial relief and are associated with side effects such as sedation, dizziness, and gastrointestinal disturbances. Moreover, the development of tolerance to symptomatic treatments can lead to diminished efficacy over time, requiring higher doses or combination therapies that increase the risk of adverse effects. Furthermore, the high cost of DMTs and other MS treatments poses a significant barrier to access, particularly in low- and middle-income countries. The financial burden of long-term therapy can be substantial, affecting both patients and healthcare systems (Rainka et al., 2023).

1.3.4.3 Therapeutic effects of cannabinoids in Multiple Sclerosis

The therapeutic potential of cannabinoids in MS has garnered significant interest due to their anti-inflammatory, neuroprotective, and symptom-relieving properties. Research has focused on the efficacy of cannabinoids in managing MS symptoms such as spasticity, pain, and bladder dysfunction. Cannabinoids have been shown to modulate the endocannabinoid system, which plays a crucial role in maintaining CNS homeostasis. The use of Sativex®, an oromucosal spray containing a 1:1 ratio of THC and CBD, has been extensively studied and demonstrated significant benefits in MS patients with treatment-resistant spasticity. In a randomized, double-blind, placebo-controlled trial, Sativex® significantly improved spasticity symptoms compared to placebo, with 77.4% of patients in the treatment group achieving a clinically relevant improvement in spasticity scores versus 32.1% in the placebo group (Markovà et al., 2019).

Moreover, cannabinoids have been found to provide substantial pain relief for MS patients. Studies have highlighted the effectiveness of THC and CBD in reducing central neuropathic pain, a common and debilitating symptom of MS. Clinical trials have shown that patients using Sativex® reported significant reductions in pain intensity compared to those receiving placebo (MSS7, MSS14). The analgesic effects of cannabinoids are believed to result from their interaction with cannabinoid receptors (CB1 and CB2), which modulate pain signaling pathways within the CNS (Hansen et al., 2021; Guger et al., 2023).

The anti-inflammatory properties of cannabinoids also contribute to their therapeutic benefits in MS. Cannabinoids can suppress the production of pro-inflammatory cytokines and promote the release of anti-inflammatory cytokines, thereby reducing

CNS inflammation (Garde & Hiebel, 2024). This immunomodulatory effect is particularly beneficial in MS, where chronic inflammation leads to progressive neuronal damage. Additionally, studies on experimental autoimmune encephalomyelitis, a model for MS, have demonstrated that cannabinoid treatment can reduce disease severity and delay disease progression by modulating immune responses (Filippini et al., 2022).

Cannabinoids have also been investigated for their potential neuroprotective effects. Research suggests that cannabinoids can protect neurons from excitotoxicity and oxidative stress, which are key contributors to neurodegeneration in MS. The activation of CB1 receptors has been shown to reduce glutamate release and excitotoxicity, while CB2 receptor activation promotes microglial cell activity that supports neuronal survival and repair (Gustavsen et al., 2021; Rainka et al., 2023). Furthermore, cannabinoids can improve quality of life for MS patients by alleviating a range of symptoms. In addition to spasticity and pain relief, cannabinoids have been reported to reduce muscle spasms, improve sleep quality, and decrease bladder dysfunction (Marková et al., 2019). The comprehensive symptom management provided by cannabinoids can lead to significant improvements in overall patient well-being and daily functioning (Jones & Vlachou, 2020).

The relevance and potential clinical use of medicinal cannabis in managing MS symptoms have been the subject of extensive research. Various clinical studies and preclinical models have provided substantial evidence supporting the efficacy and safety of cannabinoids in this context. The CAMS (Cannabinoids in Multiple Sclerosis) trial, conducted by Zajicek et al. (2003), was a multicentre, randomized, placebo-controlled study involving 667 patients. This trial assessed the effects of an oral

cannabis extract containing THC and CBD on MS symptoms, primarily spasticity. Although the Ashworth scale, a clinical measure of spasticity, did not show significant differences, patients reported subjective improvements in spasticity, pain, and walking time. Following up on the CAMS trial, Zajicek et al. (2005) continued to evaluate the long-term safety and efficacy of Cannador (a cannabis extract) in the same patient cohort. Over the course of one year, the study confirmed sustained benefits in managing spasticity, pain, spasms, and tiredness without significant new safety concerns. The MUSEC (Multiple Sclerosis and Extract of Cannabis) trial, conducted by Zajicek et al. (2012), employed a rapid titration method to the maximum tolerable dose of Cannador, focusing on muscle stiffness, pain, and sleep quality. The study included 279 patients and demonstrated significant improvements in these symptoms, confirming the superior efficacy of cannabis extract over placebo and its safety profile (Zajicek et al., 2012).

Marková et al. (2019) conducted a randomized, double-blind, placebo-controlled trial assessing the efficacy of Sativex®, an oromucosal spray containing THC and CBD, in patients with MS spasticity resistant to first-line treatments. The study involved 191 patients who self-titrated their doses up to a maximum of 12 sprays per day. The treatment group exhibited significant improvements in spasticity, pain, and sleep quality compared to the placebo group, with approximately 77.4% of patients showing clinically relevant responses. Notcutt et al. (2012) conducted a multicentre, randomized placebo-controlled study involving 37 patients over 12 weeks. The study focused on the long-term efficacy of Sativex® in treating MS symptoms. Results indicated that Sativex® maintained its effectiveness in improving spasticity and pain, with a favourable safety profile. Langford et al.'s (2013) randomized, double-blind, placebo-controlled trial included 339 patients treated with Sativex® over 14 weeks.

The study found a high response rate in reducing central neuropathic pain in MS patients, with significant improvements in pain and sleep quality maintained throughout the study period (Langford et al., 2013).

Messina et al. (2017) conducted a multicentre, open-label study involving 1597 patients over 24 weeks. The study aimed to identify effective responders to THC oromucosal spray within the first six weeks of treatment. Significant reductions in spasticity and associated symptoms were observed, reinforcing the therapeutic potential of cannabinoids in managing MS-related spasticity. Hansen et al. (2021) performed a national multicentre double-blind, placebo-controlled trial focusing on neuropathic pain and spasticity in MS patients. The study included 134 patients who received THC, CBD, a combination of both, or placebo. The results indicated significant reductions in spasticity and pain levels, highlighting the therapeutic benefits of cannabinoid treatments. Guger et al. (2023) conducted a prospective, observational study on the use of nabiximols (Sativex®) in 55 patients with MS-related spasticity. The study demonstrated substantial improvements in spasticity-associated symptoms, including pain, spasms, and sleep disturbances, with good tolerability (Guger et al., 2023).

van Amerongen et al. (2017) investigated the effects of a synthetic THC drug (ECP002A) in a randomized, placebo-controlled trial involving 24 patients. The study found significant reductions in pain and spasticity levels, though no decline in cognitive function was observed, underscoring the complexity of cannabinoid treatment in MS. Ferrè et al. (2015) conducted a real-world observational study involving 144 patients, demonstrating significant reductions in spasticity and pain with the use of nabiximols. The study confirmed the long-term benefits and safety of cannabinoid treatments in

managing MS-related symptoms. Meuth et al. (2020) analyzed data from the SAVANT study, focusing on 134 patients with moderate to severe spasticity. The study found significant reductions in spasticity and pain scores, particularly in patients with severe symptoms at baseline, demonstrating the efficacy of nabiximols as an adjunct therapy (Meuth et al., 2020).

1.3.4.4 Potential mechanisms and therapeutic strategies

It has been observed that patients with multiple sclerosis experience changes in the expression of CB1 and CB2 receptors. This phenomenon may provide an explanation for the potential therapeutic effects of cannabis-derived products in multiple sclerosis. The anti-inflammatory effect of cannabinoids, as well as their immunomodulatory and neuroprotective properties, likely assist in reducing the levels of inflammatory elements and thus suppress disease activity (Cristino et al., 2020).

CB1 receptors are widely expressed in oligodendrocytes, interneurons, astrocytes and cortical neurons in the central nervous system, as well as in multiple leukocytes infiltrating the brain. Acting through the neuronal CB1 receptor, cannabinoids reduce the excitotoxicity, and through the CB2 receptors reduce toxic effects of reactive microgliosis, enhancing the metabolic and trophic support to neurons via CB1 receptors and CB2 receptors expressed on astroglia. Activity at the presynaptic CB1 receptors causes a massive reduction in glutamate release and regulation of the glutamatergic excitability during spasticity. Glutamate is a key mediator in neuronal and oligodendrocyte damage in multiple sclerosis. Neuroprotective effects are seen in specific brain structures and also on a molecular level, enhancing neuronal survival as

it affects neurons, oligodendrocytes, resting and reactive microglia and astrocytes (Musella et al., 2014; Fernández-Ruiz et al., 2015; Ingram & Pearson, 2019).

Different formulations of cannabis-based products have been used by multiple sclerosis patients to relieve a range of symptoms, including anxiety, spasticity, pain, tremors, and sleep disturbances. In some countries, Sativex® is approved for the treatment of spasticity associated with multiple sclerosis in patients who do not respond to conventional spasticity medications (Pryce & Baker, 2015). Nabiximols have been shown to be effective in reducing MS-related pain in multiple studies. dronabinol has also been used to treat pain in multiple sclerosis patients (Langford et al., 2013).

1.3.5 Amyotrophic Lateral Sclerosis

Amyotrophic Lateral Sclerosis (ALS) is a neurological disorder that affects the motor neurons that control voluntary muscles. It is a progressive disease and can affect both the upper and lower motor neurons, in the cortex, brainstem, and spinal cord. The prevalence of ALS is between 4.1 and 8.4 per 100,000. It is characterized by a gradual loss of muscle control, which can lead to increasing muscle weakness and wasting. Some forms of ALS initially present with muscle weakness in either the patients' lower limbs or upper limbs, while others impair deglutition or the ability to talk. A number of ALS patients will present frontotemporal dementia and will experience cognitive decline as well as changes in personality and behaviour. In all cases the condition progresses to capture an increasing number of disabilities brought about by the muscle impairment until the patient is unable to breathe too. Most patients succumb

to the disease within three to five years of diagnosis, highlighting the urgent need for more effective therapeutic interventions (Ranganathan et al., 2020).

1.3.5.1 Pathophysiology of Amyotrophic Lateral Sclerosis

The disease's pathogenesis is complex and multifactorial, involving both environmental factors and genetic predispositions. ALS can be classified into familial and sporadic forms, with approximately 10% of cases being familial. These familial cases often involve mutations in specific genes such as SOD1, C9orf72, TARDBP, and FUS, which play crucial roles in cellular processes such as RNA processing, protein folding, and the response to oxidative stress. For instance, the SOD1 gene encodes for a superoxide dismutase enzyme that is instrumental in combating oxidative stress. Mutations in this gene can disrupt cellular homeostasis and promote the degeneration of motor neurons (Urbi et al., 2019; Lacroix et al., 2023).

The pathophysiology of ALS involves several key cellular mechanisms. Excitotoxicity occurs when excessive glutamate causes prolonged activation of receptors on motor neurons, leading to increased calcium influx and eventual neuronal death. Mitochondria in ALS patients show signs of damage and are less capable of producing energy, contributing to cell death. Oxidative damage in motor neurons due to imbalance between the generation of reactive oxygen species and the body's ability to detoxify the reactive intermediates or repair the resulting damage is a prominent feature of ALS. Neuroinflammation is characterized by the activation of microglial cells and astrocytes, and contributes to the neurodegenerative process. Activated glial cells release inflammatory cytokines and reactive oxygen species, exacerbating motor neuron damage (Urbi et al., 2019; Lacroix et al., 2023).

1.3.5.2 Traditional therapeutic strategies: efficacy and limitations

The management of ALS currently involves two main pharmacological treatments: riluzole and edaravone. Riluzole, an anti-glutamatergic agent, has been shown to modestly prolong survival by a few months and delay the onset of ventilator-dependence in some patients. Edaravone, an antioxidant, is thought to reduce oxidative stress, potentially slowing the functional decline in ALS. These medications target specific aspects of ALS pathophysiology such as excitotoxicity and oxidative stress, which are believed to play roles in the disease's progression (Urbi et al., 2019). The use of these drugs, while clinically approved, offers only a partial benefit, reflecting the complexity and variability of ALS. Treatment strategies often include symptomatic management to improve quality of life, such as the use of muscle relaxants for spasticity, medications for pain relief, and various supportive therapies like physical therapy and respiratory support. Despite these efforts, the treatments do not significantly alter the disease course or substantially extend life expectancy beyond the typical 3 to 5 years post-diagnosis (Aymerich et al., 2018).

While current therapies for ALS provide critical support for managing symptoms, they are limited by their inability to halt disease progression or reverse the neurological damage. Riluzole and edaravone have shown only modest effects on survival, and their impact on quality of life is minimal. Moreover, these treatments can be associated with significant side effects, such as dizziness and gastrointestinal issues, which may further impair patients' quality of life (Aymerich et al., 2018; Urbi et al., 2019). The limited efficacy of these drugs highlights a significant gap in treatment options for ALS patients, which is compounded by the disease's complex aetiology and progression. The pathophysiological mechanisms of ALS involve multiple cellular and molecular

pathways, including mitochondrial dysfunction, excitotoxicity, oxidative stress, and neuroinflammation, which are not fully addressed by current therapies. This complexity necessitates the development of multi-targeted therapeutic approaches that can more effectively slow disease progression and improve patient outcomes (Meyer et al., 2019). Moreover, the high cost of treatments like edaravone, which requires monthly intravenous infusions, can be prohibitive and limit accessibility for many patients. The need for comprehensive care, including nutritional support, respiratory care, and physical therapy, further adds to the burden on patients and healthcare systems. These limitations underscore the urgent need for innovative treatments that can offer more substantial benefits to patients suffering from this debilitating disease (Lou et al., 2022).

1.3.5.3 Therapeutic effects of cannabinoids in Amyotrophic Lateral Sclerosis

Patients with ALS often suffer from symptoms like spasticity, pain, depression, and weight loss, all of which can potentially be mitigated by cannabinoids. For instance, cannabinoids have been observed to alleviate symptoms such as spasticity and pain, which are prominent features of ALS. These compounds interact with the body's endocannabinoid system, which is involved in regulating pain, inflammation, and motor control, suggesting a therapeutic pathway that might modify disease progression and symptomatology in ALS. Upregulated CB2 receptors within the motor cortex and spinal cord of ALS patients on autopsy have also suggested that there might be use for cannabinoids in ALS therapy, considering also that they can be neuroprotective and anti-inflammatory (Cristino et al., 2020).

Preclinical research using a genetic mouse model of ALS has produced inconsistent findings regarding CB1 receptor. In comparison to healthy controls, reductions in spinal cord motor neuron CB1 receptor expression were observed in the early, pre-symptomatic stage of the ALS mouse model, with CB1 receptor expression elevated in the symptomatic stage. Ultimately, however, CB1 receptor expression was reduced in the ALS subjects, suggesting a continued decline in neuronal health (Yiangou et al., 2006; Zhao et al., 2008).

The therapeutic potential of cannabinoids in the treatment of Amyotrophic Lateral Sclerosis (ALS) has been increasingly supported by both clinical and preclinical evidence, suggesting benefits in symptom management and possibly in slowing disease progression. The utilization of cannabinoids in ALS has been documented across various studies, each highlighting different aspects of symptom management and potential effects on disease progression. For instance, the EMERALD trial, a randomized, double-blind, placebo-controlled study, examined the efficacy of a cannabis-based medicine extract (CBME) that was high in CBD and low in THC. The results indicated that CBME could potentially slow the progression of ALS, as measured by the ALS Functional Rating Scale-Revised (ALSFRS-R) and forced vital capacity (FVC) scores. This study underscored the importance of exploring cannabinoid formulations in managing ALS, not just for symptom relief but also for their potential disease-modifying effects (Urbi et al., 2019). In a different approach, Meyer et al. (2019) conducted a retrospective cohort study focusing on the real-world application of THC:CBD oromucosal spray in managing ALS-related spasticity. The study reported that patients experienced significant improvements in spasticity, highlighting the personalized nature of dosage and the positive patient-reported outcomes. This real-world evidence supports the therapeutic relevance of

cannabinoids in routine clinical management of ALS symptoms. Moreover, individual case reports, such as the one documented by Lou et al. (2022) detailed the successful management of refractory neuropathic pruritus in an ALS patient using a balanced oral cannabinoid formulation. The treatment not only improved the pruritus score significantly but also enhanced the patient's overall well-being and quality of sleep, illustrating the broader potential of cannabinoids in managing complex neuropathic symptoms associated with ALS. Alongside clinical data, preclinical studies have provided foundational insights into the mechanisms by which cannabinoids might exert their effects. These studies typically employ animal models of ALS to explore the neuroprotective properties of cannabinoids. For example, cannabinoids have been shown to modulate immune responses, reduce oxidative stress, and decrease excitotoxicity, which are all implicated in the pathophysiology of ALS. Such preclinical data are crucial as they lay the groundwork for clinical hypothesis and trials, suggesting that cannabinoids might not only palliate symptoms but also alter disease mechanisms. The integration of findings from these diverse studies, from controlled clinical trials to observational studies and preclinical models, forms a compelling argument for the inclusion of cannabinoid-based therapies in ALS treatment protocols. However, the evidence also highlights the necessity for well-structured clinical trials to further ascertain the efficacy, optimal dosages, and safety profiles of these compounds in ALS patients. The variability in patient responses noted in studies like that of Meyer et al. (2019) calls for personalized treatment approaches and further investigation into patient-specific factors that may influence efficacy (Meyer et al., 2019).

1.3.5.4 Potential mechanisms and therapeutic strategies

The exploration of medicinal cannabis in the treatment of amyotrophic lateral sclerosis (ALS) encompasses a broad spectrum of pharmacological research and clinical testing. Various studies have demonstrated the potential of cannabinoids, particularly THC and CBD, to modulate the complex pathophysiological processes associated with ALS. This section reviews the scientific literature regarding the mechanisms through which cannabinoids might impact ALS and discusses potential therapeutic strategies based on these findings. Cannabinoids are recognized for their neuroprotective properties, which are crucial given the neurodegenerative nature of ALS. Research indicates that cannabinoids can mitigate neuronal damage by modulating excitotoxicity, oxidative stress, and mitochondrial dysfunction. The cannabinoids interact with the endocannabinoid system (ECS), which is extensively expressed throughout the nervous system. This interaction helps regulate neurotransmitter release and promotes homeostasis in neural cells. For example, cannabinoids have been shown to inhibit the release of glutamate, thereby reducing excitotoxicity - a key factor in the pathogenesis of ALS (Urbi et al., 2019).

ALS is characterized by chronic inflammation, with microglial activation playing a significant role in the degeneration of motor neurons. Cannabinoids have been reported to exert anti-inflammatory effects by interacting with CB2 receptors located on immune cells. Activation of these receptors helps modulate the immune response and reduce inflammation. This mechanism is particularly important in ALS, where excessive inflammation contributes to the progression of the disease. Clinical studies, such as those reviewed in the documents, have highlighted the potential of cannabinoids to reduce biomarkers of inflammation in neurodegenerative conditions

(Meyer et al., 2019). Spasticity is a common symptom in ALS, leading to significant discomfort and pain for patients. Cannabinoids have demonstrated antispasmodic properties by acting on the central nervous system to reduce muscle spasms and associated pain. The efficacy of THC:CBD oromucosal sprays in managing ALS-related spasticity has been documented in clinical settings, providing evidence of symptom relief which enhances patient quality of life (Meyer et al., 2019; Lou et al., 2022).

While the symptomatic benefits of cannabinoids are well-documented, there is growing interest in their potential to slow the progression of neurodegenerative diseases, including ALS. The EMERALD trial, for instance, explored the use of a high-CBD, low-THC cannabis-based medicine extract, observing its effects on disease progression markers like ALSFRS-R and FVC scores. Such studies suggest that beyond symptomatic management, cannabinoids might influence the underlying disease mechanisms (Aymerich et al., 2018; Urbi et al., 2019). The therapeutic application of cannabinoids in ALS involves careful consideration of formulation, dosing, and administration methods. High-CBD formulations are favoured for their reduced psychoactive effects compared to THC-dominant options, aligning with patient preferences for minimal side effects. Oral administrations, such as capsules or oils, are commonly used, providing a controlled dosage and consistent delivery method. However, the personalized nature of cannabinoid therapy, as evidenced by varied patient responses, underscores the need for tailored treatment plans. This personalized approach ensures that individual patient needs and responses are adequately addressed, optimizing therapeutic outcomes (Lou et al., 2022; Lacroix et al., 2023).

Currently, clinical research into the use of cannabinoids in the treatment of ALS is limited. Patient surveys have suggested that medicinal cannabis may provide relief from symptoms of ALS such as spasticity, drooling and pain. However, the validity of these observations is limited as well given that only a small number of the respondent population had been exposed to cannabinoid use when interviewed (Amtmann et al., 2004). The meticulous CANALS (Cannabis sativa extract in Amyotrophic Lateral Sclerosis and other Motor Neuron Disease) study distributed nabiximols via oromucosal spray to ALS patients and reduced muscle spasticity was noted in those administered the drug (Riva et al., 2019). Although no severe adverse effects were recorded there is limited data on the safety of using medical cannabis in ALS patients due to low patient enrolment and the short trial duration. This lack of data makes it challenging to determine the potential risks and benefits of using medical cannabis in ALS patients (Riva et al., 2019).

1.3.6 Alzheimer's Disease and other dementia presentations

Alzheimer's disease (AD) and related dementias represent a significant challenge to healthcare systems and societies worldwide due to their widespread prevalence and profound impact on individuals and their families. Dementia, a broad category of brain diseases that cause a long-term and often gradual decrease in the ability to think and remember, affects approximately 50 million people globally. Alzheimer's disease accounts for 60–80% of cases, making it the most common form of dementia. These conditions not only lead to cognitive impairment but also a variety of neuropsychiatric symptoms that can cause significant distress (Sherman et al., 2018). The impact on society is immense, not only due to the increasing prevalence of these conditions but

also because of the considerable burden placed on caregivers and healthcare systems (Cooray et al., 2020)

1.3.6.1 Pathophysiology of Alzheimer's Disease

Being the most common neurodegenerative disease that contributes to around four fifths of all dementia cases worldwide, Alzheimer's Disease (AD) is a progressive neurodegenerative disorder characterized by the accumulation of amyloid- β ($A\beta$) plaques and phosphorylated tau protein tangles within the brain, leading to neuroinflammation and subsequent neuronal loss. These pathological hallmarks contribute to the cognitive decline and behavioural changes observed in AD patients (Li et al., 2023). The amyloid cascade hypothesis posits that the deposition of $A\beta$ plaques is an early and critical event in AD pathology. $A\beta$ peptides, derived from the amyloid precursor protein (APP) through sequential cleavages by β - and γ -secretases, aggregate to form insoluble fibrils and plaques that disrupt cell-to-cell communication and activate glial cells, leading to inflammation and oxidative stress (Vallée et al., 2017).

Tau proteins, which normally stabilize microtubules in neurons, become hyperphosphorylated in AD, leading to the formation of neurofibrillary tangles (NFTs). These tangles contribute to the destabilization of the cytoskeleton and impairment of axonal transport, exacerbating neuronal dysfunction and death (Murillo-Rodriguez et al., 2020; Abd-Nikfarjam et al., 2023). Neuroinflammation, driven by the activation of microglia and astrocytes in response to $A\beta$ plaques and NFTs, plays a pivotal role in the progression of AD. Chronic inflammation leads to the release of pro-inflammatory

cytokines and neurotoxic mediators, further promoting neuronal damage (Li et al., 2023).

The loss of neurons and synaptic connections in critical brain regions, including the hippocampus and cortex, underlies the cognitive deficits and memory loss characteristic of AD (Cooray et al., 2020). As the disease progresses, widespread brain atrophy is observed, with significant implications for brain function and behaviour (Cheng et al., 2014). Hippocampus atrophy and eventually frontal cortex degeneration are noted on imagery of the brain (Erkkinen et al., 2018; Scheltens et al., 2021).

1.3.6.2 Traditional therapeutic strategies: efficacy and limitations

Present therapeutic strategies for AD primarily aim to mitigate symptoms and improve quality of life, as there are no treatments available that can halt or reverse the disease's progression (Coles et al., 2022). Cholinesterase inhibitors, such as donepezil, rivastigmine, and galantamine, are used to enhance cholinergic neurotransmission and offer modest cognitive benefits for some patients, particularly in the early to moderate stages of the disease (Karl et al., 2017). Memantine, an NMDA receptor antagonist, is prescribed in the moderate to severe stages of AD to regulate glutamatergic neurotransmission, with some evidence of slowed cognitive decline (Paunescu et al., 2020; Outen et al., 2021).

However, the efficacy of these medications is limited, and they do not address the underlying disease pathology (Liu et al., 2015). Additionally, the management of neuropsychiatric symptoms often involves the use of antipsychotics, antidepressants,

and anxiolytics, which can be associated with significant side effects and do not offer a disease-modifying effect (Liu, 2024).

Current therapeutic approaches to managing Alzheimer's disease and other dementias primarily focus on symptomatic relief, as there are no treatments available that can halt or reverse the progression of these diseases. The mainstay treatments include cholinesterase inhibitors (such as donepezil, rivastigmine, and galantamine) and the NMDA receptor antagonist memantine. These drugs can offer modest cognitive benefits and may help manage certain behavioural symptoms. However, their efficacy is limited, and they do not significantly alter disease progression (Vallée et al., 2017; Weier & Hall, 2017). Additionally, the management of neuropsychiatric symptoms often involves the use of antipsychotics, antidepressants, and anxiolytics, which can have limited effectiveness and are associated with various adverse effects (Li et al., 2023).

Given the limitations of existing therapies, there is a pressing need for novel treatments that can target the underlying pathophysiological mechanisms of AD, potentially altering the disease course. The endocannabinoid system, which includes cannabinoid receptors, endogenous cannabinoids, and the enzymes responsible for their synthesis and degradation, plays a role in various physiological processes, including mood regulation, pain perception, and appetite. The potential neuroprotective and anti-inflammatory effects of cannabinoids could be relevant to the treatment of dementia, where neuroinflammation is a key pathological feature (Watt & Karl, 2017; Fonseca et al., 2023). The exploration of therapeutic targets beyond the cholinergic and glutamatergic systems is crucial. In this context, the endocannabinoid system has emerged as a potential target for novel therapeutic interventions (Li et al.,

2023). The modulation of the endocannabinoid system, which is involved in various physiological processes including neuroinflammation, oxidative stress, and neuroplasticity, may offer a multifaceted approach to AD treatment. Whether Alzheimer's Disease contributes to changes in the CB1 receptor expression is contentious and conclusions from several studies are discordant (Solas et al., 2013; Ahmad et al., 2014). On the other hand, CB2 receptor expression increases dramatically due to deposition of β -amyloid plaques (Solas et al., 2013).

Serotonin, also known as 5-hydroxytryptamine (5-HT), is a monoamine neurotransmitter involved in regulation of sleep, temperature, appetite, sexual behaviour and, most relevant within the context of Alzheimer's Disease, influences learning and memory. Serotonin receptors 5-HT_{1A} are present in the hippocampus (Solis-Guillen et al., 2021) but to a lesser degree in the brains of Alzheimer's Disease patients. Modulation of 5-HT_{1A} receptors through use of cannabinoids could address the impairment of memory in cognitive decline seen in this category of patients. In laboratory mice models the administration of intraperitoneal CBD influenced microglial activation via β -amyloid, returning cognitive ability to the subjects. This was demonstrated by the observed decrease in latency in the Morris water maze test compared to control subjects who were given a placebo (Martin-Moreno et al., 2011). THC has also demonstrated similar neuroprotective properties in laboratory mice (Franke et al., 2019).

1.3.6.3 Neuroprotective and anti-inflammatory effects of cannabinoids in Alzheimer's Disease

The relevance of the endocannabinoid system in Alzheimer's disease (AD) pathology has been increasingly recognized, with both neuroprotective and anti-inflammatory effects attributed to cannabinoids. The potential neuroprotective role of cannabinoids may be particularly crucial in AD, where the accumulation of amyloid- β plaques and tau protein tangles contributes to neuronal damage and loss. Studies suggest that THC can modulate the pathological processes of amyloid- β aggregation, thereby reducing plaque burden and its associated neurotoxicity. Similarly, CBD has been shown to possess antioxidant properties, reducing oxidative stress and neuronal inflammation, factors that are critically involved in AD progression (Li et al., 2020).

Moreover, cannabinoids have been observed to modulate neuroinflammation, a hallmark of AD that contributes significantly to neuronal damage. Through interaction with the endocannabinoid system, cannabinoids can modulate the immune response, reducing the activation of microglia and the release of pro-inflammatory cytokines (Li et al., 2023). This modulation of neuroinflammation by cannabinoids could potentially slow down the progression of AD, providing a therapeutic advantage (Vallée et al., 2017). Additionally, the endocannabinoid system has been implicated in the regulation of synaptic plasticity and neurogenesis, processes that are adversely affected in AD (Watt & Karl, 2017). Cannabinoids, through their interaction with the endocannabinoid system, may support neurogenesis and synaptic function, thereby contributing to the maintenance of cognitive functions in AD patients. This aspect of cannabinoid action represents a promising therapeutic avenue, warranting further investigation (Cooray et al., 2020).

Preclinical studies employing rodent models of Alzheimer's disease have provided valuable insights into the potential therapeutic effects of cannabinoids, including CBD, THC, and whole cannabis extracts. These studies have shown that cannabinoids can modulate AD-related pathologies, including amyloid- β plaque formation, tau protein hyperphosphorylation, and neuroinflammation, which are central to the disease's progression (Vallée et al., 2017). For instance, CBD has been demonstrated to exert antioxidant and anti-inflammatory effects, reducing oxidative stress and modulating microglial activation, thereby potentially mitigating neuronal damage in AD models (Abd-Nikfarjam et al., 2023). THC, on the other hand, has shown potential in reducing amyloid- β levels and inhibiting its aggregation, a key pathological feature of AD (Coles et al., 2022). Furthermore, whole cannabis extracts, which contain a spectrum of cannabinoids, have been suggested to offer neuroprotective benefits, possibly through synergistic interactions that enhance their therapeutic efficacy (Outen et al., 2021).

Nabilone could also assist in targeting a reduction in inflammatory markers and agitation in Alzheimer's Disease patients. Clinical studies have explored its use as a potential treatment for neurodegenerative and neuroinflammatory diseases. In a double-blind, randomized study involving patients with Alzheimer's disease, the administration of nabilone at a dose of 1-2 mg was found to decrease markers of oxidative stress and neuroinflammation, such as tumour necrosis factor- α (Ruthirakuhan et al., 2020).

The entourage effect is a concept suggesting that the therapeutic potential of cannabis is not solely due to its individual cannabinoid components but may be enhanced by the interactions between various cannabinoids and other constituents within the plant. This synergy could potentially lead to more effective treatment strategies, particularly

in complex diseases like AD, where multiple pathological processes are involved (Karl et al., 2017). Preclinical studies support the notion that multi-cannabinoid formulations, combining CBD and THC, for instance, could offer superior therapeutic benefits by targeting different aspects of AD pathology, such as neuroinflammation, oxidative stress, and amyloid- β aggregation, simultaneously (Cheng et al., 2014). This approach may also mitigate some of the adverse effects associated with THC, such as psychoactivity, by leveraging the modulatory effects of CBD and other non-psychoactive cannabinoids (Liu, 2023).

Clinical studies and pilot trials examining the effects of cannabinoid-based therapies on behavioural and psychological symptoms of dementia have yielded promising, albeit preliminary, results. Cannabinoids, particularly CBD, have been explored for their potential to alleviate symptoms such as agitation, aggression, and anxiety in dementia patients, with some studies reporting improvements in these symptoms and overall quality of life (Fonseca et al., 2023). THC, despite its psychoactive properties, has also been studied for its effects on appetite stimulation and sleep regulation in dementia patients, with mixed outcomes (Abd-Nikfarjam et al., 2023). It is worth noting, however, that clinical evidence remains limited, and the variability in study designs, cannabinoid formulations, and patient populations make it challenging to draw definitive conclusions. Moreover, the long-term safety and efficacy of cannabinoid-based therapies in the elderly, particularly those with cognitive impairments, require further investigation (Cooray et al., 2020; Li et al., 2020).

1.3.6.4 Potential Mechanisms and Therapeutic Strategies

The exploration of cannabinoids as therapeutic agents in Alzheimer's disease (AD) delves into their multifaceted mechanisms of action, including antioxidant properties, modulation of neurotransmission, and the ability to influence amyloid-beta ($A\beta$) dynamics. By neutralizing reactive oxygen species (ROS) and reducing oxidative stress, CBD may mitigate the oxidative damage that contributes to neuronal degeneration in AD (Fonseca et al., 2023). THC's interaction with CB1 receptors in the brain can modulate neurotransmitter release, potentially alleviating some symptoms associated with AD, such as behavioural disturbances and altered cognitive functions. This modulation of neurotransmission could also contribute to neuroprotective effects, safeguarding neurons from the damaging impacts of the disease (Abd-Nikfarjam et al., 2023). Emerging evidence suggests that THC might influence the processing of amyloid precursor protein (APP), thereby reducing the formation of $A\beta$ plaques, a hallmark of AD pathology. By inhibiting the aggregation of $A\beta$ and promoting its clearance, cannabinoids could directly target one of the key pathogenic processes in AD (Karl et al., 2017; Paunescu et al., 2020).

This in addition to the aforementioned entourage effect which posits that the therapeutic efficacy of cannabis is not solely due to individual cannabinoids but may be enhanced by the synergistic actions of multiple compounds found in the plant. This approach could offer several advantages in the context of AD treatment, including the synergistic effects of combined cannabinoids which may harness their individual strengths while mitigating potential adverse effects (Charernboon et al., 2021). AD is characterized by complex, multifactorial pathology. A multi-cannabinoid approach could simultaneously target various pathological processes, such as

neuroinflammation, oxidative stress, and A β accumulation, potentially offering a more comprehensive therapeutic strategy (Bahji et al., 2020). The cognitive risks associated with THC, particularly in elderly populations and those with pre-existing cognitive impairments, are a significant concern. By carefully selecting and balancing the ratios of THC to CBD and other non-psychoactive cannabinoids, it may be possible to optimize the therapeutic benefits while minimizing cognitive and psychoactive risks (Stella et al., 2021).

1.3.7 Pain

Pain is a central symptom in disease and chronic illness, originating both from inflammation and nerve injury, neuropathic pain. The two components of pain modulate immune processes and neuronal activity (Xu & Yaksh, 2011). Medicinal cannabis is deployed to treat pain, especially neuropathic pain, with potential opioid-sparing effects as synergistic effects are noted with THC and a number of opioid drugs. Chronic non-cancer pain (CNCP) and neuropathic pain represent significant public health challenges, impacting millions globally and imposing substantial burdens on healthcare systems. CNCP is characterized by pain persisting beyond the expected period of healing, typically exceeding three months, and it encompasses a variety of conditions such as osteoarthritis, fibromyalgia, and chronic lower back pain (Johal et al., 2020). Neuropathic pain, a subset of chronic pain, arises from lesions or diseases affecting the somatosensory system, leading to symptoms such as burning sensations, tingling, and allodynia, and is often observed in conditions like diabetic neuropathy, postherpetic neuralgia, and multiple sclerosis (Okusanya et al., 2020).

1.3.7.1 Pathophysiology of Pain

The pathophysiology of CNCP and neuropathic pain involves complex and multifactorial processes, including peripheral and central sensitization, inflammation, and alterations in pain signaling pathways. These mechanisms often result in heightened pain perception and decreased pain threshold, complicating the management and treatment of these conditions (Lewis et al., 2024).

Chronic non-cancer pain encompasses a range of conditions, such as osteoarthritis, rheumatoid arthritis, and chronic back pain, which persist beyond normal tissue healing time. The pathophysiology of CNCP involves peripheral and central sensitization. Peripheral sensitization results from inflammatory mediators released at the site of tissue injury, leading to a lowered threshold for activating nociceptors (pain receptors). Central sensitization occurs when continuous nociceptive input from the periphery leads to prolonged excitation and increased responsiveness of neurons in the spinal cord and brain, contributing to pain amplification and persistence. Neuropathic pain arises from direct damage to the nervous system, whether due to disease, injury, or dysfunction. It is characterized by symptoms such as allodynia (pain from normally non-painful stimuli) and hyperalgesia (increased pain from painful stimuli). The mechanisms underlying neuropathic pain include ectopic neuronal activity, ion channel dysfunction, and maladaptive plasticity within the nervous system. Damaged nerve fibres exhibit abnormal excitability and spontaneous firing, which are propagated centrally, leading to sustained pain signaling. One critical aspect of neuropathic pain is the role of microglia and astrocytes in the central nervous system. Upon nerve injury, these glial cells become activated and release pro-inflammatory cytokines, chemokines, and other mediators that enhance neuronal excitability and

contribute to central sensitization. This glial activation creates a persistent state of inflammation and neuroexcitability that underpins chronic pain states (Mlost et al., 2020).

Moreover, endocannabinoid system dysregulation has been implicated in both CNCP and NP. Endocannabinoids, such as anandamide and 2-arachidonoylglycerol (2-AG), modulate pain by acting on cannabinoid receptors (CB1 and CB2) distributed throughout the nervous system. In chronic pain conditions, the endogenous cannabinoid system often becomes dysregulated, resulting in reduced endocannabinoid levels and altered receptor expression, which can exacerbate pain perception (Schultz et al., 2021).

1.3.7.2 Traditional therapeutic strategies: efficacy and limitations

The management of CNCP and neuropathic pain involves a multifaceted approach, aiming to alleviate pain, improve function, and enhance quality of life. Various pharmacological and non-pharmacological strategies are employed to manage these complex pain conditions. Pharmacological treatments are the cornerstone of CNCP and neuropathic pain management. The primary classes of drugs used include nonsteroidal anti-inflammatory drugs (NSAIDs), opioids, anticonvulsants, and antidepressants. NSAIDs, such as ibuprofen and naproxen, are commonly used for their analgesic and anti-inflammatory properties. They are effective in treating mild to moderate pain associated with conditions like osteoarthritis and rheumatoid arthritis. Opioids, including morphine, oxycodone, and hydrocodone, are potent analgesics used for moderate to severe pain. They work by binding to opioid receptors in the central nervous system to reduce the perception of pain. However, their use is limited

by the risk of tolerance, dependence, and a range of adverse effects (Lewis et al., 2024).

Medications such as gabapentin and pregabalin are widely used in the management of neuropathic pain. They modulate neuronal excitability by affecting calcium channels, thereby reducing pain transmission. These drugs are particularly effective for conditions like diabetic neuropathy and postherpetic neuralgia (Lewis et al., 2024). Tricyclic antidepressants (TCAs) like amitriptyline and serotonin-norepinephrine reuptake inhibitors (SNRIs) such as duloxetine are used to treat neuropathic pain. These medications enhance the descending inhibitory pathways in the central nervous system and have been shown to be effective in reducing pain and improving sleep and mood (Furrer et al., 2021).

Non-pharmacological treatments also play a significant role in managing CNCP and neuropathic pain. Physical therapy, incorporating exercise and manual therapy, aims to improve function and reduce pain. Techniques like transcutaneous electrical nerve stimulation (TENS) and acupuncture are commonly used to provide additional relief. Psychological therapies, including cognitive-behavioural therapy (CBT), focus on addressing the emotional and psychological aspects of chronic pain, aiding patients in developing coping strategies and improving their overall quality of life. Interventional procedures, such as nerve blocks, epidural steroid injections, and radiofrequency ablation, target specific nerves or areas to offer localized pain relief (Chou et al., 2022).

Traditional pharmacological treatments, such as nonsteroidal anti-inflammatory drugs (NSAIDs), opioids, and anticonvulsants, provide varying degrees of relief but are frequently associated with significant side effects and the potential for dependence and abuse. Despite the availability of various therapeutic options, the management of

CNCP and neuropathic pain remains challenging due to several inherent limitations associated with existing treatments (Ang et al., 2023).

One significant issue is the limited efficacy of current pharmacological treatments. Studies have shown that less than 50% of patients achieve significant pain relief with these medications, underscoring the need for more effective therapies. Adverse effects are a major concern with many commonly used pain medications. Opioids, while effective, come with a high risk of adverse effects, including nausea, constipation, respiratory depression, and the potential for abuse and dependence. This risk has been highlighted by the ongoing opioid epidemic, where the over-prescription of opioids has led to widespread misuse and addiction problems. NSAIDs can cause gastrointestinal bleeding, cardiovascular issues, and renal impairment, further limiting their long-term use. Anticonvulsants and antidepressants, which are often prescribed for neuropathic pain, also carry side effects such as dizziness, somnolence, and weight gain, which can significantly impact patients' quality of life and adherence to treatment (Petzke et al., 2022).

Tolerance and dependence represent additional challenges, particularly with long-term opioid use. Patients often require increasing doses to achieve the same level of pain relief, which not only elevates the risk of dependence but also exacerbates the potential for severe adverse effects. This is particularly problematic given the chronic nature of CNCP and neuropathic pain, which necessitates prolonged treatment. Current therapies also fail to adequately address the underlying mechanisms of chronic pain. Most treatments focus on symptom management rather than the root causes, leading to suboptimal pain control and persistence of pain despite ongoing treatment. For example, the conventional analgesics, such as paracetamol and

NSAIDs, have not been shown to be effective in neuropathic pain, yet they are still commonly used due to the lack of better alternatives (Johal et al., 2020).

The psychological impact of chronic pain is another critical aspect that existing therapies often do not fully address. Chronic pain significantly affects mental health, contributing to conditions such as depression and anxiety. While psychological therapies like cognitive-behavioural therapy can be beneficial, they are not always readily accessible, and their effectiveness can vary widely among individuals. Moreover, the lack of personalized treatment approaches remains a significant limitation. The variability in individual responses to pain treatments necessitates a personalized approach to pain management. However, the absence of reliable biomarkers or predictive tools to guide personalized therapy often results in a trial-and-error approach, which can be frustrating for both patients and clinicians (Mücke et al., 2018).

1.3.7.3 Therapeutic effects of cannabinoids in pain

Cannabinoids have demonstrated significant potential in managing CNCP and neuropathic pain, presenting an alternative or adjunctive therapy to conventional pharmacological treatments. The therapeutic effects of cannabinoids are primarily mediated through their interaction with the endocannabinoid system, which plays a crucial role in modulating pain and inflammation (Jeddi et al., 2024).

Recent advances in the understanding of the endocannabinoid system have spurred interest in the potential therapeutic role of medicinal cannabis in managing CNCP and neuropathic pain. The endocannabinoid system, comprising endogenous ligands,

receptors (CB1 and CB2), and enzymes responsible for their synthesis and degradation, plays a crucial role in modulating pain and inflammation (Jeddi et al., 2024). Cannabinoids, the active compounds in cannabis, interact with this system to exert analgesic and anti-inflammatory effects, making them a promising alternative or adjunctive therapy for chronic pain management (Chou et al., 2022).

The considerable presence of CB1 receptors in central nervous system areas concerned with pain such as the periaqueductal grey neurons, the afferent nerve fibres, trigeminal sensory neurons and the spinal cord interneurons, as well as the receptors' expression in the peripheral nervous system dorsal root ganglia and nociceptors indicate potential pharmaceutical advantages for intervention on the endocannabinoid system via endocannabinoids. Concomitantly, CB2 receptors can regulate inflammatory pain as they are present also in the central and peripheral nervous system via microglia, astrocytes and oligodendrocytes in the former and macrophages and lymphocytes in the latter (Racz et al., 2008). The CB2 receptors of the endocannabinoid system are also present on dorsal horn sensory neurons and could therefore not only contribute to mediating inflammatory pain but also neuropathic pain (Wotherspoon et al., 2005).

The possibility of avoidance of opioid-associated adverse effects while reducing opioid use has intrigued clinical research but results have not been consistent. Some trials noted a poor dose-effect relationship, with presence of abuse of opioids to control pain despite concomitant use of dronabinol (Babalonis et al., 2019; Dunn et al., 2021). Yet other clinical trials reported reduced recurrence to opioids for pain management in patients who were being administered cannabis cotreatment to accompany opioid use (O'Connell et al., 2019; Vigil et al., 2019; Capano et al., 2020). A number of clinical

studies have provided evidence supporting the efficacy of medicinal cannabis in alleviating CNCP and neuropathic pain. For instance, randomized controlled trials have demonstrated significant pain reduction and improved quality of life in patients using cannabis-based treatments compared to placebo (Boehnke et al., 2024).

The investigation into the potential benefits of medicinal cannabis for CNCP and neuropathic pain has gained substantial momentum through a variety of clinical studies and preclinical models. This growing body of evidence supports the therapeutic efficacy of cannabinoids and underscores the need for further research to optimize their clinical use. Clinical studies have consistently demonstrated the potential benefits of cannabinoids in managing CNCP and neuropathic pain. A study by Takakuwa et al. (2020) examined the impact of medical cannabis on opioid use in patients with back pain. The retrospective cohort study revealed that over half of the patients were able to stop using opioids altogether, while others significantly reduced their opioid intake. This highlights the potential of cannabis to serve as an alternative or adjunct therapy, potentially reducing the dependence on opioids for pain management (Takakuwa et al., 2020).

Similarly, Pritchard et al. (2020) explored the effects of cannabis on opioid use among cancer patients receiving palliative care. The study found that patients using both cannabis and opioids had a slower increase in morphine equivalent daily dose (MEDD) compared to those using opioids alone. This suggests that cannabis may help in managing pain more effectively and could reduce the required opioid dosage. Preclinical models have also provided insights into the mechanisms by which cannabinoids exert their analgesic effects. Cannabinoids such as THC and CBD interact with the endocannabinoid system, which includes CB1 and CB2 receptors

found throughout the nervous system. These interactions modulate pain and inflammation, offering a dual mechanism for pain relief. Xu et al. (2020) demonstrated in animal models that cannabinoids reduce pain through both peripheral and central pathways, highlighting their potential in treating various pain conditions (Xu et al., 2020).

In addition to their analgesic properties, cannabinoids have been shown to have anti-inflammatory effects. A study by Aviram et al. (2021) emphasized the role of CBD in reducing inflammation and pain in preclinical models of arthritis. This supports the use of CBD as a non-psychoactive option for pain management, particularly for patients who may be sensitive to the psychoactive effects of THC. Clinical trials have further supported these findings. Almog et al. (2020) conducted a randomized controlled trial on the efficacy of CBD in patients with CNCP. The results indicated significant pain reduction and improvement in sleep quality among the participants, suggesting that CBD could be an effective and well-tolerated treatment for chronic pain. Moreover, the integration of cannabinoids in pain management regimens has shown promise in improving overall patient outcomes. Wallace et al. (2020) reported that patients using cannabinoids alongside their conventional pain treatments experienced enhanced pain relief and better quality of life. This holistic approach to pain management could lead to more comprehensive and effective treatment strategies (Wallace et al., 2020).

1.3.7.4 Potential mechanisms and therapeutic strategies

One of the key mechanisms by which cannabinoids alleviate pain is through the inhibition of neurotransmitter release. By binding to presynaptic CB1 receptors, cannabinoids reduce the release of excitatory neurotransmitters such as glutamate,

thereby decreasing pain signal transmission. Additionally, cannabinoids modulate pain through their anti-inflammatory effects. CBD, in particular, has been shown to inhibit the production of pro-inflammatory cytokines and enhance the release of anti-inflammatory cytokines, contributing to its analgesic properties (Okusanya et al., 2020). Preclinical studies have provided substantial evidence supporting the analgesic effects of cannabinoids. For instance, in rodent models of neuropathic pain, administration of cannabinoids resulted in significant reductions in pain behaviours. These effects are mediated through both CB1 and CB2 receptors, as well as other non-cannabinoid receptors such as TRPV1 (transient receptor potential vanilloid 1) and 5-HT1A (serotonin) receptors. These findings are corroborated by clinical studies that have demonstrated the efficacy of cannabinoids in reducing pain and improving quality of life in patients with CNCP and neuropathic pain (Lewis et al., 2024).

Therapeutic strategies involving cannabinoids often employ a combination of THC and CBD to leverage their synergistic effects. Products such as Sativex®, which contains a 1:1 ratio of THC to CBD, have been approved in several countries for the treatment of spasticity and pain associated with multiple sclerosis. Clinical trials have shown that Sativex® not only reduces pain but also improves sleep and overall quality of life in patients with neuropathic pain. Moreover, cannabinoids can be administered through various routes, including oral, sublingual, and inhalational, each offering different pharmacokinetic profiles. Oral administration provides prolonged effects but has lower bioavailability due to first-pass metabolism. Inhalational routes, such as vaporization, offer rapid onset of action, making them suitable for acute pain management. Despite the promising therapeutic potential, the use of cannabinoids in clinical practice is not without challenges. Adverse effects such as dizziness, dry mouth, and cognitive impairment can limit their use, particularly in vulnerable populations such as the

elderly. Furthermore, the variability in cannabinoid concentrations and the presence of other bioactive compounds in cannabis products necessitate careful consideration of dosing and standardization (Boehnke et al., 2024).

1.3.8 Drug addiction management

Drug addiction management encompasses a wide array of therapeutic strategies aimed at addressing the complex biological, psychological, and social dimensions of substance use disorders (SUDs). Traditional pharmacological treatments such as methadone, buprenorphine, and naltrexone have been foundational in opioid use disorder (OUD) management. Methadone and buprenorphine, partial agonists at the μ -opioid receptor, mitigate withdrawal symptoms and cravings, yet pose risks of misuse and dependence (Lucas, 2017; Reddon et al., 2024). Naltrexone, an opioid receptor antagonist, avoids these risks but suffers from adherence issues due to its impact on the endogenous opioid system (Reddon et al., 2023).

Substance use disorders will present reduced control over consumption, increased use and eventually withdrawal symptoms. A variety of substances can be involved in such vicious cycles including nicotine, cocaine, alcohol and opioids. Since the 19th century cannabis has been deemed effective in managing opiate dependency (Pisanti & Bifulco, 2018). The opioid crisis has underscored the need for innovative treatments. Medicinal cannabis has emerged as a potential adjunctive therapy, leveraging its properties to reduce harm from more dangerous substances. Evidence indicates that cannabis can serve as a substitute for opioids, decreasing the overall incidence of opioid use and related adverse outcomes (Lo et al., 2023; Fehr et al., 2024). This substitution effect is particularly pertinent in light of findings that access to cannabis

correlates with reduced opioid prescriptions and overdose mortality (Lucas, 2017; Bekier et al., 2024).

1.3.8.1 Pathophysiology of drug addiction

The pathophysiology of drug addiction involves complex neurobiological processes, with genetic and environmental factors playing critical roles. Central to addiction is the brain's reward circuitry, including the ventral tegmental area (VTA), nucleus accumbens, and prefrontal cortex, heavily modulated by dopamine, which reinforces drug-seeking behaviours (Mok et al., 2021; Lo et al., 2023). Opioid addiction specifically manipulates the endogenous opioid system, where chronic opioid use induces neuroadaptive changes that enhance tolerance and dependence (Lucas, 2017; Jin et al., 2023).

Recent research has highlighted the role of neuroinflammation in addiction. Chronic opioid use can trigger neuroinflammatory responses, increasing neuronal excitability and reinforcing drug-taking behaviours (Elkrief et al., 2023; Fehr et al., 2024). CBD, a non-psychoactive component of cannabis, shows promise in modulating these neuroinflammatory pathways. Its anti-inflammatory properties may counteract opioid-induced neuroinflammation, reducing both excitability and reinforcement (Reddon et al., 2023; Elkrief et al., 2023).

CBD has also been shown to alleviate opioid withdrawal symptoms and decrease cravings, suggesting its utility as an adjunctive therapy in OUD management (Mok et al., 2021; Lo et al., 2023). Additionally, cannabis-based interventions align with harm reduction strategies, providing a safer alternative to opioids. Studies demonstrate that

cannabis substitution can lead to decreased opioid use and lower overdose rates, a crucial benefit amidst the current overdose crisis (Lucas, 2017; Costa et al., 2024).

1.3.8.2 Traditional therapeutic strategies: efficacy and limitations

Drug addiction management employs various therapeutic strategies, each aimed at addressing different facets of substance use disorders (SUDs). One of the most prominent pharmacological treatments for opioid use disorder (OUD) is opioid substitution therapy, which includes medications like methadone and buprenorphine. These medications function as long-acting opioid agonists, providing a controlled and safer alternative to illicit opioid use. Methadone, a full agonist at the μ -opioid receptor, has been shown to reduce opioid cravings and withdrawal symptoms effectively, facilitating a more stable recovery process (Lucas, 2017). Buprenorphine, a partial agonist, offers similar benefits with a reduced risk of overdose due to its ceiling effect on respiratory depression (Fehr et al., 2024).

Another widely used pharmacological approach is naltrexone, an opioid antagonist that blocks the effects of opioids. Naltrexone is particularly beneficial for individuals who have already detoxified from opioids and are motivated to remain abstinent, as it prevents the euphoric effects of opioids and thus reduces the likelihood of relapse (Reddon et al., 2024). Extended-release formulations like naltrexone depot injections have improved adherence by reducing the frequency of dosing required (Bekier et al., 2024).

For stimulant use disorders, no FDA-approved pharmacotherapies exist, but some off-label medications have shown promise. For instance, bupropion, a norepinephrine-

dopamine reuptake inhibitor, and modafinil, a wakefulness-promoting agent, have been used to reduce cravings and withdrawal symptoms associated with stimulant use (Jin et al., 2023; Reddon et al., 2023). Behavioural therapies, including cognitive-behavioural therapy (CBT), contingency management, and motivational interviewing, play a crucial role across various substance use disorders. These therapies focus on modifying patients' behaviours and thought patterns related to substance use, enhancing motivation for recovery, and providing coping strategies to prevent relapse (Costa et al., 2024).

Furthermore, integrated treatment models that combine pharmacotherapy with behavioural interventions have demonstrated higher efficacy. These models provide a comprehensive approach to treatment, addressing the medical, psychological, and social aspects of addiction (Fehr et al., 2024). Programs like the Matrix Model, which includes elements of CBT, family education, individual counseling, and contingency management, have shown effectiveness in treating stimulant use disorders (Elkrief et al., 2023).

Despite the effectiveness of current therapeutic strategies, several limitations hinder their overall efficacy in treating substance use disorders. For opioid substitution therapy, while methadone and buprenorphine are effective, they are not without risks. Methadone's full agonist profile poses a risk of overdose if not properly managed, and both medications can lead to dependence, requiring long-term maintenance therapy that some patients may find stigmatizing or inconvenient (Lucas, 2017; Fehr et al., 2024).

Naltrexone, while effective in preventing relapse, faces significant adherence challenges. Patients must abstain from opioids before initiating treatment, which can

be a barrier for many. Additionally, the need for regular dosing with oral naltrexone or the relatively high cost of depot formulations can further impede consistent use (Reddon et al., 2024). Moreover, naltrexone does not alleviate withdrawal symptoms, which can deter individuals from initiating or continuing treatment (Bekier et al., 2024).

For stimulant use disorders, the lack of FDA-approved pharmacotherapies presents a significant treatment gap. The off-label use of medications like bupropion and modafinil offers limited efficacy and may not address the full spectrum of symptoms experienced by individuals with stimulant use disorders (Reddon et al., 2023; Jin et al., 2023). Behavioural therapies, while beneficial, require a high level of patient engagement and motivation, which can be challenging to maintain, particularly in populations with severe addiction and co-occurring mental health disorders (Costa et al., 2024).

Integrated treatment models, though effective, often require substantial resources and coordination among various healthcare providers, which can be difficult to implement consistently across different healthcare settings (Fehr et al., 2024). Additionally, these models depend on the availability of trained professionals and access to comprehensive care, which may not be universally available, especially in rural or underserved areas (Elkrief et al., 2023).

1.3.8.3 Therapeutic effects of cannabinoids in drug addiction management

Medicinal cannabis has been observed to exert positive effects on the reduction of opioid use and associated harms, supporting its relevance in the current opioid overdose crisis. Research indicates that cannabinoids can act as effective substitutes for more harmful substances, thereby reducing the incidence of overdose and

promoting harm reduction strategies (Mok et al., 2021). Cannabinoids have shown promise in managing OUD by alleviating withdrawal symptoms and reducing cravings. CBD, in particular, has been noted for its anxiolytic and anti-inflammatory properties, which can help mitigate the stress and discomfort associated with opioid withdrawal (Reddon et al., 2024). Studies have demonstrated that CBD can reduce heroin-seeking behaviour and opioid cravings, highlighting its potential as a supportive therapy in addiction treatment (Lo et al., 2023). Additionally, the synergistic effects of cannabinoids with opioids can enhance pain relief, allowing for lower opioid dosages and reduced risk of dependence (Lucas, 2017; Costa et al., 2024).

The substitution effect, where cannabis replaces the use of opioids, stimulants, and other illicit substances, has been documented in several studies. In Vancouver, a significant portion of people who use drugs reported using cannabis to reduce or eliminate their use of more harmful drugs such as heroin and cocaine (Mok et al., 2021). This substitution not only decreases the risk of overdose but also improves the overall quality of life for individuals struggling with substance use disorders (Mok et al., 2021).

The therapeutic potential of medicinal cannabis in drug addiction management has been explored through various clinical studies and preclinical models, demonstrating significant promise in reducing dependency on more harmful substances and alleviating withdrawal symptoms. A substantial body of clinical evidence supports the use of medicinal cannabis as a harm reduction strategy. A study conducted in Vancouver, Canada, involving people who use drugs, found that approximately 25% of participants reported using cannabis to reduce the use of other substances, including opioids and stimulants. This study highlights the substitution effect, where

cannabis is used as a safer alternative to more harmful drugs, potentially decreasing overdose risks and improving overall quality of life (Mok et al., 2021).

Observational studies and epidemiological research have consistently indicated that access to medicinal cannabis is associated with a reduction in opioid use and related harms. For instance, a retrospective survey of Michigan patients revealed that medical cannabis use was linked to a 64% decrease in opioid use, alongside reduced medication side effects and enhanced quality of life. Additionally, a survey of 2897 medical cannabis patients in California found that 30% reported using opioid-based pain medications, with 97% of these individuals affirming that they were able to decrease their opioid use when using medical cannabis. A cross-sectional survey of patients in Canada's national medical cannabis system showed that 63% of respondents substituted cannabis for prescription drugs, with 32% of these substitutions involving prescription opioids. The primary reasons cited for this substitution were fewer adverse side effects, greater safety, and better symptom management, underscoring the potential of cannabis to mitigate the harms associated with opioid use (Lucas, 2017).

Experiments with laboratory rodent models with dependence on amphetamines, cocaine or heroin did present diminished drug-seeking behaviours when administered CBD. Neuronal anomalies such as the changes in CB1 receptors and the AMPA receptor 1 GluR1-type receptors in the nucleus accumbens, triggered by the exposure to drugs, are also normalized (Lafuente et al., 2011; Markos et al., 2018). Such positive reactions were demonstrated by exposure to CBD but heroin use increased with THC according to some studies (Ellgren et al., 2007; Pazos et al., 2012).

Preclinical studies have also provided valuable insights into the mechanisms by which cannabinoids exert their therapeutic effects. Animal models have demonstrated that cannabinoids can enhance the antinociceptive effects of opioids, potentially allowing for lower opioid doses to achieve the same level of pain relief. This synergy between cannabinoids and opioids is mediated through interactions at the receptor level, where cannabinoids and opioids share similar therapeutic and pharmacodynamic properties, including analgesia, sedation, and inhibition of intestinal motility (Lucas, 2017). Research involving rodent models has shown that cannabidiol (CBD), a non-psychoactive component of cannabis, can significantly reduce heroin-seeking behaviour and opioid cravings. In these studies, CBD administration resulted in decreased anxiety and stress responses, which are critical factors in the relapse and continued use of opioids. Furthermore, CBD's anti-inflammatory properties can mitigate opioid-induced hyperalgesia, a condition where chronic opioid use paradoxically increases pain sensitivity (Jin et al., 2023).

The integration of medicinal cannabis into clinical practice for addiction management involves leveraging its unique pharmacological properties to enhance existing treatment protocols. Clinical guidelines and physician education are crucial to optimizing the therapeutic use of cannabis, ensuring that healthcare providers can effectively incorporate cannabis-based interventions into treatment plans. This includes determining appropriate dosing, administration routes, and patient monitoring to maximize benefits and minimize potential risks (Socías et al., 2017). The evidence from clinical studies and preclinical models collectively underscores the relevance and potential clinical use of medicinal cannabis in drug addiction management. By substituting cannabis for more harmful substances, reducing withdrawal symptoms, and enhancing the efficacy of existing treatments, medicinal cannabis offers a

promising adjunctive therapy that can significantly impact public health outcomes in the context of the ongoing opioid crisis. Continued research and well-designed clinical trials are essential to further elucidate the mechanisms of action and optimize the use of cannabis in addiction treatment protocols, ensuring its safe and effective application in diverse patient populations (Elkrief et al., 2023).

1.3.8.4 Potential mechanisms and therapeutic strategies

The therapeutic potential of cannabinoids in drug addiction management is attributed to several underlying mechanisms. Cannabinoids interact with the ECS, which plays a crucial role in regulating mood, pain, and reward pathways. The ECS includes receptors such as CB1 and CB2, which are widely distributed throughout the brain and body and are involved in modulating neurotransmitter release (Reddon et al., 2023). By influencing these receptors, cannabinoids can modulate the release of dopamine and other neurotransmitters, reducing the reinforcing effects of drugs and alleviating withdrawal symptoms (Reddon et al., 2024).

One of the key therapeutic strategies involves the use of CBD as an adjunctive treatment in opioid replacement therapies such as methadone and buprenorphine. CBD's ability to reduce anxiety and improve sleep can enhance the overall effectiveness of opioid replacement therapies by addressing some of the common side effects and barriers to adherence (Bekier et al., 2024). Moreover, the anti-inflammatory properties of CBD can help mitigate opioid-induced hyperalgesia, a condition where chronic opioid use paradoxically increases sensitivity to pain (Elkrief et al., 2023; Jin et al., 2023).

Another strategy is the integration of cannabinoids into harm reduction programs. By providing a safer alternative to more dangerous substances, cannabis can be incorporated into treatment plans to reduce the overall harm associated with drug use. This approach has been supported by observational studies that have shown decreased rates of opioid prescriptions and overdose deaths in regions with legal access to medical cannabis (Lucas, 2017; Costa et al., 2024). Furthermore, the use of cannabis for harm reduction can be tailored to individual needs, with options for non-smokable forms such as edibles and oils to cater to different patient preferences and medical conditions (Mok et al., 2021; Fehr et al., 2024).

The implementation of cannabis-based interventions requires careful consideration of dosing, administration routes, and patient monitoring to optimize therapeutic outcomes and minimize potential risks. Clinical guidelines and physician education are essential to ensure that healthcare providers can effectively incorporate cannabis into treatment protocols. Additionally, ongoing research and clinical trials are necessary to further elucidate the mechanisms by which cannabinoids exert their beneficial effects and to establish standardized treatment protocols (Elkrief et al., 2023).

1.3.9 Cancer

Cancer remains a major public health challenge globally, characterized by the uncontrolled growth and spread of abnormal cells. This complex group of diseases can affect nearly any part of the body and manifests in over a hundred different types, each with distinct biological characteristics and clinical behaviour. The symptoms associated with cancer are diverse and can significantly impair a patient's quality of life, ranging from pain, nausea, and vomiting to cachexia, anxiety, and depression

(Abrams, 2019). The journey of cancer patients often begins with a set of vague symptoms, which may include unexplained weight loss, persistent fatigue, or chronic pain. As the disease progresses, these symptoms become more pronounced and debilitating. Pain, a prevalent symptom, can arise from the tumour itself pressing on bones, nerves, or other organs, or as a result of treatment interventions like surgery, chemotherapy, and radiation therapy. For instance, cancer-related pain is experienced by 20% to 40% of cancer patients, necessitating comprehensive pain management strategies (Sawtelle & Hall, 2021).

Nausea and vomiting are also common, particularly among patients undergoing chemotherapy. These symptoms can lead to further complications such as dehydration, electrolyte imbalances, and malnutrition, exacerbating the patient's overall condition. Chemotherapy-induced nausea and vomiting (CINV) have been a major focus of supportive cancer care, and cannabinoids have shown promise in mitigating these effects where traditional antiemetics may fall short (Sawtelle & Hall, 2021). Appetite loss and cachexia are severe issues faced by cancer patients, often resulting in significant weight loss and muscle wasting. This syndrome affects not only the patient's physical strength and ability to tolerate treatments but also their overall prognosis. Studies have shown that cannabinoids, including THC and CBD, may help stimulate appetite and improve caloric intake, thereby addressing aspects of cancer-related cachexia (Whitcomb et al., 2020).

Beyond these physical symptoms, cancer patients frequently contend with psychological burdens such as anxiety and depression. These conditions can stem from the stress of the diagnosis, the side effects of treatments, or the impact of the disease on daily life. Effective management of these symptoms is critical, as they

significantly influence a patient's quality of life and their ability to cope with cancer (Sawtelle & Hall, 2021; Valente et al., 2024).

The historical context of medicinal cannabis in cancer care highlights its longstanding use for symptomatic relief. Despite its potential benefits, the legal and regulatory landscape has often hindered its research and clinical application. For centuries, cannabis has been used medicinally across various cultures, from East Asia to the Arab world, and was introduced to Western medicine in the 19th century. However, its classification as a Schedule I substance in the 20th century created significant barriers to its study and utilization in medical practice (Abrams, 2019). In recent years, the landscape has started to shift, with increasing legalization and acceptance of cannabis for medicinal purposes. This has renewed interest in its potential benefits for cancer patients, particularly in managing symptoms that are refractory to conventional treatments. Studies and anecdotal evidence suggest that cannabinoids can offer relief from pain, nausea, and appetite loss, while also helping to improve mood and sleep (Abu-Amna et al., 2021).

1.3.9.1 Cancer-related symptoms

Palliative benefits of cannabinoids include relieving nausea and acting as an antiemetic induced by chemotherapy. They have also been utilized in this category of patients for their orexigenic, antidepressant, analgesic and antinociceptive properties as they alleviate symptoms caused by either the therapy or the cancer itself. The antiemetic properties of cannabinoids have several anecdotal evidence in support alongside numerous animal studies do prove their efficacy in combatting these adverse effects of chemotherapeutic agents by engaging the 5-hydroxytryptamine and

CB1 receptors (Darmani et al., 2001; Parker et al., 2004). Clinical studies have also proven the superior efficacy of nabilone and dronabinol as antiemetic agents when compared to dopamine antagonists such as alizapride and domperidone (Smith et al., 2015). Combination therapy for antiemesis was also found to be superior to using the conventional dopamine antagonist treatment to address emesis (Meiri et al., 2007).

Cannabinoids have also been demonstrated to antagonize depression and anxiety (Crippa et al., 2010; de Mello Schier et al., 2014). Such disorders are common in cancer patients and anxiolytic effects of cannabinoids have improved taste, mood, sleep disturbances and provided a better sense of well-being (Zhang et al., 2018).

Neuropathic pain, allodynia and hyperalgesia are alleviated with cannabinoid use as corroborated via a number of laboratory animal models, further confirming the role cannabinoids can have in regulating pain (Rahn et al., 2007; Khasabova et al., 2011; Khasabova et al., 2012). In clinical studies pain in cancer patients was diminished with use of cannabinoids and compared more favourably to use of opioids and anti-inflammatory agents that are less effective at reducing pain of inflammatory origin in this subset of patients (Johnson et al., 2010; Johnson et al., 2013), while also registered a positive reduction in use of antiemetics, opioids, antidepressants and NSAIDs (Maida et al., 2008).

A frequent clinical use of cannabinoids is as an appetite stimulant. Cerebral CB receptors forming part of the endocannabinoid system are involved in regulation of appetite with endocannabinoid activity, such as that of 2-AG, influencing the limbic forebrain, hypothalamic and intestinal systems as its levels are increased in fasting states (Kirkham et al., 2002). Cannabinoids in cannabis-based medication assists in

returning an appetite to cancer patients even at an advanced stage of disease (Ben Amar, 2006; Brisbois et al., 2011; Turcott et al., 2018).

1.3.9.2 Therapeutic Potential of Cannabinoids in Cancer and Cancer-Related Symptoms

Cannabinoids found in the *Cannabis sativa* plant have garnered increasing attention in oncology for their potential to manage cancer-related symptoms and, in some cases, exert antitumor effects. The therapeutic application of cannabinoids in cancer patients primarily focuses on alleviating symptoms such as pain, nausea, vomiting, cachexia, and psychological distress, which are common and often debilitating consequences of cancer and its treatment (Nathan et al., 2023; Sharon et al., 2023).

Cancer-associated pain is a prevalent and challenging symptom to manage, affecting over 50% of cancer patients (Nathan et al., 2023). Cannabinoids have been found to modulate pain through their action on CB1 receptors in the central and peripheral nervous systems, which are involved in pain transmission and modulation (Nathan et al., 2023). Studies have demonstrated that THC, the primary psychoactive component of cannabis, exerts significant analgesic effects by activating CB1 and CB2 receptors (Malhotra et al., 2021; Sharon et al., 2023). Clinical trials have shown that cannabinoids can be effective in reducing pain intensity, particularly in patients who do not respond adequately to opioids. For instance, a randomized controlled trial reported significant pain reduction with THC/CBD combinations compared to placebo (Johnson et al., 2010; Portenoy et al., 2012).

Nausea and vomiting are common side effects of chemotherapy and can severely impact patients' quality of life and adherence to treatment. Cannabinoids have long been used to treat these symptoms, with evidence supporting the efficacy of THC and synthetic cannabinoids like dronabinol and nabilone in reducing CINV (Meiri et al., 2007; Sharon et al., 2023). These compounds activate CB1 receptors in the brain regions that regulate nausea and vomiting, thereby providing symptomatic relief (Smith et al., 2015; Whiting et al., 2015; Almeida et al., 2021). Cachexia, a complex metabolic syndrome characterized by severe weight loss and muscle wasting, affects a significant proportion of cancer patients and is associated with poor prognosis. Cannabinoids, particularly THC, have been shown to stimulate appetite and increase caloric intake, thus helping to manage cancer-related cachexia (Malhotra et al., 2021; Johnson et al., 2013). While the overall quality of evidence remains variable, some studies indicate that cannabinoids can improve appetite and food enjoyment, although they may not always result in significant weight gain (Jatoi et al., 2002; Strasser et al., 2006; Nahler, 2022).

Beyond physical symptoms, cancer patients often experience psychological distress, including anxiety and depression. Cannabinoids, notably CBD, have demonstrated anxiolytic and antidepressant properties in various studies. CBD interacts with the serotonin receptor 5-HT1A, which is known to influence mood and anxiety (Sharon et al., 2023). Clinical observations have noted improvements in anxiety and depression scores among patients using medical cannabis, suggesting its potential as an adjunct therapy for managing psychological symptoms associated with cancer (Bar-Lev Schleider et al., 2018; Bimonte et al., 2023). In addition to symptom management, there is emerging evidence suggesting that cannabinoids may possess antitumor properties. Preclinical studies have shown that cannabinoids can induce apoptosis,

inhibit tumour growth, and prevent metastasis in various cancer cell lines (Malhotra et al., 2021). For example, cannabinoids have been reported to reduce tumour size in gliomas and pancreatic cancers when used in combination with traditional therapies like chemotherapy and radiation (Scott et al., 2014; Yasmin-Karim et al., 2018). However, clinical data on the anticancer efficacy of cannabinoids are still limited, and more rigorous trials are needed to substantiate these findings (Lichtman et al., 2018; Bimonte et al., 2023).

1.3.9.3 Potential mechanisms of action of the anti-cancer properties of cannabinoids

CBD and THC have shown promising anti-cancer properties through various mechanisms. For a number of years medicinal cannabis products have fulfilled a purpose as supportive treatment for cancer patients who have to deal with the accompanying symptoms of the disease or as a result of undergoing chemotherapy. Some studies have also focused on the cytotoxic properties of cannabinoids that might assist in anti-cancer therapy. Cannabinoids interact with the endocannabinoid system, which includes receptors, endogenous ligands, and enzymes involved in cannabinoid metabolism. The anti-cancer effects of cannabinoids are largely attributed to their ability to modulate signaling pathways that regulate cell proliferation, apoptosis, and metastasis (Pellati et al., 2018). A number of mechanisms of action have been proposed and these include disruption of the cell cycle, inhibition of tumour cell proliferation and invasion, metastasis, DNA synthesis, angiogenesis, signalling pathways such as EGF/EGFR or PI3K/AKT/mTOR/AMPK and induction of apoptosis (Ramer et al, 2013; Scott et al., 2014; Singer et al., 2015; Scott et al., 2017).

Cannabinoids exert significant anti-proliferative effects on cancer cells. One primary mechanism involves the activation of cannabinoid receptors CB1 and CB2, which are G-protein-coupled receptors widely distributed in the body, including in cancer cells. Activation of these receptors can inhibit the proliferation of cancer cells and induce apoptosis. For instance, THC has been shown to induce apoptosis through the CB1 receptor by modulating the ceramide pathway, which is crucial for cell cycle arrest and apoptosis (Pellati et al., 2018). Moreover, cannabinoids can induce endoplasmic reticulum stress, leading to apoptosis. Endoplasmic reticulum stress is associated with the accumulation of misfolded proteins within the endoplasmic reticulum, activating the unfolded protein response. Persistent endoplasmic reticulum stress can trigger apoptotic pathways, and cannabinoids have been found to enhance this process in cancer cells. This mechanism is particularly relevant in glioma cells, where cannabinoid-induced apoptosis is linked to endoplasmic reticulum stress and autophagy (Amaral et al., 2021).

In addition to promoting apoptosis, cannabinoids can disrupt cancer cell signalling by modulating various kinase pathways, which are essential for cell growth and proliferation. For instance, CBD has been found to inhibit the activation of the AKT and ERK pathways, both of which are critical for the proliferation and survival of cancer cells (Nabissi et al., 2013). By interfering with these pathways, cannabinoids can reduce cell viability and potentially prevent the progression of cancer. This mechanism was particularly noted by Ma et al. (2016), who observed that inhibition of these pathways could lead to decreased cancer cell viability and altered migration patterns, indicative of reduced metastatic potential. The tumour microenvironment plays a crucial role in cancer progression and metastasis, involving various cell types,

signalling molecules, and inflammatory processes. Cannabinoids can significantly impact this microenvironment, contributing to anti-cancer effects (Ma et al., 2016).

Cannabinoids have anti-inflammatory properties which can alter the tumour microenvironment by reducing the production of pro-inflammatory cytokines such as TNF-alpha and IL-6. These cytokines are often elevated in cancerous tissues and can promote tumour growth and metastasis by stimulating angiogenesis and suppressing immune surveillance. By reducing these cytokine levels, cannabinoids can inhibit these processes and potentially reduce tumour growth. Lucas and Walsh (2017) have documented the use of cannabinoids to substitute prescription opioids, indirectly highlighting their role in reducing inflammation-related tumour progression (Lucas & Walsh, 2017).

Beyond reducing inflammation, cannabinoids can inhibit the process of angiogenesis – the formation of new blood vessels – which tumours exploit to obtain the nutrients and oxygen needed for growth. This effect is mediated through the downregulation of pro-angiogenic factors like VEGF (Vascular Endothelial Growth Factor). By limiting the availability of these growth factors, cannabinoids can starve tumours of necessary resources, hindering their growth and metastatic potential (Blázquez et al., 2004). Velasco et al. (2016) discussed how cannabinoids regulate cell survival and death pathways in gliomas, including modulation of immune cell functions, which can lead to suppressed tumour growth and promotion of cancer cell death (Velasco et al., 2016). Another significant aspect of the tumour microenvironment influenced by cannabinoids is the recruitment and activity of various immune cells. Cannabinoids can modulate the infiltration of immune cells such as macrophages, neutrophils, and T cells into the tumour. Notably, cannabinoids have been shown to alter the phenotype of

macrophages within the tumour from a pro-tumour type (M2) to an anti-tumour type (M1), which is associated with tumour suppression. This modulation can shift the balance towards a more anti-tumorigenic state. Ferro et al. (2018) discussed how cannabinoids could enhance the efficacy of chemotherapeutics like gemcitabine, which also involves modulating the immune environment to combat pancreatic cancer more effectively (Ferro et al., 2018).

Cannabinoids also exhibit anti-angiogenic properties, which inhibit the formation of new blood vessels necessary for tumour growth and metastasis. This anti-angiogenic effect is mediated through the inhibition of vascular endothelial growth factor (VEGF) pathways. CBD, for example, downregulates the expression of VEGF in cancer cells, thereby reducing angiogenesis and the subsequent spread of the tumour (Lal et al., 2021). Additionally, cannabinoids can inhibit the migration and invasion of cancer cells. They affect various signaling pathways, including the matrix metalloproteinases (MMPs) and the focal adhesion kinase (FAK) pathways, which are critical for cell migration and invasion. By modulating these pathways, cannabinoids reduce the metastatic potential of cancer cells, limiting their ability to spread to distant organs (Pellati et al., 2018; Lal et al., 2021).

Beyond the CB1 and CB2 receptors, cannabinoids interact with other non-cannabinoid receptors, such as transient receptor potential vanilloid type 1 (TRPV1) and peroxisome proliferator-activated receptor gamma (PPAR γ). These interactions further contribute to the anti-cancer effects of cannabinoids. For instance, the activation of TRPV1 by CBD leads to increased intracellular calcium levels, promoting apoptosis in cancer cells. Similarly, PPAR γ activation by cannabinoids induces anti-proliferative and pro-apoptotic effects in various cancer types (Amaral et al., 2021).

Cannabinoids also modulate the immune system, which can contribute to their anti-cancer properties. By interacting with CB2 receptors, which are predominantly expressed in immune cells, cannabinoids can alter the production of cytokines and other immune responses. This immunomodulatory effect can enhance the ability of the immune system to recognize and destroy cancer cells, providing an additional mechanism by which cannabinoids exert their anti-cancer effects (Lal et al., 2021). A pivotal area of interest is the modulation of signalling pathways which can influence the behaviour of cancer cells. Cannabidiol (CBD) has been demonstrated to induce apoptosis in glioma cells through a multi-faceted mechanism involving the enhancement of reactive oxygen species (ROS) production within these cells (Lorente et al., 2009; Galve-Roperh et al., 2000). This increase in ROS can lead to oxidative stress, which damages cellular structures including proteins, lipids, and DNA. In response to this oxidative stress, glioma cells exhibit a decrease in the expression of certain pro-survival proteins such as Bcl-2 and Bcl-xL, proteins known to inhibit apoptotic processes and enhance cell survival. The downregulation of these proteins, therefore, promotes apoptosis and can inhibit the growth of tumours. This specific pathway of ROS induction and subsequent apoptosis has been explored in studies like those by Nabissi et al., 2013, which showed that CBD increased the susceptibility of glioblastoma cells to chemotherapeutic agents by similar mechanisms (Nabissi et al., 2013).

1.3.9.4. Beneficial effects of cannabinoids in cancer care

Cannabinoids have been demonstrated to alleviate chronic pain associated with cancer. Studies indicate that cannabinoids can modulate pain pathways, providing

relief to patients who do not respond adequately to traditional pain management strategies, including opioids (Häuser et al., 2019; Wang et al., 2021). For instance, clinical trials have shown that cannabinoids like THC and CBD can reduce the reliance on opioids, thus minimizing their adverse effects (Vinette et al., 2022). A randomized trial revealed that patients using a combination of THC and CBD reported significant pain relief compared to those on placebo, suggesting cannabinoids as a viable adjunctive therapy for cancer pain management (Clarke et al., 2022; Braun et al., 2024).

Cannabinoids are effective in controlling CINV, a common and debilitating side effect of cancer treatment. dronabinol and nabilone have been approved for use in CINV refractory to standard antiemetic therapies. Studies demonstrate that these cannabinoids can enhance the antiemetic effect, thus improving patients' overall treatment experience and adherence to chemotherapy regimens (Vinette et al., 2022). A phase II/III trial highlighted the efficacy of a THC combination in reducing CINV, where a significant proportion of patients preferred the cannabinoid treatment over placebo (Braun et al., 2024).

Cancer cachexia, characterized by severe weight loss and muscle wasting, is a critical concern in oncology. Cannabinoids have shown promise in stimulating appetite and improving nutritional intake in cancer patients (Wang et al., 2019; Simon et al., 2021). The activation of CB1 receptors has been associated with increased food intake and weight stabilization, which can be particularly beneficial for patients experiencing anorexia-cachexia syndrome (Hammond et al., 2021). Clinical evidence supports that THC, in particular, can enhance appetite and taste sensation, contributing to weight gain and improved quality of life (Razmovski-Naumovski et al., 2022).

Beyond physical symptoms, cannabinoids also offer benefits in managing psychological symptoms such as anxiety, depression, and insomnia, which are prevalent among cancer patients. The anxiolytic and sedative properties of cannabinoids help in reducing stress and improving sleep quality, thus enhancing the overall well-being of patients. Studies have reported that patients using medical cannabis experience better mood stabilization and reduced anxiety levels, which can significantly contribute to their mental health during the strenuous cancer treatment process (Christensen et al., 2022; Braun et al., 2024).

Tumorigenic modulation is a cannabinoid property that has been investigated in preclinical trials and documented in case reports for endocannabinoids, phytocannabinoids and synthetic cannabinoids. The endocannabinoid system has a somewhat unclear role in cancer, but multiple studies point to an overexpression of endogenous ligands and cannabinoid receptors in tumour tissue. (Velasco et al., 2016; Daris et al., 2019). Phytocannabinoid cytotoxic activity is also seen to be enhanced by terpenoid contribution (Namdar et al., 2019).

Cannabinoid receptor activation, endogenous ligands in the tumour cells, metabolic enzymes in the endocannabinoid system and signalling pathways in this system contribute to cancer pathogenesis (Bifulco et al., 2008; Cridge et al., 2013; Massi et al., 2013). Reports of some measure of efficacy have noted effects in various cancers such as lung, bone, colon, skin, testicular, breast, prostatic, gastric, lymphomas, neuroblastomas, leukaemias and glioblastomas (Caffarel et al., 2010; Kampa-Schittenheim et al., 2016; Raup-Konsavage et al., 2018; Zhang et al., 2019).

The exploration of cannabinoids in the context of cancer treatment and symptom management has gained considerable momentum, backed by an expanding body of

both preclinical and clinical evidence. Preclinical studies have provided robust evidence supporting the anti-cancer properties of cannabinoids. For instance, research has demonstrated that cannabinoids can induce apoptosis and inhibit proliferation in various cancer cell lines. One notable study by Velasco et al. (2016) showed that cannabinoids could regulate cell survival and death pathways in gliomas, suggesting a potential therapeutic role beyond palliative care. Furthermore, studies by Galve-Roperh et al. (2013) and Guzmán et al. (2006) highlighted the ability of cannabinoids to effectively target and kill malignant cells while sparing healthy ones through mechanisms including apoptosis and autophagy (Guzmán et al., 2006; Galve-Roperh et al., 2013).

The synergistic potential of cannabinoids when used with traditional chemotherapeutic agents has also been explored. For instance, CBD has been shown to enhance the cytotoxicity of bortezomib in myeloma cells, suggesting that cannabinoids can increase the chemosensitivity of cancer cells (Morelli et al., 2014). Similarly, CBD has been found to improve the efficacy of chemotherapeutic agents like carmustine and doxorubicin in glioblastoma models, indicating potential for lower required dosages of these drugs (Nabissi et al., 2013). These findings are supported by studies demonstrating that CBD can facilitate the entry of doxorubicin into tumour cells, allowing for reduced dosages while maintaining therapeutic effects (Neumann-Raizel et al., 2019).

Clinical trials and studies involving human subjects have further validated the therapeutic potential of cannabinoids in cancer care. Clinical trials are limited and from what has been reported thus far with glioma patients some have not responded to the phytocannabinoid treatment while others showed improvement with increased

survivability (Guzman et al., 2006). Other clinical trials are still ongoing with use of both phytocannabinoids and synthetic cannabinoids. There seems to be some encouraging signs but more answers from robust clinical trials are required. A randomized trial conducted by Zylla et al. (2021) evaluated the feasibility, dose requirements, impact on pain, opioid use, safety, and overall patient satisfaction of medical cannabis in patients with stage IV cancers. The study found that patients who used medical cannabis reported significant improvements in pain control and a reduction in opioid use, without serious safety concerns. This suggests that cannabinoids can be effectively incorporated into standard oncology care to enhance pain management and reduce reliance on opioids (Zylla et al., 2021).

The antiemetic properties of cannabinoids have also been well-documented in clinical settings. Studies have shown that cannabinoids such as dronabinol and nabilone are effective in controlling CINV, which are common and debilitating side effects of cancer treatment (Ferreira Almeida et al., 2021). These cannabinoids activate CB1 receptors in brain regions that regulate nausea and vomiting, providing significant symptomatic relief (Ferreira Almeida et al., 2021). In addition to managing physical symptoms, cannabinoids have been found to improve psychological well-being in cancer patients. Clinical observations and trials have reported reductions in anxiety and depression among patients using medical cannabis, highlighting its potential as an adjunct therapy for managing psychological distress associated with cancer (Irrera et al., 2021).

Several meta-analyses and case studies have explored potential benefits of cannabinoids in cancer care. For example, a systematic review and meta-analysis conducted by Hammond et al. (2021) evaluated the efficacy of cannabis-based medicinal products in treating anorexia-cachexia syndrome. The review concluded

that while the quality of evidence was low, cannabinoids showed potential in increasing appetite and improving quality of life for patients suffering from cachexia, a common condition in advanced cancer (Hammond et al., 2021).

Moreover, cannabinoids have demonstrated promising anti-tumour effects in specific cancer types. Studies on glioblastoma, pancreatic cancer, and melanoma have shown that cannabinoids can reduce tumour viability and inhibit metastasis, further supporting their potential role in cancer treatment (Ferro et al., 2018; Adamska et al., 2018; Domenichini et al., 2019). For instance, a study by Nabissi et al. (2016) explored the effects of combining THC and CBD with carfilzomib, showing decreased cell viability and migration in multiple myeloma cell lines (Nabissi et al., 2016).

1.3.9.5 Limitations of cannabis-based therapy in cancer care

The use of cannabis-based therapies in the treatment of cancer and its symptoms presents several potential limitations that must be considered. Despite its therapeutic potential, several factors can impede its effectiveness and acceptance in clinical practice. The variability in cannabis strains and preparations presents a significant challenge. Different strains of cannabis contain varying levels of cannabinoids such as THC and CBD, which can result in inconsistent therapeutic effects. This variability makes it difficult to standardize doses and predict patient responses accurately. The lack of standardized dosing guidelines further complicates the clinical use of cannabis-based therapies, making it challenging for healthcare providers to recommend appropriate doses for their patients (Woerdenbag et al., 2023).

Another limitation is the potential for adverse effects. While cannabinoids offer potential therapeutic benefits, they are not without side effects. Common adverse effects include dizziness, dry mouth, fatigue, and impaired cognitive function (Sharon et al., 2023). Importantly, cannabinoids have a favourable safety profile compared to many conventional medications, with no reported cases of fatal overdose due to cannabinoid use (Abuhasira et al., 2018; Whiting et al., 2015).

The interaction of cannabinoids with conventional cancer therapies is another area of concern. There is a potential for cannabinoids to interfere with the metabolism of other medications, which could either reduce the efficacy of conventional treatments or increase their toxicity. This interaction necessitates careful consideration and monitoring by healthcare providers to avoid adverse drug interactions (Irrera et al., 2021). Furthermore, there is a significant need for more robust clinical evidence. While preclinical studies and some small-scale clinical trials have shown promise, the lack of large, randomized controlled trials means that the efficacy and safety of cannabis-based therapies are not yet well-established. This gap in high-quality evidence makes it challenging to develop evidence-based guidelines and for clinicians to make informed treatment decisions (Woerdenbag et al., 2023).

1.3.10 Post-Traumatic Stress Disorder

Post-Traumatic Stress Disorder (PTSD) is a complex and often debilitating mental health condition that arises following exposure to a traumatic event (Forsythe & Boileau et al. 2013). Characterized by symptoms such as intrusive memories, nightmares, hypervigilance, avoidance of trauma-related stimuli, and significant disturbances in cognition and mood, PTSD affects approximately 6.8% to 8.7% of the

U.S. population during their lifetime (Hindocha et al., 2018). The prevalence is notably higher among women, with lifetime rates estimated at 9.7% compared to 3.6% in men (LaFrance et al., 2020). This disparity highlights the necessity for gender-sensitive approaches in understanding and treating PTSD (LaFrance et al., 2020).

The development and persistence of PTSD are influenced by various neurobiological processes. Acute stress triggers the autonomic nervous system and prompts the release of metabolic hormones and neurotransmitters, such as glucocorticoids, monoamines, and glutamate. Chronic stress can lead to sustained neurobiological changes, including excessive neuronal activation and allostatic overload, potentially resulting in psychological pathologies (Abizaid et al., 2019). Key brain regions implicated in PTSD include the medial prefrontal cortex, anterior cingulate cortex, hippocampus, and the amygdala. Dysfunction in these areas is associated with the core symptoms of PTSD, such as hyperarousal, anxiety, and impaired fear extinction (Abizaid et al., 2019; Hill et al., 2018).

1.3.10.1 Pathophysiology of post-traumatic stress disorder

The pathophysiology of PTSD involves a range of neurobiological alterations that affect various brain regions associated with fear processing, emotional regulation, and memory. Central to these changes are the amygdala, hippocampus, prefrontal cortex, and the hypothalamic-pituitary-adrenal (HPA) axis. The amygdala is crucial for the processing and expression of emotions, particularly fear. In individuals with PTSD, the amygdala is often hyperactive, which contributes to heightened fear responses and emotional dysregulation. This hyperactivity is thought to be a result of increased glutamatergic activity and altered GABA signaling within the amygdala (Cohen et al.,

2020). Additionally, the basolateral amygdala (BLA) consolidates fearful memories through long-term potentiation (LTP), a process facilitated by N-methyl-D-aspartate (NMDA) receptors. Blocking these receptors can decrease fear responses and aid in fear extinction (Cohen et al., 2020).

The hippocampus is involved in contextualizing memories and modulating stress responses. PTSD is associated with hippocampal atrophy, which is believed to impair the ability to distinguish between past and present experiences, leading to persistent re-experiencing of traumatic events. The reduced hippocampal volume in PTSD patients can also affect the regulation of the HPA axis, further exacerbating stress responses (Hindocha et al., 2018). The medial prefrontal cortex (mPFC) is involved in executive functions and the regulation of emotions. In PTSD, the mPFC often shows reduced activity, which is associated with diminished regulation of the amygdala and impaired fear extinction. This hypoactivity can lead to difficulties in managing emotional responses and a reduced ability to extinguish conditioned fear responses (Bonn-Miller et al., 2022).

The HPA axis, which regulates the body's response to stress, is dysregulated in PTSD. Normally, acute stress activates the HPA axis, leading to the release of cortisol, which helps modulate stress responses. However, in PTSD, this system becomes dysregulated, often resulting in altered cortisol levels that may either be excessively high or abnormally low. This dysregulation can perpetuate the stress response, contributing to the persistence of PTSD symptoms (Cohen et al., 2020). The ECS, which includes cannabinoid receptors CB1 and CB2, plays a role in modulating stress, fear, and emotional responses. Dysregulation of the ECS has been implicated in PTSD, with evidence showing reduced levels of endocannabinoids like anandamide.

This reduction is linked to increased amygdala activity and heightened stress responses. Cannabinoids, such as those found in cannabis, may help restore balance to the ECS, offering potential therapeutic benefits for PTSD (Passie et al., 2012). Genetic predispositions and epigenetic modifications also contribute to the risk of developing PTSD. Specific genes, such as those involved in the regulation of the HPA axis and neurotransmitter systems, can influence an individual's susceptibility to PTSD. Additionally, traumatic experiences can lead to epigenetic changes that alter gene expression, further affecting the neurobiological pathways involved in PTSD (Orsolini et al., 2019).

The pathophysiology of PTSD is multifaceted, involving significant alterations in brain structure and function, neurochemical signaling, and genetic and epigenetic factors. Understanding these complex interactions is crucial for developing effective treatments. Medicinal cannabis, by modulating the ECS and potentially correcting some of these dysregulations, represents a promising area of research for PTSD therapy. However, further studies are needed to fully elucidate the mechanisms and efficacy of cannabis-based treatments for PTSD (Hill et al., 2018).

1.3.10.2 Traditional therapeutic strategies: efficacy and limitations

PTSD is a complex psychiatric condition that often requires a multi-modal therapeutic approach. Current therapeutic strategies for PTSD encompass both pharmacological and psychotherapeutic interventions. The first-line pharmacological treatments typically include SSRIs and SNRIs such as sertraline, paroxetine, and venlafaxine. These medications aim to alleviate symptoms by modulating neurotransmitter systems implicated in mood and anxiety regulation. However, their efficacy is limited, with

remission rates ranging from 20% to 30%, and they are often associated with side effects that can lead to poor adherence and discontinuation of treatment (Forsythe & Boileau et al., 2013; Abizaid et al., 2019; Cohen et al., 2020)

Second-generation antipsychotics like risperidone and quetiapine are sometimes used, particularly for managing severe symptoms or when first-line treatments are insufficient (Bonn-Miller et al., 2022). However, these medications come with their own set of potential side effects and risks, including metabolic syndrome and increased cardiovascular risk (Hindocha et al., 2018; Orsolini et al., 2019). Another promising pharmacological approach involves the use of prazosin, an alpha-1 adrenergic antagonist, which has shown efficacy in reducing nightmares and sleep disturbances associated with PTSD (Hill et al., 2018). Non-pharmacological therapies are also a cornerstone of PTSD treatment. Trauma-focused psychotherapies such as CBT, prolonged exposure therapy, and eye movement desensitization and reprocessing have demonstrated effectiveness. These therapies focus on helping patients process and integrate traumatic memories, reduce avoidance behaviours, and alleviate distressing symptoms (Cohen et al., 2020; McKee et al., 2021).

Despite the availability of these therapeutic options, significant limitations persist. One major issue with pharmacological treatments like SSRIs and SNRIs is their delayed onset of action, which can be particularly challenging for patients in acute distress. Additionally, the partial efficacy of these drugs means that many patients do not achieve full remission, and the side effects, such as sexual dysfunction, weight gain, and sleep disturbances, can further reduce their attractiveness and adherence (Passie et al., 2012; Forsythe & Boileau et al., 2013). Psychotherapeutic interventions, while effective, are resource-intensive. They require a substantial time commitment from

both patients and therapists and can be costly. Access to qualified therapists can be limited, particularly in under-resourced areas, making it difficult for many patients to receive the recommended trauma-focused therapies. Moreover, not all patients are willing or able to engage in the intensive process of exposure-based therapies, which can be distressing (Orsolini et al., 2019; Bonn-Miller et al., 2022).

Another limitation is the variability in treatment response. Factors such as comorbidities, the severity of PTSD symptoms, and individual differences in biology and trauma history can influence how well a patient responds to a given treatment. For instance, patients with comorbid substance use disorders (SUD) often experience more severe symptoms and poorer treatment outcomes, which complicates the therapeutic process (Hindocha et al., 2018; Abizaid et al., 2019; McKee et al., 2021).

1.3.10.3 Therapeutic effects of cannabinoids in post-traumatic stress disorder

Post-traumatic stress disorder (PTSD) can originate from exposure to a traumatic event that consequently triggers a psychological and behavioural reaction that encompasses a varying list of symptoms, depending on the original cause and the individual experiencing it. Studies with veterans had reported benefits with use of medicinal cannabis that included improved sleep, reduced nightmare episodes, reduced anxiety and PTSD severity (Cameron et al., 2014; Greer et al., 2014; Betthausen et al., 2015; Jetly et al., 2015; Mizrachi et al., 2016; Browne et al., 2018). Most side effects reported for PTSD patients on medicinal cannabis treatment were mild and included brain fog, headaches, dizziness and a dry mouth (Mashiah, 2012; Browne et al., 2018) with one study noting a more severe adverse effect related to an increase in the violent behaviour of the patient (Bedard-Gilligan et al., 2018).

The potential therapeutic effects of cannabinoids on PTSD are increasingly recognized in both clinical and preclinical studies. The ECS with its endogenous cannabinoids anandamide and 2-arachidonoylglycerol, and the enzymes that degrade these cannabinoids, plays a crucial role in regulating mood, memory, and stress responses. Dysregulation of the ECS has been implicated in PTSD, suggesting that modulation of this system may offer therapeutic benefits (Cohen et al., 2020). Clinical studies have demonstrated that cannabinoids can help reduce core symptoms of PTSD, such as anxiety, sleep disturbances, and hyperarousal. For instance, nabilone has been shown to reduce nightmares and improve sleep quality in PTSD patients (Hill et al., 2018; Stanciu et al., 2021). Moreover, evidence suggests that cannabinoids can facilitate the extinction of fear memories and reduce the retrieval of aversive memories, which are critical processes in managing PTSD (LaFrance et al., 2020; Lynskey et al., 2024).

Real-world data also support the use of cannabinoids in PTSD treatment. A study involving military veterans indicated that cannabis use led to significant reductions in PTSD symptoms such as intrusive thoughts, flashbacks, and irritability immediately following cannabis inhalation. Another study using the Strainprint® app, which tracks symptom changes in medical cannabis users, found that cannabis use resulted in more than a 50% reduction in PTSD-related symptoms (LaFrance et al., 2020).

Cannabinoids appear to have a role in managing PTSD-related comorbid conditions. For example, a study from Project Twenty21 in the UK reported that patients with PTSD and comorbid depression experienced significant improvements in both PTSD and depressive symptoms after three months of cannabinoid treatment (Lynskey et al., 2024). This suggests that cannabinoids not only target PTSD symptoms but also enhance overall mental health and quality of life. The potential mechanisms underlying

the beneficial effects of cannabinoids in PTSD involve the modulation of several brain regions associated with fear, stress, and emotional regulation. The amygdala, hippocampus, and prefrontal cortex, all of which express high levels of cannabinoid receptors, are key areas where cannabinoids exert their effects (Hindocha et al., 2018). By enhancing endocannabinoid signaling in these regions, cannabinoids may help reduce hyperactivity and improve emotional regulation (Mizrachi Zer-Aviv et al., 2016).

Cannabinoids have been extensively studied for their potential therapeutic effects on PTSD through various clinical and preclinical models. These studies suggest that cannabinoids may offer significant benefits in managing PTSD symptoms, particularly when conventional treatments fall short. Jetley et al. (2015) conducted a preliminary randomized double-blind placebo-controlled crossover study to investigate the effectiveness of nabilone in reducing PTSD-associated nightmares. The study involved Canadian male military personnel with persistent nightmares despite standard treatments. Results showed a significant reduction in nightmare frequency and intensity in the nabilone group compared to the placebo group, suggesting that nabilone may be an effective treatment for trauma-related nightmares. LaFrance et al. (2020) performed an observational study using archival data from 404 PTSD sufferers who used the Strainprint® app. Participants self-administered inhaled cannabis and reported over a 50% reduction in PTSD symptoms such as intrusions, flashbacks, irritability, and anxiety immediately after cannabis use. This study highlights the potential of cannabis to provide immediate symptom relief. Fraser (2009) conducted an open-label clinical trial with 47 PTSD patients experiencing continuous nightmares. The study found that 72% of patients reported cessation or significant reduction in nightmares after nabilone treatment, along with improvements in sleep quality and

reductions in daytime flashbacks and night sweats, indicating the potential utility of nabilone in managing treatment-resistant nightmares in PTSD. Reznik et al. (2012) conducted a naturalistic observational study involving 167 adult PTSD patients. The study found significant improvements in quality of life and pain scores with medical cannabis, particularly among patients with comorbid conditions like chronic pain and depression. This study suggests that medical cannabis can be beneficial for managing PTSD and its associated conditions. Mashiah (2012) presented an open pilot study involving 29 Israeli male combat veterans with chronic PTSD. The study reported notable reductions in PTSD symptoms and improvements in sleep quality following cannabis treatment, although the small sample size and lack of a control group limit the generalizability of these findings (Mashiah; 2012).

Rabinak et al. (2013) explored the effects of synthetic THC on fear extinction in a controlled experimental study with healthy volunteers. The study found that THC enhanced the retention of extinction learning, suggesting that cannabinoids might prevent the relapse of fear, a core component of PTSD treatment. Das et al. (2013) conducted a study on the effects of CBD on fear memory extinction and consolidation. The study demonstrated that CBD enhanced the consolidation of extinction learning without significantly affecting the acquisition phase, indicating its potential as an adjunct to extinction-based therapies for anxiety disorders, including PTSD. Hill et al. (2022) performed an observational study using data from the National Health and Resilience in Veterans Study. The study suggested that frequent cannabis use among veterans with PTSD was associated with improvements in symptom management, although it also highlighted the need for caution due to potential adverse psychiatric and functional outcomes. Bonn-Miller et al. (2022) conducted a longitudinal prospective controlled observational study involving 150 participants with PTSD. The

study found that cannabis users reported significant reductions in PTSD symptoms over a year compared to non-users, suggesting the potential long-term benefits of cannabis in managing PTSD symptoms (Bonn-Miller et al., 2022).

1.3.10.4 Potential mechanisms and therapeutic strategies

The therapeutic potential of cannabinoids in treating PTSD is increasingly supported by both preclinical and clinical studies. The ECS plays a critical role in regulating mood, memory, and stress responses. It is essential for regulating fear, anxiety, and stress responses, which are central to PTSD. CB1 receptors, predominantly located in brain regions such as the amygdala, hippocampus, and prefrontal cortex, are integral in modulating neurotransmitter release and synaptic plasticity. These brain regions are vital for processing traumatic memories and emotional responses. Studies indicate that PTSD patients often exhibit lower levels of endocannabinoids, which might contribute to the chronic stress and anxiety characteristic of the disorder (Black et al., 2019).

THC, a partial agonist at CB1 receptors, can modulate neurotransmitter release, reduce amygdala reactivity, and enhance fear extinction processes. These actions can help mitigate the hyperarousal and intrusive memories experienced by PTSD patients (Müller-Vahl, 2024). CBD, on the other hand, does not directly bind to CB1 receptors but influences ECS activity through other mechanisms, such as inhibiting the degradation of endocannabinoids, reducing inflammation, and modulating serotonin receptors. These actions contribute to its anxiolytic and antipsychotic properties, making CBD a promising candidate for PTSD treatment (Steenkamp et al., 2017).

Pharmacological strategies that enhance endocannabinoid signaling are being explored as novel treatments for PTSD. For instance, inhibitors of fatty acid amide hydrolase, the enzyme that degrades anandamide (AEA), can elevate endocannabinoid levels and have shown promise in preclinical models of anxiety and PTSD (McKee et al., 2021) . Similarly, inhibitors of monoacylglycerol lipase, which degrades 2-AG, are being studied for their potential to modulate ECS activity beneficially (Bonn-Miller et al., 2022).

Clinical trials are underway to assess the efficacy of these approaches. Preliminary studies suggest that cannabinoids can reduce PTSD symptoms such as anxiety, sleep disturbances, and hyperarousal. For example, a study by Das et al. (2013) demonstrated that CBD enhanced the consolidation of extinction learning in a fear-conditioning paradigm, indicating its potential as an adjunct to extinction-based therapies for anxiety disorders, including PTSD (Stanciu et al., 2021). Moreover, real-world evidence from studies like Project Twenty21 has documented substantial reductions in PTSD symptoms with the use of medicinal cannabis, highlighting its therapeutic potential. These findings underscore the need for more rigorous clinical trials to establish standardized dosing regimens and long-term safety profiles (Lynskey et al., 2024).

1.3.11 Anxiety and depression

Anxiety disorders are a common type of mental disorder and are estimated to affect approximately 4% of the global population (World Economic Forum, 2019). They are more common in women than in men, and the prevalence tends to increase with age. Anxiety disorders can cause significant distress and can interfere with a person's

ability to carry out daily activities. They often co-occur with other mental disorders, such as depression and substance abuse. The prevalence of anxiety disorders may vary depending on the specific type of anxiety disorder and the population being studied. Some studies have suggested that certain subtypes of anxiety disorders, such as generalized anxiety disorder and panic disorder, may be more common in certain parts of the world than others. Brain regions associated with control of emotions and anxiety include the hypothalamic nuclei, prefrontal cortex, amygdala and hippocampus (Marcinkiewicz et al., 2016). All of which indicate significant presence of both CB1 and 5-HT1A receptors and an indirect effect on the regulation of anxiety, as demonstrated in animal studies (Lesch et al., 2005). CB2 receptors within the central nervous system and also the peripheral nervous system have also been deemed to play a role in modulating anxiety (Liu et al., 2017; Patel et al., 2017).

Anxiety disorders represent a significant public health concern, affecting millions of individuals worldwide. Generalized Anxiety Disorder (GAD) is the most prevalent form, characterized by persistent and excessive worry lasting for at least six months, often accompanied by symptoms such as restlessness, fatigue, difficulty concentrating, irritability, muscle tension, and sleep disturbances (Ergisi et al., 2022). The impact of GAD on individuals is profound, leading to reduced health-related quality of life, increased risk of suicidality, and substantial socioeconomic burdens due to healthcare utilization and loss of productivity (Stack et al., 2023).

Pharmacological treatments for anxiety disorders typically include SSRIs, SNRIs, and benzodiazepines. However, these treatments often come with limitations such as side effects, variability in patient response, and the potential for dependence, particularly with benzodiazepines (Ergisi et al., 2022). Consequently, there is a growing interest in

alternative therapies, including medicinal cannabis, due to its potential anxiolytic properties (Sarris et al., 2020). The endocannabinoid system, which plays a crucial role in modulating anxiety and stress responses, has become a focal point for research into new anxiolytic treatments. CBD has shown promise in preclinical studies for its ability to modulate anxiety-related behaviours. Studies suggest that CBD exerts its effects through interaction with the serotonin 5-HT_{1A} receptor and the cannabinoid CB₁ receptor, which are involved in anxiety regulation (Sarris et al., 2020; Ergisi et al., 2022).

Depression is another prevalent mental health condition that significantly impacts individuals' lives, characterized by persistent feelings of sadness, loss of interest in previously enjoyed activities, significant changes in weight or appetite, sleep disturbances, fatigue, feelings of worthlessness or excessive guilt, and impaired concentration or decision-making abilities (Botsford et al., 2020). The burden of depression extends beyond the individual, affecting families, communities, and healthcare systems globally. Traditional treatment options for depression include antidepressants, such as SSRIs and SNRIs, and psychotherapy. While these treatments can be effective, they are not universally successful and are often accompanied by side effects that can lead to non-compliance (Black et al., 2019).

This has led to an increased interest in exploring the therapeutic potential of medicinal cannabis and its components for managing depressive symptoms. Research into the effects of cannabis on depression has yielded mixed results. Some studies suggest that cannabis use may be associated with an increased risk of developing depression, particularly with early and heavy use during adolescence (Kuhns et al., 2022). However, other studies indicate that cannabis components, particularly CBD, may

have antidepressant properties, potentially offering a new avenue for treatment (Botsford et al., 2020). Cannabinoids' antidepressant effects are thought to be mediated through various mechanisms, including the modulation of the endocannabinoid system and interaction with serotonin receptors. These interactions can influence neuroplasticity, stress response, and inflammation, all of which play roles in the pathophysiology of depression (Botsford et al., 2020). Despite the potential benefits, more rigorous clinical trials are necessary to fully understand the efficacy and safety of medicinal cannabis in treating depression (Quick et al., 2022).

1.3.11.1 Pathophysiology of anxiety and depression

Anxiety disorders, characterized by excessive fear and worry, are associated with significant morbidity. The pathophysiology of anxiety involves multiple neural circuits, neurotransmitter systems, and hormonal pathways. Central to these mechanisms is the amygdala, which plays a pivotal role in the processing of fear and anxiety. Dysregulation of the amygdala's response to stress and threat, often observed in anxiety disorders, is mediated by neurotransmitters such as serotonin, norepinephrine, and GABA. Additionally, the HPA axis, responsible for stress hormone regulation, often shows hyperactivity in individuals with anxiety, leading to an increased release of cortisol (Beletsky et al., 2024).

The ECS has emerged as a critical modulator of anxiety-related processes. Cannabinoid receptors, particularly CB1 receptors located in the brain, modulate neurotransmitter release and have been implicated in anxiety regulation. Preclinical studies have demonstrated that activation of CB1 receptors can produce anxiolytic effects, whereas their blockade may lead to increased anxiety. CBD has shown

promise in reducing anxiety through its interaction with the 5-HT_{1A} receptor and its ability to modulate the ECS (Li et al., 2024).

Recent studies indicate that chronic cannabis use may lead to an altered anxiety state. While some individuals use cannabis for its anxiolytic effects, evidence suggests a dose-dependent relationship where low doses may reduce anxiety, but higher doses can exacerbate it. Moreover, the self-medication hypothesis suggests that individuals with anxiety may use cannabis to alleviate their symptoms, potentially leading to dependence and exacerbating the anxiety disorder in the long term (Botsford et al., 2020; Beletsky et al., 2024). Furthermore, the interaction of cannabinoids with the HPA axis and the resultant modulation of cortisol levels highlights the complex role of the ECS in anxiety regulation (Li et al., 2024).

Depression, a leading cause of disability worldwide, is a complex disorder with multifactorial etiology involving genetic, biochemical, and environmental factors. Central to the pathophysiology of depression is the monoamine hypothesis, which posits that deficiencies in neurotransmitters such as serotonin, norepinephrine, and dopamine play a crucial role. This hypothesis is supported by the efficacy of antidepressants that enhance monoaminergic transmission (Botsford et al., 2020). The HPA axis is also implicated in depression. Hyperactivity of the HPA axis, resulting in elevated cortisol levels, is a common finding in depressed individuals. Chronic stress and prolonged exposure to high cortisol levels can lead to hippocampal atrophy and dysfunction, contributing to the symptoms of depression (Poleszak et al., 2018).

The ECS is increasingly recognized for its role in mood regulation and the pathophysiology of depression. The ECS modulates the release of neurotransmitters and is involved in the stress response. Dysregulation of the ECS, including alterations

in endocannabinoid levels and CB1 receptor function, has been observed in depression. For instance, upregulation of CB1 receptors in the prefrontal cortex has been associated with depressive symptoms, and polymorphisms in the CB1 receptor gene have been linked to an increased risk of depression (Botsford et al., 2020). Studies on the antidepressant effects of cannabinoids, particularly CBD, suggest potential therapeutic benefits. CBD has been shown to exert antidepressant-like effects in animal models by enhancing serotonergic and glutamatergic signaling through the 5-HT_{1A} receptor. However, the dual effects of cannabis on mood, with both potential therapeutic and depressogenic effects, underscore the need for further research to delineate the conditions under which cannabinoids might be beneficial for treating depression (Onaemo et al., 2021).

1.3.11.2 Traditional therapeutic strategies: efficacy and limitations

Commonly used drugs as part of pharmacotherapy for addressing anxiety in patients are serotonergic, such as azapirones and selective serotonin reuptake inhibitors. Among their adverse effects are suicidal ideation, serotonin syndrome, movement disorders and sexual dysfunction (Hammell et al., 2016; Rissardo & Caprara, 2020). These medications are often effective in reducing symptoms of anxiety, but their efficacy varies among individuals, and they can have side effects such as drowsiness, dependence, and withdrawal symptoms (Fonseca et al., 2023). This is an incentive to veering towards use of cannabis-based treatments, however it has to be borne in mind that THC has shown counterproductive effects in this category of patients given the psychoactive properties and anxiety-inducing effects (Garcia-Gutierrez et al., 2020; Kayser et al., 2020). CBD, on the other hand, has shown promise with some animal

studies indicating anxiolytic effects at moderate doses and also with chronic use while others noted negligible anxiolytic effects (Guimaraes et al., 1990; Long et al., 2010; Elbatsh et al., 2012).

For depression, first-line pharmacological treatments include SSRIs, SNRIs, and atypical antidepressants such as bupropion and mirtazapine. These medications can alleviate depressive symptoms by modulating neurotransmitter levels in the brain, particularly serotonin and norepinephrine. Despite their widespread use, these drugs often require several weeks to achieve full therapeutic effects and may cause adverse effects like gastrointestinal disturbances, sexual dysfunction, and increased suicidal ideation in some populations, particularly adolescents (Garcia-Gutierrez et al., 2020).

Psychotherapy is another cornerstone in the management of anxiety and depression. CBT is one of the most effective psychotherapeutic approaches for both conditions. CBT helps patients identify and challenge maladaptive thought patterns and behaviours, fostering healthier coping mechanisms. Other therapeutic modalities include interpersonal therapy, which focuses on improving interpersonal relationships and social functioning, and dialectical behaviour therapy (DBT), which is particularly effective for individuals with borderline personality disorder comorbid with depression and anxiety (Garcia-Gutierrez et al., 2020). Combination therapies, which integrate pharmacological and psychotherapeutic interventions, are often employed to enhance treatment efficacy. This approach can be particularly beneficial for patients who do not respond adequately to monotherapy. For example, combining SSRIs with CBT has been shown to improve outcomes in both anxiety and depression, leveraging the pharmacological benefits of symptom relief and the cognitive restructuring provided by therapy (Tourjman et al., 2023).

Despite the availability of various treatment options for anxiety and depression, existing therapies have notable limitations. Pharmacological treatments, while effective for many, do not work for all patients. Approximately 30-50% of individuals with MDD and anxiety disorders do not achieve remission with first-line pharmacotherapy. This treatment-resistant population faces ongoing challenges in managing their symptoms (Rifkin-Zybutz et al., 2023). Side effects are a significant concern with pharmacological treatments. SSRIs and SNRIs, while generally considered safe, can cause side effects such as nausea, weight gain, sexual dysfunction, and increased risk of suicidal thoughts, particularly in young adults. Benzodiazepines, although effective for acute anxiety relief, carry a high risk of dependency and withdrawal symptoms, limiting their long-term use (Li et al., 2024).

Psychotherapy, while effective, is not without its limitations. Access to qualified therapists can be a barrier, particularly in low-resource settings. Additionally, psychotherapy requires a significant time commitment from patients, which can be challenging for those with severe symptoms or other life responsibilities. The success of therapy also heavily relies on the patient-therapist relationship, which can vary widely (Garcia-Gutierrez et al., 2020). Combination therapies, while often more effective than monotherapy, can be complex to manage and may increase the burden of side effects. Furthermore, the optimal combination and duration of treatments can vary greatly among individuals, requiring personalized treatment plans that may not be readily available in all healthcare settings (McKee et al., 2021; Rifkin-Zybutz et al., 2023).

1.3.11.3 Therapeutic effects of cannabinoids in anxiety and depression

CBD has been shown to exert anxiolytic effects through multiple mechanisms. One significant pathway involves its action on the serotonin 5-HT_{1A} receptor, where it acts as a partial agonist, contributing to its calming effects. Additionally, CBD's role as a low-potency, full agonist at transient receptor potential vanilloid type 1 (TRPV1) receptors has been implicated in reducing oxidative stress, which is closely related to inflammation, pain, anxiety, and depression. This complex interaction suggests that CBD may modulate anxiety symptoms through both direct and indirect pathways (Narayan et al., 2022).

Preclinical studies have supported these findings, indicating that high doses of CBD may lead to the desensitization of TRPV1 receptors, facilitating neurotransmission of glutamate and GABA across the brain. However, high doses can also produce paradoxical anxiogenic effects due to TRPV1 expression in brain regions associated with anxiety, such as the medial prefrontal cortex and hippocampus (Narayan et al., 2022). Despite these complexities, clinical evidence suggests that CBD can reduce anxiety in individuals with generalized social anxiety disorder (SAD) during stressful situations, such as public speaking (Stanciu et al., 2021).

The therapeutic potential of CBD extends to depression as well. Studies have shown that CBD can positively influence the ECS, which plays a crucial role in mood regulation. CBD's ability to reduce oxidative stress and inflammation, both of which are linked to depression, highlights its potential as an antidepressant. Moreover, CBD's interaction with the ECS can correct imbalances that are often observed in individuals with depression (Narayan et al., 2022).

In contrast, THC, the psychoactive component of cannabis, has a more complex relationship with anxiety and depression. While some studies suggest that low doses of THC can reduce anxiety and improve mood, higher doses are often associated with increased anxiety and paranoia, particularly in individuals with a predisposition to psychiatric disorders (Narayan et al., 2022). This biphasic effect of THC necessitates careful consideration of dosage and individual patient profiles when considering its use for therapeutic purposes. Clinical trials and real-world evidence provide a mixed picture regarding the efficacy of THC-dominant treatments. For instance, while THC may offer short-term relief of depressive symptoms, chronic use has been associated with an increase in baseline depression over time (Onaemo et al., 2021). The potential for THC to exacerbate psychiatric conditions, especially in individuals with comorbid anxiety and depression, further complicates its therapeutic use. The current body of evidence underscores the urgent need for well-controlled, randomized clinical trials (RCTs) to better understand the therapeutic actions of THC and CBD, both as monotherapies and in combination. Such studies should focus on their effects on the ECS, dosage optimization, and the identification of specific patient populations that may benefit from cannabinoid-based treatments (Tourjman et al., 2023).

Clinical studies diverged in the cannabis formulation administered to the patients, but all seemed to have anxiolytic effects (Almeida et al., 2013; Capano et al., 2020). Some recorded also physiological responses to stress rather than simply subjective self-reporting of patients and they too seemed to denote beneficial anxiolytic effects (Crippa et al., 2010; Bergamaschi et al., 2011; Crippa et al., 2011) especially with administration of CBD (Garcia-Gutierrez et al., 2020).

Several clinical trials have demonstrated the anxiolytic and antidepressant effects of CBD. For instance, Crippa et al. (2011) conducted a study on treatment-naïve Portuguese men with generalized SAD. Participants were administered 400 mg of oral CBD, which resulted in a significant reduction in anxiety without notable adverse effects. Similarly, Bergamaschi et al. (2011) found that a single dose of 600 mg of oral CBD administered to undergraduates with SAD before a simulated public speaking test led to a less pronounced increase in anxiety compared to the placebo group. Another significant study by Masataka (2019) involved Japanese teenagers diagnosed with SAD who were given 300 mg of CBD oil daily for four weeks. This regimen resulted in substantial symptom improvements compared to the placebo group. These findings are corroborated by de Meneses-Gaya et al. (2021), who reported no significant differences in anxiety measures between CBD and placebo groups but highlighted the safety and tolerability of CBD at various dosages (Meneses-Gaya et al., 2021).

For depression, case studies such as Berger et al. (2020) have shown that high doses of CBD, up to 800 mg administered daily can lead to sustained improvements in anxiety and depressive symptoms over several months, confirming the safety and efficacy of CBD in treating refractory anxiety and depression. Additionally, Shannon et al. (2019) reported that daily doses of CBD, ranging from 25 mg to 175 mg, resulted in significant reductions in Hamilton Anxiety Rating Scale (HAM-A) scores, indicating decreased anxiety levels over three months (Shannon et al., 2019).

The effects of THC on anxiety and depression have been more variable. Grimm et al. (2018) found that while THC can increase anxiety shortly after intake, its effects vary significantly depending on the dosage and individual patient profiles. Studies have

also shown that low doses of THC may provide anxiolytic effects, but higher doses often exacerbate anxiety and paranoia. This biphasic effect underscores the need for careful dose management in clinical applications (Grimm et al., 2018).

Preclinical models have provided insights into the mechanisms underlying the therapeutic effects of cannabinoids. Research on animal models has demonstrated that CBD can enhance serotonergic and glutamatergic transmission, which are critical pathways in the regulation of mood and anxiety. These studies suggest that CBD may exert its anxiolytic and antidepressant effects through the modulation of the ECS and interactions with neurotransmitter systems such as serotonin and GABA. In animal studies, the administration of CBD has been shown to reduce stress-induced anxiety behaviours and depressive-like symptoms. For example, a study by de Almeida et al. (2021) demonstrated that CBD administered over a prolonged period led to significant reductions in anxiety and depressive behaviours in rodent models, highlighting its potential for long-term therapeutic use. THC's effects in preclinical models have similarly highlighted its complex role in anxiety and depression. While low doses of THC have been shown to produce anxiolytic effects, higher doses often result in increased anxiety and depressive-like behaviours in animal models. These findings are consistent with clinical observations and emphasize the importance of dosage in the therapeutic application of THC (Almeida et al., 2021).

1.3.11.4 Potential mechanisms and therapeutic strategies

THC acts as a partial agonist of cannabinoid type 1 (CB1) receptors. These receptors are abundantly present in brain regions associated with emotional processing, such as the prefrontal cortex, amygdala, and hippocampus. Activation of CB1 receptors by

THC can result in both anxiolytic and anxiogenic effects depending on the dosage and the specific brain regions involved. For instance, low doses of THC can produce anxiolytic effects by stimulating CB1 receptors in the prefrontal cortex, while higher doses may induce anxiety through CB1 receptor activation in the amygdala (Li et al., 2024).

CBD exhibits a more complex interaction with the ECS and other receptor systems. It has been shown to inhibit the reuptake and breakdown of anandamide, an endogenous cannabinoid, thereby enhancing endocannabinoid signaling. This inhibition occurs through the suppression of fatty acid amide hydrolase (FAAH), the enzyme responsible for anandamide degradation. Increased anandamide levels can lead to enhanced CB1 receptor activation, which is associated with reduced anxiety and improved mood (Narayan et al., 2022). Moreover, CBD's therapeutic effects extend beyond the ECS. It interacts with several other receptor systems, including the serotonin 1A (5-HT1A) receptors, which are known to play a pivotal role in anxiety and depression. CBD's agonist action at 5-HT1A receptors is believed to contribute significantly to its anxiolytic and antidepressant effects. This receptor interaction suggests a mechanism similar to that of SSRIs, which are commonly prescribed for anxiety and depression (Garcia-Gutierrez et al., 2020). Another important aspect of CBD's mechanism involves its impact on the HPA axis. Dysregulation of the HPA axis is a hallmark of chronic stress, anxiety, and depression. CBD has been shown to modulate the HPA axis, thereby normalizing cortisol levels and reducing stress responses. Additionally, CBD promotes neurogenesis, particularly in the hippocampus, a brain region critically involved in mood regulation and cognitive function. This neurogenic effect is thought to be mediated through its interactions with cannabinoid receptors and serotonin receptors, highlighting its potential to repair and

maintain brain plasticity under conditions of chronic stress (Garcia-Gutierrez et al., 2020).

The therapeutic strategies involving cannabinoids also consider the entourage effect, where different cannabis compounds work synergistically to enhance therapeutic outcomes. This effect underscores the importance of using full-spectrum cannabis extracts, which contain a wide range of cannabinoids, terpenes, and flavonoids, rather than isolated compounds. The combined action of these components can potentiate the beneficial effects while minimizing adverse reactions, offering a balanced approach to managing anxiety and depression (Narayan et al., 2022; Beletsky et al., 2024).

1.3.12 Eating disorders

The endocannabinoid system plays a role in many physiological processes, including appetite and metabolism. It is involved in the regulation of hunger and satiety. Activation of CB1 receptors has been shown to stimulate appetite and increase food intake. The endocannabinoid anandamide, which activates CB1 receptors, has also been shown to increase food intake (Rinaldi-Carmona et al., 1994; Simiand et al., 1998). In contrast, CB2 receptors, found mainly in immune cells, trigger an opposite effect on appetite as activation of CB2 receptors has been shown to reduce food intake and body weight, with potential benefits to be considered for weight loss pharmacotherapies (Verty et al., 2015).

One of the recognized uses of cannabis in medicine, in fact, is as an appetite stimulant in cachexic oncology patients and HIV patients, with THC-based drugs such as

nabilone and dronabinol inducing a higher caloric intake and assisting in extending survival rates (Jatoi et al., 2022). Results were not always corroborated by some clinical trials, which found no benefits in weight gain or survival for cancer patients when using CBD or CBD and THC products in comparison to placebo (Brisbois et al., 2011). Nonetheless, numerous studies have recognized both THC and CBD as having orexigenic properties, promoting its use with cancer, HIV, anorexia and hepatitis C patients (Costiniuk et al., 2008).

1.3.12.1 Pathophysiology of eating disorders

Eating disorders such as anorexia nervosa and bulimia nervosa are complex psychiatric conditions characterized by disturbances in eating behaviours and body image. The pathophysiology of these disorders involves a multifactorial etiology, including genetic, neurobiological, and psychosocial factors. Genetic predisposition plays a significant role in the development of eating disorders. Variability in genes related to the endocannabinoid system (ECS) has been associated with psychiatric comorbidities in anorexia nervosa, suggesting a genetic underpinning that influences both eating behaviours and mood regulation (Rogers & Pacanowski, 2023). The ECS, which includes cannabinoid receptors CB1 and CB2, endocannabinoids such as anandamide and 2-arachidonoylglycerol, and the enzymes involved in their synthesis and degradation, is crucial for maintaining energy homeostasis and reward mechanisms. Dysregulation in this system has been implicated in the abnormal eating behaviours seen in eating disorders (Taylor et al., 2024).

CB1 receptors are primarily located in the central nervous system, including regions such as the hypothalamus and the mesolimbic pathway, which are critical for appetite

regulation and the rewarding aspects of eating (Rogers & Pacanowski, 2023). Activation of CB1 receptors by endocannabinoids or exogenous cannabinoids like Δ^9 -THC can influence feeding behaviour, promoting appetite and food intake. In contrast, CB2 receptors, found in peripheral tissues and the immune system, play a role in inflammation and immune response, which are also relevant to the pathology of eating disorders (Rosager et al., 2021).

Hormonal dysregulation is another critical aspect of the pathophysiology of eating disorders. Hormones such as leptin and ghrelin, which regulate hunger and satiety, interact with the ECS. Leptin typically inhibits appetite, while ghrelin stimulates it. Studies have shown that the anorexigenic effects of leptin and the orexigenic effects of ghrelin are dependent on CB1 receptor activation (Scharmer et al., 2020). Disruptions in this hormonal balance can contribute to the persistent hunger and satiety issues observed in individuals with eating disorders (Rosager et al., 2021). Additionally, insulin-like growth factor 1 (IGF-1) and cortisol levels are often altered in patients with anorexia nervosa, reflecting changes in stress response and metabolic function. For instance, lower IGF-1 and higher cortisol levels are typical in severe anorexia nervosa, indicating a state of chronic stress and catabolism (Alderman et al., 2022; Rogers & Pacanowski, 2023).

Neurotransmitter systems, particularly those involving serotonin and dopamine, are also implicated in the pathophysiology of eating disorders. The serotonergic system is crucial for mood regulation and has been linked to both anxiety and depression, which commonly co-occur with eating disorders. Serotonin dysregulation can affect appetite and eating behaviours, contributing to the restrictive and compulsive eating patterns seen in these disorders. Similarly, the dopaminergic system, which is involved in

reward processing, can influence binge-eating and purging behaviours through its effects on pleasure and motivation (Rosager et al., 2021).

Psychosocial stressors, including societal pressures for thinness, traumatic experiences, and family dynamics, significantly contribute to the development and maintenance of eating disorders. These factors can exacerbate underlying genetic and neurobiological vulnerabilities, leading to the onset of pathological eating behaviours (Scharmer et al., 2020; Alderman et al., 2022).

The potential therapeutic use of cannabinoids in eating disorders is based on their interaction with the ECS and their effects on appetite, mood, and anxiety. $\Delta 9$ -THC and CBD have shown promise in modulating the ECS, which may help normalize eating behaviours and reduce anxiety in patients with eating disorders. For example, $\Delta 9$ -THC can stimulate appetite and enhance the pleasure associated with eating, which could be beneficial in treating anorexia nervosa (Rogers & Pacanowski, 2023). However, the use of cannabinoids must be approached with caution due to the risk of dependency and other adverse effects, such as cannabinoid hyperemesis syndrome (McKee et al., 2021).

1.3.12.2 Traditional therapeutic strategies: efficacy and limitations

Current therapeutic strategies for eating disorders such as anorexia nervosa and bulimia nervosa encompass a multidisciplinary approach that includes medical, nutritional, and psychological interventions. One of the most commonly used methods is CBT, which has been shown to be effective in reducing the symptoms of bulimia nervosa and binge-eating disorder. CBT focuses on modifying dysfunctional thoughts

and behaviours related to food, weight, and body image, and it has been established as a first-line treatment in several clinical guidelines (McKee et al., 2021).

For anorexia nervosa, family-based therapy (FBT) is widely recommended, especially for adolescents. FBT involves the patient's family in the treatment process, empowering them to help restore their child's weight and improve their eating behaviours. Studies have shown that FBT can be particularly effective in the early stages of anorexia nervosa, leading to significant improvements in weight and psychological health (McKee et al., 2021; Rogers & Pacanowski, 2023). Pharmacological treatments, although not primary, play a supportive role in managing eating disorders. SSRIs like fluoxetine are often prescribed, particularly for bulimia nervosa, where they have been shown to reduce binge-eating and purging behaviours. However, their efficacy in treating anorexia nervosa is less clear, with mixed results reported in various studies (Scharmer et al., 2020).

Nutritional rehabilitation is a cornerstone of treatment for anorexia nervosa. This involves carefully monitored and structured meal plans to restore healthy eating patterns and weight. Nutritional counseling is essential, and the involvement of dietitians in the treatment team is critical for the success of this intervention (Alderman et al., 2022). In addition to these therapies, there are also inpatient and outpatient programs designed to provide intensive support for individuals with severe eating disorders. These programs offer a combination of medical monitoring, nutritional support, and various forms of psychotherapy, and they are crucial for patients who are at high medical risk due to their eating disorder (Rosager et al., 2021).

Despite the availability of these therapeutic strategies, there are significant limitations in the current treatment landscape for eating disorders. One major issue is the high

relapse rate, particularly in anorexia nervosa, where up to 50% of patients may relapse after treatment. This underscores the chronic nature of the disorder and the need for ongoing support and intervention (Scharmer et al., 2020). Another limitation is the variable response to treatment. While CBT and FBT have shown efficacy, not all patients respond to these interventions, and there is a subset of individuals with treatment-resistant eating disorders. This variability in treatment response highlights the need for personalized approaches and the development of new therapeutic modalities (Alderman et al., 2022; Rogers & Pacanowski, 2023).

Pharmacological treatments, while helpful in managing some symptoms, often have limited efficacy and can be associated with side effects. For instance, SSRIs, while beneficial for bulimia nervosa, do not significantly impact weight restoration in anorexia nervosa and can sometimes exacerbate anxiety or other psychiatric symptoms (Scharmer et al., 2020). Nutritional rehabilitation, although essential, can be a slow and challenging process. Patients with severe anorexia nervosa often require long-term inpatient care to achieve and maintain a healthy weight, which can be resource-intensive and costly. Additionally, the psychological aspects of eating disorders are not always fully addressed by nutritional interventions alone, necessitating a comprehensive and integrated treatment approach (McKee et al., 2021; Rosager et al., 2021). Furthermore, the stigma associated with eating disorders can hinder individuals from seeking help, and there are often delays in treatment initiation. Early intervention is crucial for better outcomes, but many patients do not receive timely care, leading to more entrenched and severe symptoms by the time treatment is started (Taylor et al., 2024).

1.3.12.3 Therapeutic effects of cannabinoids in eating disorders

Cannabinoids have shown potential benefits in the treatment of eating disorders, particularly anorexia nervosa, due to their effects on appetite stimulation and weight gain. Studies have highlighted that Δ 9-THC and its synthetic analog dronabinol can influence the ECS, which plays a crucial role in regulating appetite, energy balance, and reward mechanisms. Research has demonstrated that cannabinoids can stimulate appetite by activating CB1 receptors in the hypothalamus and mesolimbic pathways, areas of the brain involved in hunger and reward processing. For example, dronabinol has been associated with a significant increase in weight in patients with anorexia nervosa when compared to placebo. In one randomized controlled trial, patients receiving dronabinol gained an average of 1 kg over four weeks compared to those on placebo (Rosager et al., 2021). In addition to weight gain, cannabinoids may also alleviate some of the psychological symptoms associated with eating disorders. Δ 9-THC has been shown to reduce anxiety and improve mood in patients with anorexia nervosa, which can be beneficial given the high comorbidity of anxiety disorders in this population. These effects are believed to be mediated through interactions with the CB1 receptors in the brain, which modulate neurotransmitter release and synaptic plasticity (McKee et al., 2021).

Cannabinoids might offer therapeutic benefits by modulating the endocrine system. They have been shown to influence levels of hormones such as leptin and ghrelin, which are crucial regulators of appetite and energy homeostasis. For instance, leptin typically suppresses appetite, whereas ghrelin stimulates it. Cannabinoids can enhance the orexigenic effects of ghrelin and mitigate the anorexigenic effects of leptin through CB1 receptor activation (Rosager et al., 2021). However, the therapeutic use

of cannabinoids in eating disorders is not without its challenges. While the appetite-stimulating effects of Δ^9 -THC and dronabinol are promising, high doses can lead to adverse effects such as increased anxiety, paranoia, and psychosis. Therefore, dosing strategies need careful optimization to balance efficacy and safety. Additionally, the long-term effects of cannabinoid therapy on mental health and metabolic function require further investigation (Scharmer et al., 2020).

The exploration of cannabinoids in the treatment of eating disorders such as anorexia nervosa has gained significant interest due to their potential to stimulate appetite and modulate psychological symptoms. Clinical and preclinical studies have provided insights into the efficacy and mechanisms of these compounds, although results have been mixed and warrant further investigation. A pivotal study by Andries et al. (2014) conducted a prospective randomized double-blind controlled crossover trial with 25 women diagnosed with chronic anorexia nervosa. Participants received 2.5 mg of dronabinol twice daily for four weeks. The study demonstrated a statistically significant mean weight gain of 0.73 kg compared to placebo without severe psychotropic adverse effects, suggesting that low-dose dronabinol can be an effective adjunct in promoting weight gain in anorexia nervosa patients (Andries et al., 2014).

Another study by Andries et al. (2015a) evaluated the impact of dronabinol on physical activity and related metabolic parameters in 24 women with anorexia nervosa. The study found that while there was no significant change in the total duration of physical activity, the intensity of physical activity increased by 20% during dronabinol treatment compared to placebo. Additionally, energy expenditure was higher during the dronabinol phase, and there was a correlation between leptin levels and physical activity intensity, indicating that cannabinoids may influence metabolic and

behavioural aspects of anorexia nervosa. Further research by Andries et al. (2015b) focused on the hormonal effects of dronabinol in anorexia nervosa. This study included 24 women and explored changes in insulin-like growth factor I (IGF-I), urinary free cortisol (UFC), and adipokines. While there were no significant changes in IGF-I or adipokines, a notable decrease in UFC levels was observed during dronabinol treatment, suggesting a potential alleviation of hypercortisolaemia typically seen in anorexia nervosa (Andries et al., 2015b).

Scharmer et al. (2020) conducted a cross-sectional study with 137 cannabis users who reported symptoms of eating disorders. Participants believed that cannabis could reduce restrictive eating behaviours, preoccupation with body shape, and fear of eating, though it might increase binge-eating behaviours. However, there was no significant association between these expectancies and the frequency of cannabis use or related problems, highlighting the need for further research in clinical settings to understand these perceptions and their impacts. Avraham et al. (2017) carried out an open-label pilot study involving 10 women with anorexia nervosa who received 1 mg/day of Δ 9-THC for the first week, increasing to 2 mg/day for the subsequent three weeks. The study reported significant improvements in self-reported psychological symptoms such as body care, sense of ineffectiveness, asceticism, and depression, although no significant changes in body mass index (BMI) were noted. This suggests that low-dose Δ 9-THC may help manage psychological symptoms in anorexia nervosa without notable effects on weight (Avraham et al., 2017).

A case report by Graap et al. (2017) described the treatment of a 27-year-old male with chronic anorexia nervosa using dronabinol. The patient showed a significant reduction in the urge to be physically active and improvements in eating disorder-

specific cognitions and compulsive behaviours. The study suggested that higher doses of dronabinol, up to 7.5 mg twice daily, were effective and well-tolerated without psychotropic side effects, emphasizing the potential of cannabinoids in treating symptoms resistant to standard therapies. Gross et al. (1983) conducted a double-blind randomized placebo-controlled crossover study with 11 women diagnosed with anorexia nervosa. The study used an escalating dose of Δ^9 -THC, starting at 7.5 mg per day and increasing to 15 mg. The results showed no significant weight gain and noted several adverse psychological effects at higher doses, such as increased somatization and sleep disturbances. This indicates that while Δ^9 -THC has some potential, its efficacy and safety at higher doses need careful consideration (Gross et al., 1983).

Preclinical models have also provided valuable insights into the mechanisms through which cannabinoids may influence eating behaviours. Studies have shown that activation of CB1 receptors by cannabinoids can enhance the hedonic response to food and modulate hunger and satiety signals in the brain, particularly in the hypothalamus and mesolimbic pathways. These effects are crucial in understanding how cannabinoids could potentially be used to stimulate appetite and manage weight in patients with eating disorders (Rosager et al., 2021). In animal models, cannabinoids have been shown to interact with neurotransmitter systems such as dopamine and serotonin, which are involved in reward processing and mood regulation. For instance, cannabinoids can increase dopamine release, enhancing the pleasure associated with food consumption, which may be particularly beneficial in conditions like anorexia nervosa where the reward response to food is diminished (Taylor et al., 2024). The modulation of the endocrine system by cannabinoids has also been explored. Cannabinoids can influence levels of hormones like leptin and

ghrelin, which regulate appetite and energy homeostasis. By enhancing the orexigenic effects of ghrelin and mitigating the anorexigenic effects of leptin, cannabinoids could help restore normal eating behaviours in individuals with eating disorders (Rosager et al., 2021).

1.3.12.4 Potential mechanisms and therapeutic strategies

The potential mechanisms through which cannabinoids exert their effects in eating disorders are primarily related to the modulation of the endocannabinoid system, which is integral in the regulation of appetite, mood, and energy balance. CB1 receptors are particularly relevant to eating behaviours. Activation of these receptors by cannabinoids such as Δ^9 -THC leads to increased appetite and food intake. This is achieved through several pathways, including the enhancement of the hedonic response to food and the modulation of hunger and satiety signals (Alderman et al., 2022).

Cannabinoids may also influence the dopaminergic system, which is involved in the reward processing of eating. By increasing dopamine release in the brain, cannabinoids can enhance the pleasure associated with food consumption, which is often diminished in individuals with eating disorders. This effect can be particularly beneficial in conditions like anorexia nervosa, where patients may have a reduced reward response to food (Rosager et al., 2021). Another potential mechanism is the interaction with the serotonergic system. Cannabinoids have been shown to modulate serotonin levels, which can affect mood and anxiety. Given the high prevalence of mood disorders in individuals with eating disorders, the anxiolytic and antidepressant effects of cannabinoids could provide significant therapeutic benefits (Taylor et al.,

2024). Therapeutic strategies involving cannabinoids need to consider the balance between efficacy and safety. Low doses of dronabinol have been shown to promote weight gain without significant adverse effects, suggesting that careful dose titration is essential. Additionally, combining cannabinoid therapy with other treatments, such as CBT and nutritional counseling, may enhance overall treatment outcomes by addressing both the psychological and physiological aspects of eating disorders (Taylor et al., 2024).

1.3.13 Insomnia

Insomnia is a sleep disorder characterized by difficulty falling asleep, staying asleep, or getting restful sleep. Insomnia can be acute (short-term) or chronic (long-term). Acute insomnia is often caused by temporary factors, such as stress, a change in sleep schedule, or a new environment. Chronic insomnia is defined as difficulty falling or staying asleep at least three nights a week for at least three months. The condition can often accompany other conditions, as already referred to earlier in association with cases of post-traumatic stress disorder (Walsh et al., 2021). In most scenarios the use of medicinal cannabis has been found to have a positive correlation with improved sleep quality (Whiting et al., 2015). CBD use has been mostly associated with improved sleep although some studies have not been consistent in corroborating this, yet use of THC-based products has not given a positive overall picture with an increase in sleeping time for acute cases of sleep disorder but sleep disturbance when used for longer periods of time to address chronic insomnia, proving counterproductive and possibly also generating vivid dream symptoms on withdrawal of medication (Kaul et al., 2021).

1.3.13.1 Pathophysiology of insomnia

Insomnia is a multifactorial disorder characterized by persistent difficulty in initiating or maintaining sleep, resulting in significant daytime impairment. The pathophysiology of insomnia involves a complex interplay of genetic, psychological, and environmental factors, often conceptualized through a biopsychosocial model that includes predisposing, precipitating, and perpetuating factors (Babson et al., 2017). Genetic predisposition plays a crucial role in the susceptibility to insomnia. Studies suggest that certain genetic markers may influence sleep regulation and vulnerability to insomnia. Neurobiological factors, such as dysregulation in the central nervous system's arousal mechanisms, contribute significantly. Individuals with insomnia often exhibit heightened arousal levels, evidenced by increased metabolic activity in brain regions associated with arousal, such as the hypothalamus and thalamus (Ins4) . Psychological traits, including hyperarousal and heightened stress responsiveness, are also significant predisposing factors (Vivek et al., 2024).

Precipitating factors trigger the onset of insomnia in predisposed individuals. Common precipitating factors include acute stressors such as major life events, medical conditions and psychiatric disorders. These conditions can disrupt sleep through various mechanisms, including pain, respiratory issues, and mood disturbances (Cairns et al., 2023). Once insomnia develops, certain behaviours and cognitive patterns can maintain or exacerbate the condition, leading to chronic insomnia. Maladaptive sleep habits, such as irregular sleep schedules and excessive time spent in bed awake, are common perpetuating factors. Cognitive factors, including worry about sleep and dysfunctional beliefs about sleep, also play a crucial role. The

continued presence of medical or psychiatric conditions further perpetuates insomnia (Bhagavan et al., 2020).

At the neurobiological level, insomnia is associated with dysregulation in several neural systems and neurotransmitter pathways. The hyperarousal model suggests that insomniacs have increased activation in both the central and autonomic nervous systems. Neuroimaging studies show increased metabolic activity in the brain's arousal centres even during sleep, indicating a state of hyperarousal mediated by increased levels of arousal-promoting neurotransmitters like norepinephrine and cortisol and decreased levels of inhibitory neurotransmitters such as GABA (Choi et al., 2020). The role of the ECS in sleep regulation is an emerging area of interest. Cannabinoid receptors are widely distributed in brain regions implicated in sleep regulation, such as the cerebral cortex and basal ganglia. Endogenous cannabinoids like anandamide promote sleep, and dysregulation in the ECS has been suggested as a potential mechanism underlying sleep disturbances, including insomnia (Bhagavan et al., 2020; Murphy et al., 2024).

The potential therapeutic use of medicinal cannabis for insomnia stems from its action on the ECS. THC and CBD interact with cannabinoid receptors in the brain. THC has sedative effects that can help reduce sleep latency, but its long-term use may lead to tolerance and diminished effectiveness. CBD has anxiolytic effects, potentially improving sleep quality by reducing anxiety. However, the clinical use of medicinal cannabis for insomnia requires further investigation to determine optimal dosing, safety, and long-term efficacy (Corroon, 2021).

1.3.13.2 Traditional therapeutic strategies: efficacy and limitations

Current therapeutic strategies for insomnia include both pharmacological and non-pharmacological approaches. The first-line treatment for chronic insomnia is CBT for insomnia (CBT-I), which has shown efficacy in various meta-analyses. CBT-I involves techniques such as sleep restriction, stimulus control, relaxation training, and cognitive restructuring aimed at improving sleep patterns and addressing maladaptive thoughts and behaviours related to sleep (Lavender et al., 2023). Pharmacological treatments are often considered when CBT-I is insufficient or inaccessible. The most commonly prescribed medications include benzodiazepines and non-benzodiazepine hypnotics, also known as Z-drugs. Benzodiazepines, such as temazepam and lorazepam, work by enhancing the effect of the GABA at the GABA-A receptor, thereby inducing sedation and sleep. However, these medications are associated with risks such as dependency, tolerance, and cognitive impairment (Lavender et al., 2023).

Zolpidem and eszopiclone, also target the GABA-A receptor but are structurally different from benzodiazepines. They are generally preferred for their lower risk of dependence and side effects. However, they still carry risks of cognitive and psychomotor impairment, especially with long-term use (Velzeboer et al., 2022). Melatonin, a hormone that regulates the sleep-wake cycle, is another treatment option. It is particularly useful in cases of circadian rhythm disorders and for elderly patients with insomnia. Melatonin has a favourable safety profile and is generally well-tolerated, although its efficacy in improving sleep latency and quality is still under investigation (Kaul et al., 2021; Vivek et al., 2024).

Antidepressants with sedative properties, such as trazodone and mirtazapine, are sometimes used off-label for insomnia, especially when comorbid depression or

anxiety is present. These medications can improve sleep continuity but are associated with side effects such as weight gain and daytime sedation (Murphy et al., 2023; Suraev et al., 2020).

Despite the availability of these therapeutic strategies, several limitations persist in the treatment of insomnia. CBT-I, while effective, requires significant time, effort, and access to trained therapists, which can be barriers for many patients. Additionally, the benefits of CBT-I are often not immediate, which may lead patients to seek quicker pharmacological solutions (Lavender et al., 2023). Pharmacological treatments, although effective in the short term, have several drawbacks. Benzodiazepines and Z-drugs carry risks of tolerance, dependence, and withdrawal symptoms. Long-term use of these medications can lead to cognitive impairment and increased risk of falls, especially in older adults. These medications can also alter sleep architecture, reducing the amount of restorative deep sleep and REM sleep (Velzeboer et al., 2022).

Melatonin, while deemed safer, has variable efficacy, and its long-term effects are not well understood. The effectiveness of melatonin can also be influenced by factors such as dosage and timing of administration (Bhagavan et al., 2020; Kaul et al., 2021). The use of sedating antidepressants for insomnia is often limited by their side effect profiles, which can include daytime sedation, weight gain, and the potential for exacerbating comorbid conditions. Their off-label use for insomnia is not always supported by robust clinical evidence (Murphy et al., 2023).

1.3.13.3 Therapeutic effects of cannabinoids in insomnia

The use of cannabinoids has shown promise in the treatment of insomnia, interacting with the ECS which plays a significant role in the regulation of sleep. CBD has been shown to increase total sleep time and improve sleep quality in various studies. For instance, CBD administration has demonstrated efficacy in increasing sleep duration and decreasing the latency to REM sleep in both animal models and human trials (Kaul et al., 2021). Furthermore, CBD has anxiolytic properties that may contribute to its sleep-promoting effects, as anxiety is a common comorbidity with insomnia (Narayan et al., 2022). THC has been found to reduce sleep latency, allowing individuals to fall asleep faster. However, its long-term use can lead to tolerance and a decrease in total sleep time. Despite this, THC has been beneficial in improving sleep in patients with chronic conditions such as fibromyalgia and PTSD, where it helps reduce pain and anxiety, contributing to better sleep quality (Kaul et al., 2021).

A combination of THC and CBD may offer synergistic effects. For example, in a study comparing nabilone with amitriptyline in fibromyalgia patients, nabilone was found to be superior in reducing insomnia severity and improving sleep restfulness (Sarris et al., 2020). These effects suggest that cannabinoids could be a viable alternative or adjunct to traditional insomnia therapies, especially for patients who have not responded well to other treatments (Shustorovich et al., 2024).

Clinical studies have offered mixed but generally promising results regarding the use of cannabinoids for improving sleep quality and reducing insomnia symptoms. For instance, Nicholson et al. (2004) conducted a double-blind, placebo-controlled crossover study to investigate the effects of THC and CBD on nocturnal sleep and early-morning behaviour in young adults. The study revealed that while a 15 mg dose

of THC alone had minimal effects on nocturnal sleep parameters, combined doses of THC and CBD led to a decrease in stage 3 sleep and increased wakefulness. The following day, participants experienced increased sleepiness and mood changes, indicating that cannabinoids could influence sleep architecture and subsequent daytime functioning (Nicholson et al., 2004).

Another study by Ware et al. (2010) examined the effects of nabilone on sleep in patients with fibromyalgia, a condition often associated with chronic pain and sleep disturbances. This randomized controlled trial demonstrated that nabilone significantly improved sleep quality compared to placebo, with patients reporting reduced insomnia severity and enhanced restfulness. These findings suggest that cannabinoids might be beneficial in managing sleep disorders linked to chronic pain. The potential of cannabinoids in paediatric populations was highlighted by Shannon and Opila-Lehman (2016) in a case report involving a ten-year-old girl with PTSD and associated insomnia. The administration of CBD oil resulted in maintained decreases in anxiety levels and significant improvements in sleep quality and quantity over a five-month period, with no adverse effects reported. This case underscores the potential of CBD as a safe and effective treatment for anxiety-related insomnia in children (Shannon and Opila-Lehman, 2016).

Tringale and Jensen (2011) conducted a retrospective analysis to assess the effects of cannabis on sleep latency and overall sleep quality in a clinical setting. The study included 147 patients and found that cannabis use was associated with a significant reduction in the time taken to fall asleep and improvements in sleep quality for the majority of patients. These results support the potential use of cannabis as a therapeutic option for managing sleep disorders (Tringale and Jensen, 2011).

Preclinical models have also contributed to understanding the effects of cannabinoids on sleep. Studies in animal models have shown that CBD can decrease slow-wave sleep latency and increase the duration of slow-wave sleep, while THC has been found to reduce sleep latency and alter sleep architecture. For example, in rodent models, CBD was shown to significantly decrease slow-wave sleep latency and increase total sleep time, suggesting a direct impact on sleep-promoting pathways. A study by Carley et al. (2018) explored the effects of dronabinol, a synthetic THC, on obstructive sleep apnoea (OSA), a condition characterized by repeated interruptions in breathing during sleep. The double-blind, placebo-controlled trial included 73 participants and found that dronabinol significantly reduced the apnoea-hypopnea index (AHI) and improved sleepiness ratings compared to placebo, indicating potential benefits for sleep quality and daytime functioning in OSA patients. Further evidence from preclinical studies indicates that cannabinoids might affect various aspects of sleep regulation. For instance, studies have shown that cannabinoids can modulate neurotransmitter systems involved in sleep, such as GABA, serotonin, and dopamine. These interactions suggest that cannabinoids might promote sleep by enhancing inhibitory neurotransmission and reducing arousal (Kesner & Lovinger, 2020; Vaseghi et al., 2021).

1.3.13.4 Potential mechanisms and therapeutic strategies

The therapeutic potential of cannabinoids in treating insomnia is largely attributed to their interaction with the ECS. The CB1 receptors, predominantly located in the central nervous system, are involved in the regulation of sleep-wake cycles. Activation of CB1 receptors by endocannabinoids or phytocannabinoids like THC can influence various

neurotransmitter systems, including those of GABA, dopamine, and serotonin, which are critical in sleep regulation (Velzeboer et al., 2022).

THC exerts its effects primarily through partial agonism at the CB1 receptor, leading to sedative effects that can promote sleep onset. However, the psychoactive properties of THC necessitate careful dose management to avoid adverse effects such as cognitive impairment and dependency (Kaul et al., 2021). CBD, on the other hand, does not directly activate CB1 or CB2 receptors but modulates the ECS by inhibiting the breakdown of endocannabinoids, thereby enhancing their availability and action. Additionally, CBD influences other receptor systems, such as the serotonin 5-HT1A receptor, which may contribute to its anxiolytic and sleep-promoting effects (Suraev et al., 2020; Kaul et al., 2021).

Recent studies have also explored the potential of CBN which has been suggested to have sedative properties. CBN is a product of THC degradation and may offer a less psychoactive option for sleep aid, although more research is needed to confirm its efficacy and safety (Lavender et al., 2023). Therapeutic strategies involving cannabinoids for insomnia should consider the specific sleep disturbances experienced by the patient. For instance, CBD may be more suitable for patients with insomnia linked to anxiety, while THC or a combination of THC and CBD might be beneficial for those with pain-related sleep disturbances (Narayan et al., 2022; AminiLari et al., 2022).

1.4 Availability of cannabinoid formulations

Numerous early clinical studies prompted scientists to investigate and propose a variety of cannabis-based products and synthetic cannabinoids for medicinal use differing in their THC/CBD profile, dosage form formulations and licensing status. Cannabis based products are defined as products containing plant derived cannabinoids (THC and CBD), covered by different aspects of legislation entailing regulatory and clinical implications (Freeman et al, 2019).

In a number of US states there are multiple cannabis products with various methods of administration, including topical application, such as using salves or lotions, baked products, tinctures, oils and extracts orally, or by inhaling the product as in the vaporized extracts or smoking. Not all forms of product are allowed in all US states. These products vary in their cannabinoid proportions and concentrations and this information would ideally be indicated on an accompanying label. The inconsistencies that this gave rise to when comparing the available products was also due to the variation in laws regulating dispensaries and growers, making for a non-standardized production (Vandrey et al., 2015). More recently quality control has been introduced and regularization is improving the products available. This also entails legislation for doctors prescribing medicinal cannabis products, with some states requiring that physicians obtain authorization before being able to issue prescriptions and others demanding attendance to a programme for instruction about the products and prescription processes (Baratta et al., 2022).

Cannabis preparations containing raw cannabis (flower or oil extract) which is processed pharmaceutically by a licensed manufacturer for medicinal use are also available on the market. Examples include Bedrocan® (EMCCDA, 2018)¹. Cannabis

preparations and cannabis-based products are available in various dosage forms at different strengths. Ingrid Bonello in her study entitled: “Different dosage forms of cannabis” gives a detailed review of these products whilst presenting an analysis of advantages and disadvantages in relation to respective dosage forms and routes of administration (Bonello, 2019).

Cannabis based products for medicinal use (CBMP) carry a marketing authorization which stipulates the legal content of THC and CBD ratios in the respective product (Hauser et al, 2018). Sativex® is a cannabis based medicinal product, consisting of synthetic THC and CBD and licensed for spasticity in multiple sclerosis formulated as oral spray. Epidiolex®, another cannabis based medicinal product, consists of pure CBD formulated as oral solution licensed for Lennox-Gastaut syndrome and Dravet syndrome. Both products are authorized in the United States and the United Kingdom (EMCCDA, 2018)¹.

Synthetic cannabinoids for medicinal use refer to medicinal products which carry a marketing authorization, and which are synthetically produced to mimic the effects of THC. Examples include products with a marketing authorization which contain dronabinol and nabilone. The formulations with authorization for the pharmaceutical market after rigorous testing for efficacy and safety are briefly discussed.

1.4.1 Cesamet®

Cesamet® (or Canemes®) is the trade name for nabilone, an orally administered synthetic cannabinoid mimicking THC available in capsule form, which has received FDA authorization in 1985, as well as the European Medicines Agency (EMA), for

chemotherapy-induced nausea and vomiting (at 5mg PO 3-4 daily doses) when alternative first line treatments have proven inefficient (Ciccone et al., 2016; Bryce et al., 2022).

Adverse effects that have been reported include relatively minor ones such as dry mouth, mild dyspnoea, vertigo, orthostatic hypotension, headache, fatigue, euphoria and drowsiness. Psychoactive properties are present in nabilone and that explains why it is a Schedule II drug. It can in fact also present a more serious side effect in rare instances, psychosis (Udow et al., 2018).

Among the clinical applications for which nabilone has demonstrated benefits are an improvement in motor function and pain but not cognitive function in multiple sclerosis, anti-inflammatory properties in patients with Alzheimer's Disease (Ruthirakuhan et al., 2020), a reduction in the use of cannabis by cannabis addicts, control of obsessions and compulsions in OCD patients when used as an adjunct to behavioural therapy (Kayser et al., 2020), amelioration of non-motor and motor symptoms in Parkinson's Disease patients (Peball et al., 2020). Despite its effects on nausea and vomiting induced by chemotherapy no effects were noted in attenuating the same symptoms after elective surgery in a randomized-controlled trial (Levin et al., 2017).

¹European Monitoring Centre for Drugs and Drug Addiction. Medical use of cannabis and cannabinoids: Questions and answers for policy making. Luxembourg. Publications office of the European Union. 2018. Available from: http://www.emcdda.europa.eu/system/files/publications/10171/20185584_TD0618186ENN_PDF.pdf

1.4.2 Marinol®

Marinol® (or Syndros®) is the trade name for dronabinol, a synthetic analogue of THC available both as capsules and as an oral solution. FDA approval was acquired in 1985 for chemotherapy-induced nausea and vomiting (at 5mg PO 1-3 hours pre-session on an empty stomach and followed by 5mg every 2-4 hours for a total of 4 to 6 daily doses) and HIV-induced anorexia (2.5mg PO BD an hour before a meal). It also has European Medicines Agency (EMA) authorization (O'Donnell et al., 2022).

In terms of the clinical application of dronabinol for reduction of pain intensity and perception, especially with management of acute pain, the results have not been consistent (Babalonis et al., 2019; Dunn et al., 2021). dronabinol is classified as a Schedule III drug with the only rare severe adverse effect reported being depersonalization. More frequent but minor side effects include abdominal pain, euphoria, heart palpitations, amnesia, dry mouth and fatigue (Legare et al., 2022).

1.4.3 Epidiolex®

Epidiolex® is formulated from 98% pure CBD derived from the cannabis plant. It has received FDA authorization in 2018 and has received the approval of the European Medicines Agency (EMA) as well. It comes as an oral solution, administered at doses of 2 to 5 mg/kg per day up to a maximum of 25 mg/kg per day, and it is approved as therapy for treatment-resistant seizures that are associated with tuberous sclerosis complex, Dravet Syndrome and Lennox-Gastaut Syndrome (Leehey et al., 2020).

It has also received attention for clinical use with Parkinson's Disease patients whose sleep, mood and tremors noted benefits from use of Epidiolex®, patients

demonstrating lower limb neuropathies and those with chronic pain who were helped to wean off opioids. Major side effects were not recorded but among the minor adverse events patients exhibited fatigue, drowsiness, liver toxicity, diarrhoea and reduced appetite (Capano et al., 2020, Xu et al., 2020).

1.4.4 Sativex®

Sativex®, the trade name for nabiximols, comes as an oromucosal spray containing both CBD and THC in near equal amounts, 2.5mg and 2.7mg respectively. It has received authorization in the United Kingdom in 2010 with later approval for use in a number of countries that form part of the European Union, for the treatment of spasticity associated with multiple sclerosis when other treatments have failed to provide relief (Collin et al., 2007; Markova et al., 2019). In some countries it is also authorized to address neuropathic pain associated with multiple sclerosis. It has been approved for use in New Zealand, Canada and other countries but not yet in the USA where it is currently in phase 3 clinical trials (Abuhasira et al., 2018).

With regards to its indication for multiple sclerosis spasticity the recommended use is 1 to 12 sprays daily, while for attenuating pain in advanced cancer patients the number of sprays per day can be from 1 to 16. Among the minor adverse effects reported for nabiximols are nausea, dizziness and sedation, with no major side effects noted (Ciccone et al., 2016).

Spasticity has also been reported as reduced in patients with motor neuron disease (Riva et al., 2019). Pain control in patients with advanced cancer was improved according to patient reports (Johnson et al., 2010; Fallon et al., 2017; Lichtman et al.,

2018). It was also noted that individuals with a dependence on cannabis reported reduced cravings when under nabiximols treatment (Trigo et al., 2018; Lintzeris et al., 2019). Another clinical use of the nabiximols is for reduction of overactivity of the detrusor bladder muscle in patients with multiple sclerosis (Kavia et al., 2010).

1.4.5. Inflorescence

Numerous cannabis inflorescence products have been made available by the pharmaceutical industry, delivering bioactive metabolites that are mostly present in the female flowers and which can produce varied and hypothetically superior effects in clinical scenarios (Spitzer-Rimon et al., 2019). This is due to the entourage effect hypothesis which relies on the assumption that synergistic processes, involving a variety of cannabinoids and terpenes present in the cannabis plant, will provide enhanced responses due to interactions of which there is currently limited knowledge (Stella et al., 2021; Baratta et al., 2022).

Both CBD and THC are considered the most prominent of the cannabinoids. They have been the most researched and have acquired approval as drugs to address certain conditions. However as mentioned earlier, besides the two cannabinoids there are various other phytoconstituents in the cannabis plant that might have biochemical significance in terms of biological activities it can deliver (Spitzer-Rimon et al., 2019).

Consequently, the formulations available differ in terms of quantities of CBD and THC, as indicated in the table below listing the various inflorescence products available (Table 1.1). The largest pharmaceutical producer in Europe is a Dutch company, Bedrocan which markets five different products with diverse THC:CBD ratio:

Bedrocan, Bedrobinol, Bediol, Bedica and Bedrolite. Another European location for the manufacture of medicinal cannabis as an active pharmaceutical product is Florence, Italy, at the Stabilimento Chimico Farmaceutico Militare di Firenze (SCFM). Two varieties are produced on the peninsula: FM2 and FM1. Across the Atlantic, Aurora/Pedarios in Canada produce three inflorescence variants: Pedarios 22/1, Pedarios 8/8 and Pedarios 1/9 (Russo et al., 2021).

Current knowledge of additional cannabis plant constituents such as minor cannabinoids CBDVA, CBCA and THCVA, in relation to their biological activity, biological targets and how they interact with the human body on a molecular level, is still not developed enough. Analyzing cannabis varieties with elevated levels of cannabinoids other than CBD and THC can provide insight into their biological effects. Characterizing these varieties using analytical methods will help to understand the modulation of major cannabinoids by additional cannabis constituents on endogenous receptors and improve the clinical application of cannabis (Baratta et al., 2022).

1.5 Legislation of cannabis for medicinal use

Between the mid-19th century up to the early 20th century, there was an unexpected reversal of policies in the West, which restricted use of cannabis even for medicinal purposes despite the multiple advantages physicians had reported in its application. However, the use of the plant for recreational purposes had become a worrying trend for lawmakers. With the composition of the pharmaceutical formulations available at the time and the effectiveness of medicinal cannabis not demonstrating consistently in treatment, it was also inevitable that more proven and predictable drugs like aspirin

MANUFACTURER	PRODUCT	THC:CBD RATIO
Bedrocan	Bedrocan	THC 22% : CBD <1%
	Bedrobinol	THC 13.5% : CBD <1%
	Bediol	THC 6.3% : CBD 8%
	Bedica	THC 14% : CBD <1%
	Bedrolite	THC <1% : CBD 7.5%
SCFM	FM2	THC 5-8% : CBD 7.5-12%
	FM1	THC 13-20% : CBD <1%
Aurora /Pedanios	Pedanios 22/1	
	Pedanios 8/8	
	Pedanios 1/9	

Table 1.1. *Products of pharmaceutical-grade medicinal cannabis. Inflorescence product variants from three major manufacturers, with indications of the THC:CBD ratio of each.*

and other early anti-inflammatories and analgesics would eclipse medicinal cannabis (Bostwick, 2012). By 1925, prominent Western powers alongside Japan, Russia, Persia and China had agreed on restricting circulation and use of cannabis, and in

1937 the United States imposed harsh financial penalties on entities dealing in the plant for any purposes including in textile manufacturing (Riboulet-Zemouli, 2025). Despite opposition from medical lobby groups, by 1932 cannabis had been removed from the British Pharmacopoeia and the United States Pharmacopoeia followed suit in 1941 just four years after the government's heavy taxation on cannabis use (Peschel, 2016). As more and more drugs were being used for recreational purposes in the United States in the two decades following that law, cannabis was in 1960 classified as an unlawful drug of abuse (Collins, 2021).

Since then, more permissive policies have been introduced in different parts of the World with regards to the use of cannabis in recent years. In some countries this has been in relation to its recreational use but, more extensively, many have explored its potential on the therapeutic front in the form of medicinal cannabis. This trend is not only derived from a rediscovery of more natural products to ameliorate health and address ailments but more specifically to the plant's reported efficacy in alleviating a multitude of symptoms (Rhee & Rosenheck, 2023).

1.5.1 Maltese legislative framework

From a legal perspective, cannabis remains a drug which requires legal control worldwide (Aguilar et al, 2018). Countries and states have their own national legislation and policies with respect to recreational cannabis, cannabis for medicinal purposes and cannabis for research purposes. Within Europe, Israel and the Netherlands were the first countries to legalise medicinal cannabis use for specific conditions. Other countries such as Switzerland in 2011, Australia in 2016 and Germany in 2017 followed suit (EMCDD, 2018)¹. In 2018, Malta implemented a

radical change in its legislative framework focusing on medicinal cannabis as a clinical application and for research purposes. In March 2018 Drugs Dependence Act (Treatment not Imprisonment 2014) was amended allowing the clinical use of authorised medicinal cannabis products. Subsequently in April 2018, the Production of Cannabis for Medicinal and Research Purposes Act (2018) which provides a legal framework to allow the production of cannabis for medicinal and research purposes in Malta, was enacted.

1.6 Aim of the research

The aim of this research is to explore and evaluate the perceptions and concerns of healthcare professionals in Malta regarding the use of medicinal cannabis, investigating scientific evidence in relation to clinical indications for medicinal cannabis. By examining these attitudes, the research seeks to identify key issues and uncertainties that may influence the integration of medicinal cannabis into patient care. Furthermore, the study aims to review existing administration and prescription practices of medicinal cannabis across various conditions, drawing insights from previous clinical trials, take an overview of a well-structured and appropriate clinical framework for clinical trials in medicinal cannabis. The research explores potential educational initiatives local healthcare professionals would be responsive to, with the aspiration being to inform the potential adoption of medicinal cannabis in niche clinical scenarios within the Maltese healthcare system.

¹European Monitoring Centre for Drugs and Drug Addiction. Medical use of cannabis and cannabinoids: Questions and answers for policy making. Luxembourg. Publications office of the European Union. 2018. Available from: http://www.emcdda.europa.eu/system/files/publications/10171/20185584_TD0618186ENN_PDF.pdf

The objectives of the research are to:

- i. analyse current international literature in terms of medicinal indications, contraindications and cautions for medicinal cannabis;
- ii. capture the perceptions and concerns of the Maltese healthcare on the use of medicinal cannabis;
- iii. propose educational initiatives intended to address knowledge gaps and concerns that emerge from healthcare professionals' data;
- iv. review existing trials and studies for which medicinal cannabis was trialled, noting administration modalities;
- v. put forward a simplified stepwise framework for clinical trials in medicinal cannabis

Chapter 2 - Methodology

2.1. Study Design

The research consisted of four phases. Phase 1 relates to a literature review focusing on the historical and contemporary use of cannabis, emphasizing its medicinal benefits. This review explored the interaction of cannabis with the endocannabinoid system, detailing the clinical applications for various conditions and the development of formulations currently approved for specific indications.

Phase 2 looks at capturing the perceptions and concerns of healthcare professionals on medicinal cannabis. Phase 3 deals with putting forward validated educational initiatives in order to address the knowledge gaps and concerns identified among healthcare professionals. Phase 4 focuses on clinical trials and studies in the area of medicinal cannabis providing an analytic summary of trials and studies carried out. Phase 5 provides a framework of steps required to be undertaken to facilitate clinical trials and studies using medicinal cannabis in clinical settings.

Ethical approval was granted by the UREC (Appendix 1).

2.2. Phase 1: Literature review

The systematic review was conducted in accordance with the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) 2020 guidelines (Page et al., 2021). The relevant databases consulted were PubMed (1946 to present), Embase through Ovid (1947 to present), Web Of Science (1946 to present) and Cochrane (1996 to present). The search terms employed in mining for data focused on medicinal cannabis, its clinical applications and efficacy levels as reported for a variety of conditions. Any duplicate entries were excluded. Keywords at the basis of the search

protocol were 'medicinal cannabis' and 'clinical use', as well as keywords referring to a variety of conditions, both general terms and specific, including 'neurodegenerative disorders', 'psychiatric disorders', 'epilepsy', 'huntington disease', 'parkinson disease', 'multiple sclerosis', 'amyotrophic lateral sclerosis', 'alzheimer disease', 'pain management', 'addiction', 'cancer', 'post-traumatic stress disorder', 'anxiety', 'eating disorders', and 'insomnia'.

Related MeSH terms retrieved for PubMed and used alongside search words derived from the keywords mentioned included: *"Medical Marijuana"[Mesh]*, *"Medical Marijuana/therapeutic use"[Mesh]*, *"Medical Marijuana/classification"[Mesh]*, *"Medical Marijuana/administration and dosage"[Mesh]*, *"Neurodegenerative Diseases"[Mesh]*, *"Mental Disorders"[Mesh]*, *"Epilepsy"[Mesh]*, *"Huntington Disease"[Mesh]*, *"Parkinson Disease"[Mesh]*, *"Multiple Sclerosis"[Mesh]*, *"Amyotrophic Lateral Sclerosis"[Mesh]*, *"Alzheimer Disease"[Mesh]*, *"Pain Management"[Mesh]*, *"Substance-Related Disorders/therapy"[Mesh]*, *"Neoplasms"[Mesh]*, *"Cancer Pain"[Mesh]*, *"Stress Disorders, Post-Traumatic"[Mesh]*, *"Anxiety"[Mesh]*, *"Feeding and Eating Disorders"[Mesh]*, *"Sleep Initiation and Maintenance Disorders"[Mesh]*, , *"Medical Marijuana/adverse effects"[Mesh]*.

In Ovid Embase database alongside the relevant search terms the subject headings used included *'medical cannabis/dt'*, *'cannabis/dt'*, *'epilepsy/'*, *'Huntington chorea/'*, *'Parkinson disease/'*, *'multiple sclerosis/'*, *'amyotrophic lateral sclerosis/'*, *'Alzheimer disease/'*, *'analgesia/'*, *'addiction/dm, dt, rh [Disease Management, Drug Therapy, Rehabilitation]'*, *'cancer pain/'*, *'posttraumatic stress disorder/'*, *'anxiety/'*, *'eating disorder/'*, *'insomnia/'* and *'adverse event/'*.

The MeSH terms used in the Cochrane database were *'Medical Marijuana'*, *'Epilepsy'*, *'Huntington Disease'*, *'Parkinson Disease'*, *'Multiple Sclerosis'*, *'Amyotrophic Lateral Sclerosis'*, *'Alzheimer Disease'*, *'Pain Management'*, *'Addiction Medicine'*, *'Neoplasms'*, *'Cancer Pain'*, *Feeding and Eating Disorders'*, *'Sleep Initiation and Maintenance Disorders'* and *'Drug-Related Side Effects and Adverse Reactions'*.

2.3. Phase 2: Questionnaire development, validation and distribution

The questionnaire 'The Healthcare Professionals' Questionnaire on Use of Medicinal Cannabis' (Appendix 2) was developed with the intent to explore the predispositions of healthcare professionals in Malta with regards to use of medicinal cannabis for clinical purposes, thereby assessing their perceptions and concerns. 'The Healthcare Professionals' Questionnaire on Use of Medicinal Cannabis' was made available only in the English language. The questions focused on the current knowledge of the subject and whether it was felt that more could be done to inform the medical community about how medicinal cannabis could be utilized with specific patient subgroups to address particular conditions. It also tapped into the attitudes of the medical community in relation to a subject that is currently still controversial and might polarize viewpoints when delving into aspects of ethics and suitability of care.

2.3.1. Questionnaire development

In total, 'The Healthcare Professionals' Questionnaire on Use of Medicinal Cannabis' presented 25 questions and it was estimated that completion would take approximately 5 to 10 minutes. The two opening questions captured demographic

data, namely sex and age, with the two subsequent questions, 3 and 4, concerning the profession of the participant and the area of practice in medicine or pharmacy.

Questions 5 to 17 were all presented with pre-set options of agreement on a seven-point Likert scale. In all instances of Likert scale utilization in the questionnaire (17 in total) the seven options presented graded levels of agreement and disagreement, with an option to express neutrality to the statement when selecting 'no opinion'. The agreement and disagreement options consisted of three possibilities for each, designated with the following adverbs to signal varied selections of support: 'strongly', 'mostly' and 'somewhat'. In that order they would represent decreasing intensity for the sentiment expressed in relation to the statement, with 'strongly' indicating higher agreement or disagreement and 'somewhat' denoting less conviction in agreement or disagreement.

The fifth question, the first in the Likert scale series, enquired about whether the respondent thought if patients would benefit from medicinal cannabis and the sixth whether the healthcare professional would be comfortable discussing the subject with patients. The two questions that follow assessed knowledge of therapeutic and side effects of medicinal cannabis, with a subsequent question concerning the confidence of the participant in dealing with patients exhibiting side effects from use of medicinal cannabis.

Question 10 considered the level of confidence of the healthcare professional in answering patient questions about the subject. Question 11 concerned the ethics of therapy, asking the respondents whether they had any ethical reservations on patients using medicinal cannabis. The twelfth question asked about knowledge of which patients would benefit from use medicinal cannabis and question 13 tapped into

whether the respondent would be comfortable prescribing medicinal cannabis. The three questions that followed all concerned the prescription of medicinal cannabis, exploring whether reservations would be present due to the conviction that harm outweighs benefit, that there is a risk of abuse and dependence, and that side effects are more prevalent than if conventional therapy was used. In question 17 the participants are asked to rate how knowledgeable they are about modalities and indications for medicinal cannabis prescription.

In question 18 respondents were given 11 options to choose from, without limitations and with the last being an exclusionary statement labelled 'none of the above', to answer a question asking which conditions should medicinal cannabis be used for. The subsequent question enquired about what other drugs the respondent thought that medicinal cannabis is less dangerous than, providing seven different categories and with the possibility of choosing one of three options for each of the categories: 'agree', 'I don't know' and 'disagree'.

Questions 20, 21 and 22, were seven-point Likert scale questions that addressed education about medicinal cannabis. Question 20 asked participants about their confidence levels with regards to how much the population understands the use of medicinal cannabis. The following question, 21, was related to the respondents' conviction about introducing the subject to the curricula of medical and pharmacy students. Question 22 enquired about the healthcare professionals' own formal institutional instruction about medicinal cannabis. An open-ended question, question 23, asked about the methods through which the participant has gained insight into the subject. The last two questions still focused on the educational aspect with a final seven-point Likert scale question exploring the participants' interest in attending

educational activities about medicinal cannabis, and the concluding question seeking the preferred respondents' methods for acquiring more knowledge about the subject. This last question offered seven different options that included the more common formats as well as a final option labelled 'other' that allowed the participant to define alternatives.

2.3.2. Questionnaire validation

'The Healthcare Professionals' Questionnaire on Use of Medicinal Cannabis' was validated by an expert panel consisting of an academic pharmacist, a community pharmacist, a pharmacist from the pharmaceutical industry, a consultant psychiatrist, a general practitioner and a layperson. A validation questionnaire in Google form (Appendix 3) was compiled and distributed to the expert panel electronically. The validation questionnaire explained briefly the purpose of the research and consisted of questions aimed at capturing the experts' feedback on the questionnaire in terms of appropriateness, validity and practicality of the questionnaires. The validation questionnaire consisted of a final section where the experts could note their comments or suggestions. "*The Healthcare Professionals Questionnaire on use of medicinal cannabis*" was amended according to recommendations put forward by the expert panel.

2.3.3. Questionnaire dissemination and analysis

'The Healthcare Professionals' Questionnaire on Use of Medicinal Cannabis' was developed via Google Forms to facilitate dissemination. In order to participate in the

questionnaire participants were only required to click on the link provided to access the form. Anonymous answers were collected via Google Forms for subsequent analysis.

The Superintendence of Public Health and the Pharmacy Council were contacted for assistance with distribution of the questionnaire to their members via mailshot, reaching out to them through e-mail. The e-mail for distribution to the members was prepared, containing the link to the questionnaire and an introductory message outlining the scope of the research and the aim of 'The Healthcare Professionals' Questionnaire on Use of Medicinal Cannabis'.

For analysis purposes, the 25 questions were grouped into categories pertaining to general areas. This was intended to facilitate analysis and the development of clearer patterns of interpretation. Apart from the self-explanatory sections concerning demographics and profession, the additional named categories were 'conviction and knowledge about benefits to patients' (Section 3.2.1.) which grouped questions 5 and 12, 'discussing medicinal cannabis with patients' (Section 3.2.2.) comprising questions 6 and 10, 'clinical awareness about medicinal cannabis' (Section 3.2.3.) which considered questions 7, 8 and 9, 'prescription of medicinal cannabis' (Section 3.2.4.) which included questions 11, 13, 14, 15, 16 and 17, 'clinical conditions and medicinal cannabis' (Section 3.2.5.) covering question 18, 'danger levels of medicinal cannabis' (Section 3.2.6.) addressing question 19, and 'education about medicinal cannabis' (Section 3.2.7.) grouping together questions 20 to 25. Analysis of 'The Healthcare Professionals' Questionnaire on Use of Medicinal Cannabis' is presented in Chapter 3 Results.

All statistical analyses were conducted using SPSS (version 25.0). The data were assessed for normality and analyzed using parametric tests. To facilitate a side-by-side comparison of the survey results between the two professional groups, independent samples t-tests were employed to determine statistically significant differences between doctors and pharmacists. Furthermore, relationships between variables were assessed using Pearson product-moment correlation analyses, and hierarchical regression analysis was performed to identify predictive factors within the study population.

2.4. Phase 3: Educational initiatives

The research puts forward a two-dimensional educational initiatives approach. The first approach stems directly from research findings related to the 'The Healthcare Professionals' Questionnaire on Use of Medicinal Cannabis' and targets healthcare professionals. The second approach focuses on education to patients making use of medicinal cannabis products clinically.

2.4.1. Development and validation of an educational programme for healthcare professionals

Findings from 'The Healthcare Professionals' Questionnaire on Use of Medicinal Cannabis' highlighted a number of gaps that could be addressed through an educational framework. 'The Healthcare Professionals' Questionnaire on Use of Medicinal Cannabis' indicated that healthcare professionals preferred online lectures and webinars as their primary modes of learning about medicinal cannabis. In

response to this, the research developed a framework for a comprehensive continuous educational programme (Appendix 4, Appendix 5), consisting of 16 lectures covering topics such as the pharmacology of medicinal cannabis, its therapeutic applications, regulatory considerations, patient selection criteria, and safety concerns. Each lecture in the series was planned to ensure that it covered the most pertinent information in a clear and accessible manner. To reinforce the knowledge imparted during these lectures, a 10-question post-lecture quiz was developed for each session. These quizzes were designed to assess the participants' understanding of the material and to identify any areas that might require further clarification or additional resources.

In order to ensure the quality and relevance of the educational content, a validation form (Appendix 4) was created for the educational programme. The validation form was presented to a validation panel composed of a senior university lecturer, a regulatory affairs industry pharmacist, a medical doctor, a community pharmacist and a patient with a rheumatology condition in representation of a layperson, who provided feedback on the content, structure, and delivery of the lectures. The recommendations gathered by the expert panel were taken into account to refine the educational materials and ensure that the educational content meets the needs of the target audience.

2.4.2. Development and validation of an educational leaflet for patients on medicinal cannabis

Another key educational initiative involved the development and validation of a patient information leaflet intended for patients making use of prescribed medicinal cannabis. The patient information brochure (Appendix 6) was designed to provide patients with

clear, concise information about the benefits, potential risks, contraindications, and safety considerations associated with medicinal cannabis. The leaflet was designed in adherence with principles of the Baker Able Leaflet Design (BALD) criteria. This comprehensive approach ensures that the brochure is not only informative but also accessible and user-friendly for its intended audience. The BALD criteria, a cornerstone in the design of effective health communication materials, emphasizes key elements such as clarity of language, engaging layout, and the thoughtful use of visual aids to enhance understanding. By employing the BALD criteria, the ease of readability and the overall aesthetic appeal of the brochure were prioritized, ensuring that critical health information is conveyed in a manner that is both engaging and easy to comprehend. This methodological approach encompasses a careful consideration of factors such as the length of text lines, the spacing between lines, the size and type of fonts used, and the strategic use of white space to create a visually appealing and reader-friendly document. Furthermore, the BALD criteria guide the selection of paper quality and the overall design characteristics, ensuring that the physical attributes of the patient information brochure contribute positively to the user's experience. The patient information brochure should be a commitment to responsible patient care providing information that is not only informative but also empowering, enabling readers to make informed health decisions with confidence. The objective of the patient information brochure is to bridge the gap between complex medical information and patient understanding, facilitating a better healthcare experience for all. The patient information brochure was validated by an expert panel comprising a senior university lecturer, a regulatory affairs industry pharmacist, a medical doctor, a community pharmacist and a patient with a rheumatology condition, via a form

(Appendix 6) assessing content and whether the patient information brochure met its intended purpose.

2.5. Phase 4: Analysis of studies and respective journal metrics

A significant portion of this phase involved a detailed examination of the dosages used in various trials conducted over the years, for a variety of clinical conditions, including chemotherapy-induced nausea and vomiting, sleeping disorders, multiple sclerosis spasticity, amyotrophic lateral sclerosis, Huntington's disease, Alzheimer's disease, Parkinson's disease, obsessive-compulsive disorder, epilepsy, mood disorders, post-traumatic stress disorder, drug addiction management, and pain, among others.

Comprehensive bibliometric data pertaining to the journals in which the retrieved studies were published were meticulously gathered and compiled. The statistical analysis of these journal metrics provided a robust framework to assess the degree of support in the literature for the clinical use of medicinal cannabis across various conditions, with prospects of seeking potential cases for justifying clinical use of medicinal cannabis due to practice-based evidence.

2.5.1. Analytic summary of clinical trials and studies

A comprehensive literature search was undertaken to identify studies investigating the clinical use of medicinal cannabis across a range of conditions. The search was systematically conducted in four major electronic databases: PubMed (1946 to present), Embase through Ovid (1947 to present), Web of Science (1946 to present), and the Cochrane Library (1996 to present). This broad temporal coverage ensured

that both historical and contemporary evidence were considered. The databases were chosen for their extensive biomedical and health-related literature, and the date ranges allowed for the capture of updated research in the field.

For PubMed, the search strategy incorporated both Medical Subject Headings (MeSH) and free-text terms. For example, MeSH terms such as "Cannabis," "Cannabinoids," and condition-specific headings, such as "Nausea," "Multiple Sclerosis," "Alzheimer Disease") were combined with free-text keywords like "medical marijuana," "chemotherapy-induced nausea and vomiting," and "palliative care" using Boolean operators (AND, OR) to maximize sensitivity and specificity. Parenthetical grouping and truncation were used to capture variations in terminology. A similar approach was applied to Embase via Ovid, where both Emtree terms and text words were utilized. The strategy here involved mapping analogous terms such as "cannabis," "cannabinoid," "chemotherapy-induced nausea" to Embase's controlled vocabulary, while ensuring that condition-specific free text searches covered diverse terminologies used in the literature.

In Web of Science, the search was executed using topic searches that scanned titles, abstracts, and keywords. The strategy involved a combination of free text searches for both cannabis-related terms and the listed medical conditions. Due to the broad nature of Web of Science, citation tracking and reference list screening were also employed to ensure relevant studies that might have been missed by the initial search terms were captured. For the Cochrane Library, the search strategy was similarly structured, with a focus on high-quality systematic reviews and clinical trials. Keywords and phrases corresponding to both medicinal cannabis and the specified conditions were searched within titles, abstracts, and keyword fields. Filters for study design and

publication type were applied to isolate high-quality evidence, given Cochrane's emphasis on systematic reviews and controlled trials.

These strategies, tailored to the specific features and indexing systems of each database, ensured a robust and comprehensive retrieval of the literature on the clinical use of medicinal cannabis across a diverse array of conditions. The combination of controlled vocabulary and free-text searching, along with the use of Boolean logic and database-specific filters, provided a rigorous methodological approach to the evidence synthesis process. Gaps in the current research that need to be addressed to advance the clinical use of medicinal cannabis were identified, noting the need for more standardized dosing guidelines and a better understanding of the pharmacokinetics and pharmacodynamics of different cannabis formulations.

2.5.2. Publication journals' metrics analysis

Detailed information on the journal metrics for the retrieved studies was systematically sought and compiled. This process involved extracting specific bibliometric data from the journals in which the studies were published, ensuring that relevant parameters, such as the impact factor, were accurately recorded for each publication. These data points were essential in providing an objective measure of the journals' reputations and the potential reach of the studies under review.

The compiled metrics were organized into tables that corresponded to the clinical trial tables presented earlier, with each table focusing on one of the specific conditions for which the clinical use of medicinal cannabis was investigated. For every study included in these tables, the impact factor of the publishing journal was retrieved and recorded. In addition to the bibliometric data, the tables also featured the reported outcomes of

the studies, categorizing them as either positive or neutral/non-positive with respect to the use of medicinal cannabis for the specific condition being studied. For each table, the total number of journals that were classified as presenting positive outcomes was enumerated alongside those classified as having neutral or non-positive outcomes. Within these two categories, several statistical measures were calculated to further characterize the data: the median impact factor, the proportion of high-impact journals, and the weighted average of the impact factor. These statistical calculations provided a robust framework for comparing the influence and quality of the publications across different outcome groups.

Using the outcomes and impact factor data collected from the various publications, the evaluation facilitated an assessment of which conditions demonstrated a higher consensus for the clinical use of medicinal cannabis. This analysis allowed for a nuanced understanding of the evidence landscape, highlighting conditions where the literature was more supportive of medicinal cannabis use. For certain conditions, such as certain forms of epilepsy, chemotherapy-induced nausea and vomiting, and multiple sclerosis spasticity, there are already licensed medicinal cannabis products approved for use by regulatory bodies such as the FDA and/or the EMA. For conditions lacking such licensed products, the comprehensive tables and corresponding statistical analyses serve as a valuable tool. They provide evidence-based support that could be instrumental in making a case for recommending the clinical use of medicinal cannabis based on practice-based evidence.

2.6. Phase 5: Guided clinical trial framework for medicinal cannabis

This phase of the research attempts to put forward a stepwise guide intended to facilitate interested researchers in conducting and registering clinical trials and studies on medicinal cannabis in clinical settings. The methodology undertaken included the review of literature on the design and execution of clinical trials involving medicinal cannabis. This included guidelines from international regulatory bodies as well as published research on the ethical considerations, methodological challenges, and regulatory hurdles specific to medicinal cannabis trials. Best practices for data collection, management, and reporting were analysed. Thematic analysis of areas and topics that need to be taken into account from a regulatory aspect, an ethical aspect, clinical setting, research setting and logistics were identified. These include patient selection criteria, dosing strategies, placebo control, blinding techniques, and the importance of long-term follow-up to assess both efficacy and safety of medicinal cannabis.

Methodological aspects of conducting cannabis trials, such as randomization techniques, appropriate sample sizes, measures to minimize bias, and statistical analysis plans, with an emphasis for the need for trials to be double-blind and placebo-controlled wherever possible, to ensure that the results are robust and generalizable, were taken into consideration for setting up the framework. The clinical trial framework was reviewed by an expert panel via use of a validation form (Appendix 7) and the necessary amendments were incorporated following the panel's recommendations.

Chapter 3 - Results

3. Results

3.1. Phase 1: Literature review

The initial search strategy, incorporating comprehensive queries across four major databases, resulted in a sizeable amount of literature, from which duplicate records were first removed. Specifically, after the application of automated de-duplication procedures, 1102 duplicate entries were identified and excluded, leaving a total of 5121 records for further evaluation. These records were then subjected to an initial title and abstract screening process, where 4655 records were excluded due to irrelevance based on predefined inclusion and exclusion criteria. This preliminary screening was critical in narrowing the focus to studies that were potentially pertinent to the clinical applications of medicinal cannabis across a wide range of conditions.

Following the screening phase, 466 reports underwent full-text assessment to evaluate their methodological rigor and relevance to the research objectives. During this detailed evaluation, an additional 107 reports were excluded due to factors such as inadequate reporting, non-conformance with the clinical criteria, or methodological limitations. The application of inclusion criteria at this stage resulted in 359 reports being deemed eligible for inclusion in the literature review.

In addition to the database searches, the review process incorporated citation searching, a method that yielded an extra 3 reports that had not been identified through the initial search strategy. This approach ensured that relevant studies, which might have been overlooked due to variations in indexing or publication practices, were also considered. The integration of these additional reports brought the final total

to 362 studies included in the literature review. This comprehensive and methodologically rigorous process ensured that the review encompassed a robust evidence base, capturing a wide spectrum of relevant literature on the clinical use of medicinal cannabis.

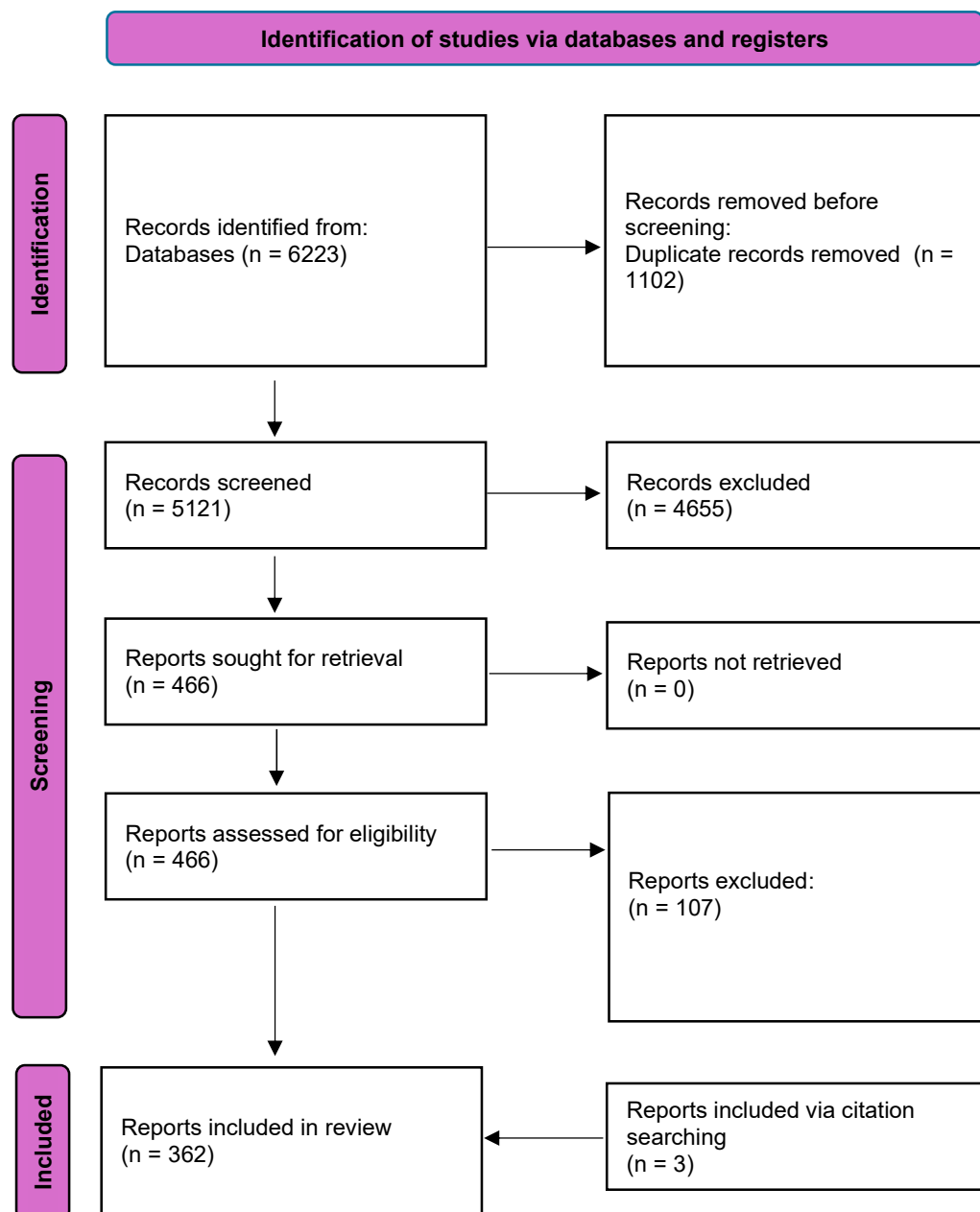


Figure 3.1. Flow diagram as per updated PRISMA guidelines demonstrating phases of study.

3.2. Phase 2: Healthcare Professionals' Questionnaire on use of medicinal cannabis

A total of 200 responses to the 'Healthcare Professionals' Questionnaire on use of medicinal cannabis' were received from Malta-based healthcare professionals. 109 were from females (54.5%) and 91 from males (45.5%). The median age of the participants was 45.5 years.

The majority of participants identified themselves as being either a doctor or a pharmacist with 98 doctors (49%) and 90 pharmacists (45%). The rest of the respondents, 12, were dentists (6%).

Almost half of the doctors practiced in hospital (n=48; 45.7%). Twenty-six doctors (24.8%) were involved in primary care and 16 (15.2%) in community care (Figure 3.2). Among the pharmacists, 12 (12.8%) were employed in hospital, another 12 pharmacists (12.8%) were engaged in industry, 17 (18.1%) were in the regulatory sector while the majority, 37 (39.4%) practiced within a community setting (Figure 3.3).

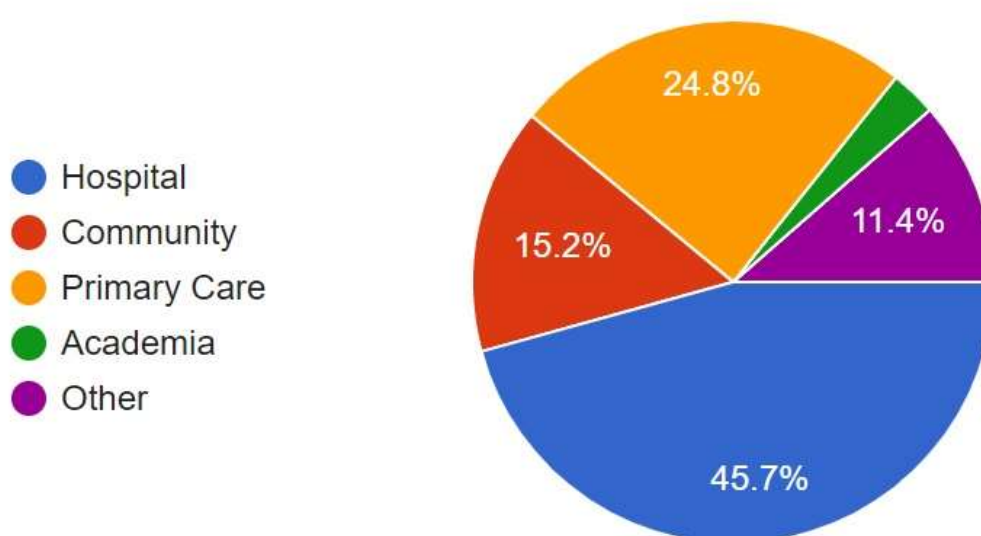


Figure 3.2. Areas of practice for physician participants.

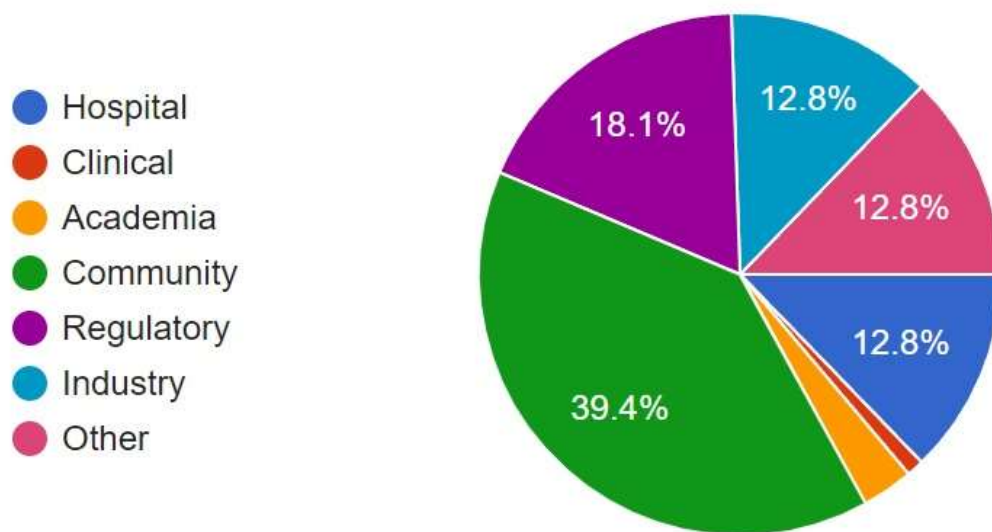


Figure 3.3. *Areas of practice for pharmacist respondents.*

3.2.1. Knowledge about benefits to patients

Respondents were asked whether they believed that there are patients who would enjoy therapeutic benefit from medicinal cannabis. The most prevalent answer was 'somewhat agree' (n=72), followed by 'strongly agree' (n=56) and 'mostly agree' (n=44) (Figure 3.4). The participants that signaled some level of agreement with the statement ('There are patients who could benefit from use of medicinal cannabis') amounted to 172 (86%). Fourteen claimed no opinion and the same number of respondents expressed disagreement at differing degrees.

There are patients who could benefit from use of medicinal cannabis.

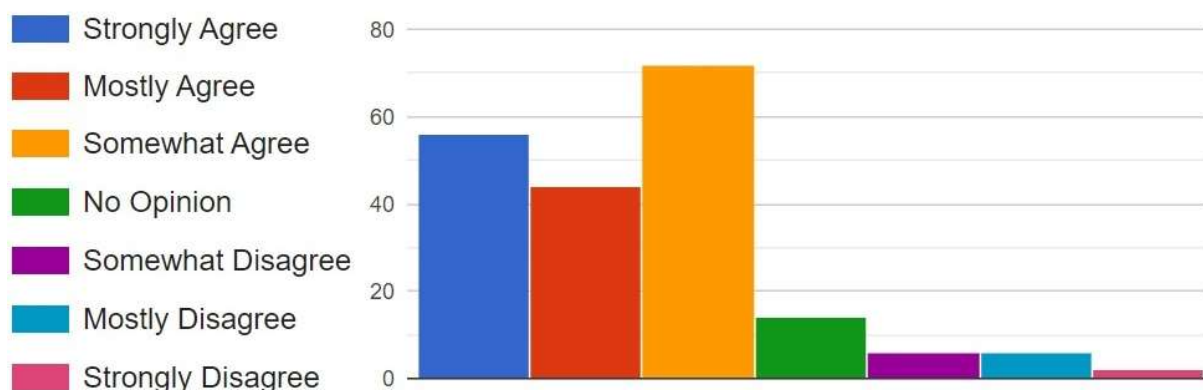


Figure 3.4. *Perception of healthcare professionals with regards to the fact that patients could benefit from medicinal cannabis.*

When the participants were asked whether they were knowledgeable about which patients can derive beneficial effects from medicinal cannabis the majority of healthcare professionals (n=130; 65%) were in agreement, with the highest ranking response being 'somewhat agree' (n=68; 34%) (Figure 3.5).

I am knowledgeable about which patients can derive beneficial effects from medicinal cannabis.

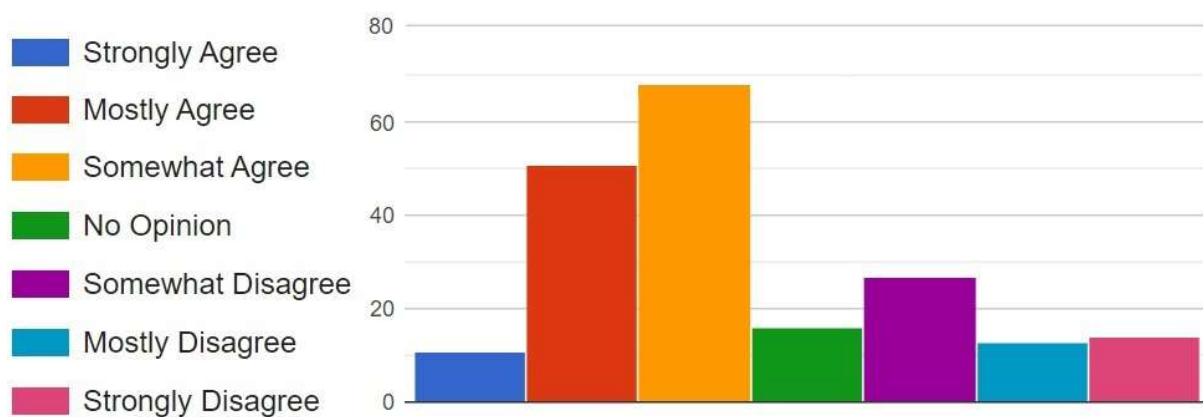


Figure 3.5. *Healthcare professionals' knowledge about which patients can derive benefits from medicinal cannabis.*

3.2.2. Discussing medicinal cannabis with patients

The most popular response among participants when addressing the statement 'I feel comfortable discussing medicinal cannabis with patients' was 'mostly agree' (n=53; 26.5%) followed by 'somewhat agree' (n=45; 22.5%) (Figure 3.6). In total 127 healthcare professionals showed a form of agreement with the statement. The total disagreement, at various degrees, amounted to 57 (28.5%) with 16 respondents indicating 'no opinion' as their answer.

I feel comfortable discussing medicinal cannabis with patients.

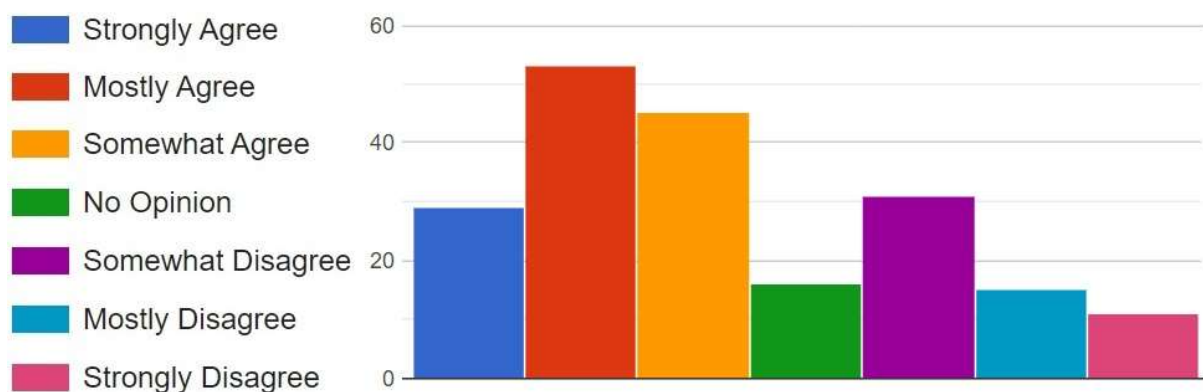


Figure 3.6. *Comfort rating of healthcare professionals in discussing medicinal cannabis with patients.*

With regards to confidence in answering patient questions about medicinal cannabis the 'somewhat disagree' answer was chosen by 41 (20.5%) healthcare professionals (Figure 3.7). It was the second most selected response, closely followed by 'mostly agree' (n=38; 19%). The most popular choice was 'somewhat agree' (n=54; 27%). 15 respondents had no opinion in this instance with 104 respondents (52%) distributed on the agreement spectrum and 81 (40.5%) on the disagreement side.

I am confident in answering questions put forward by patients on the use of medicinal cannabis.

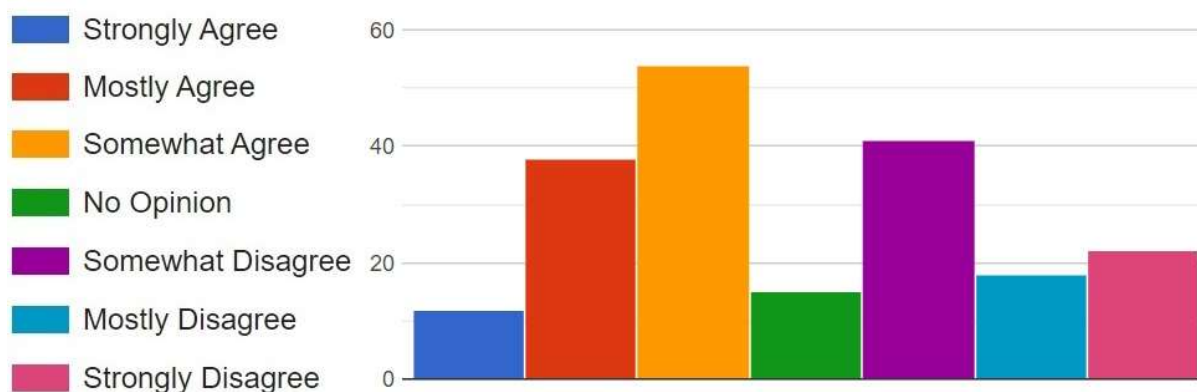


Figure 3.7. Confidence of healthcare professionals in answering patient questions on the use of medicinal cannabis.

3.2.3. Clinical awareness about medicinal cannabis

Three questions captured the healthcare professionals' awareness of the therapeutic effects and side effects of medicinal cannabis, as well as knowledge in dealing with patients exhibiting side effects after using medicinal cannabis.

With regards to therapeutic effects' knowledge 81 participants (40.5%) selected 'somewhat agree', 44 (22%) opted for 'mostly agree' and 26 (13%) chose 'somewhat disagree' (Figure 3.8). The number of healthcare professionals that opted for 'mostly disagree' was 14 (7%). A further 26 participants were split evenly into the 'strongly agree' and 'strongly disagree' categories. 13 (6.5%) in each (Figure 3.8).

I am knowledgeable about the therapeutic effects of medicinal cannabis.

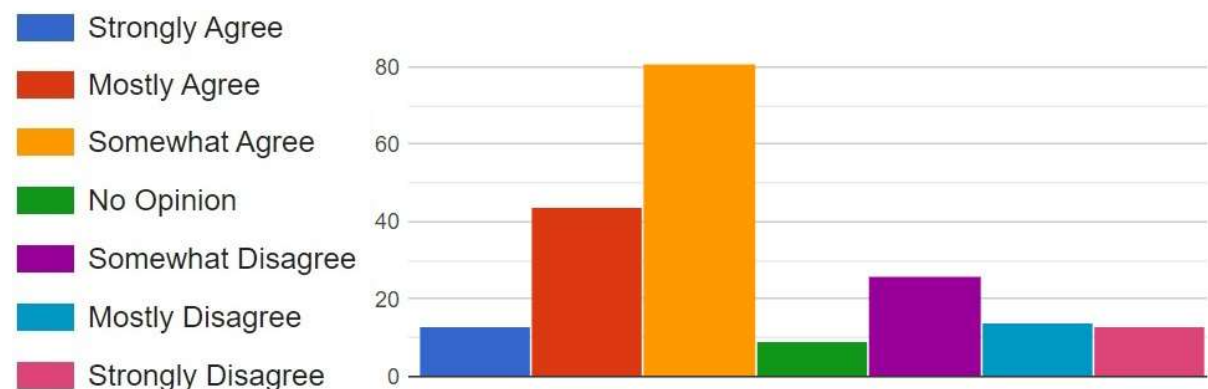


Figure 3.8. Knowledge of therapeutic effects of medicinal cannabis.

When participants were asked whether they felt they were knowledgeable about side effects of medicinal cannabis, the three most popular categories still ‘somewhat agree’, ‘mostly agree’ and ‘somewhat disagree’, in that order with 63 (31.5%), 49 (24.5%) and 34 (17%) selections respectively (Figure 3.9).

I am knowledgeable about the side effects of medicinal cannabis.

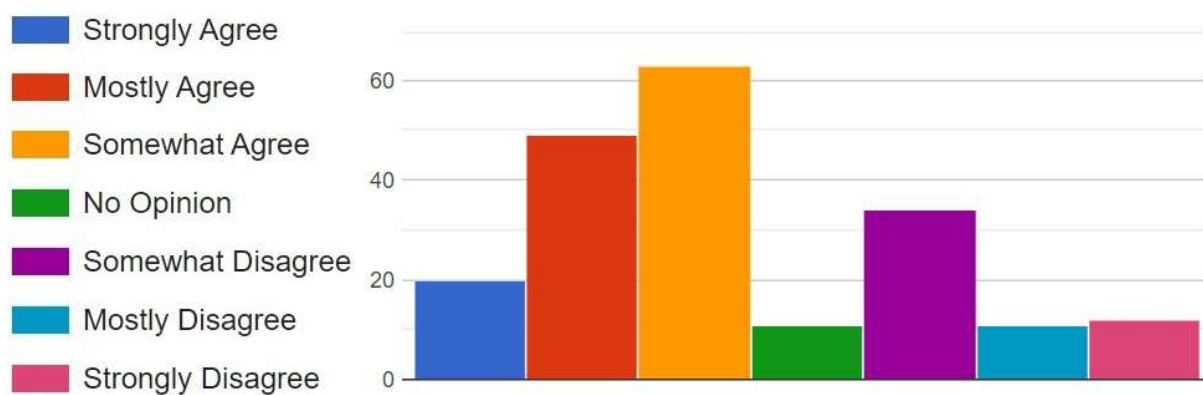


Figure 3.9. *Knowledge of side effects of medicinal cannabis.*

When tapping into the confidence levels of healthcare professionals in dealing with patients that show side effects from medicinal cannabis use 51 (25.5%) participants answered 'somewhat agree' and 50 (25%) respondents chose 'somewhat disagree' (Figure 3.10).

I am confident in dealing with patients exhibiting side effects due to use of medicinal cannabis.

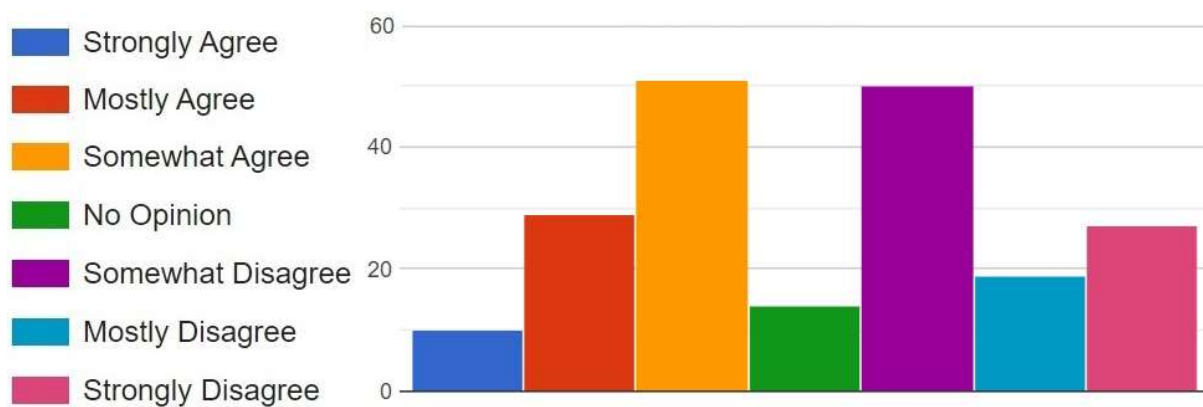


Figure 3.10. *Confidence in dealing with side effects of medicinal cannabis.*

3.2.4. Prescription of medicinal cannabis

The 'Healthcare Professionals' Questionnaire on use of medicinal cannabis' included six questions related to the prescription of medicinal cannabis. Five of these questions assumed the possibility for the healthcare professional of prescribing medicinal cannabis. Pharmacists were therefore largely excluded from expressing a level of agreement with the statements and the option 'no opinion' for these statements ranged between 68 and 79.

For the statement 'I do not prescribe medicinal cannabis because it is not an ethical form of therapy' 77 participants (38.5%) chose 'no opinion' (Figure 3.11).

Among the rest of the responses a total of 87 (43.5%) expressed varying degrees of disagreement with the statement., indicating that ethics would not be a reason for them not to prescribe medicinal cannabis. 'Strongly disagree' was chosen by 45 respondents (22.5%), followed by the 'mostly disagree' option (n=27, 13.5%) and the 'somewhat disagree' answer (n=15, 7.5%) (Figure 3.11).

I do not prescribe medicinal cannabis because it is not an ethical form of therapy.

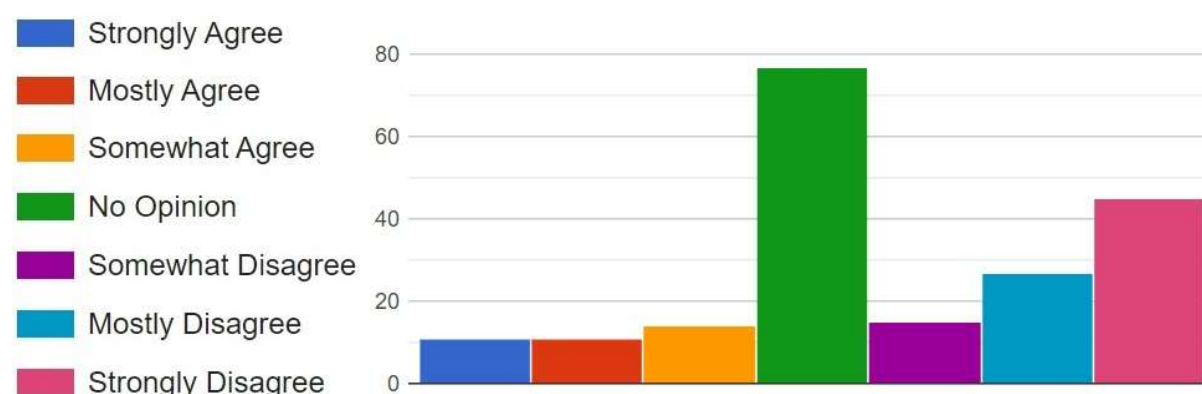


Figure 3.11. *Reservations in prescribing medicinal cannabis due to ethical concerns.*

A second statement connected to the prescription of medicinal cannabis (I feel comfortable prescribing medicinal cannabis to patients) was addressed for the most part by medical practitioners. There were 71 selections for 'no opinion'. The majority of responses from those left (n=129) were concentrated mostly on the disagreement spectrum (n=85; 42.5%), with the highest number of responses in disagreement with the statement aggregating in the 'strongly disagree' category (n=38; 19%) followed by the 'mostly disagree' option (n=29; 14.5%) (Figure 3.12).

I feel comfortable prescribing medicinal cannabis to patients.

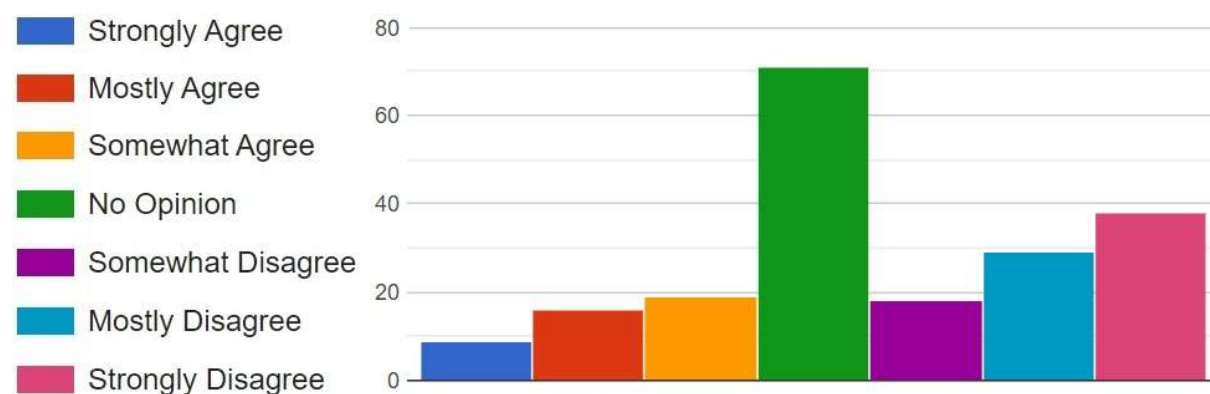


Figure 3.12. *Comfort in prescribing medicinal cannabis to patients.*

The statement 'I do not prescribe medicinal cannabis because the harm caused outweighs the benefit' presented a total of 72 'no opinion' responses (36%). The disagreement options were once again more than the selections in agreement with the statement; 82 (41%) and 46 (23%). Thirty-three healthcare professionals (16.5%) opted for 'mostly agree' and 29 (14.5%) chose 'strongly disagree'. Figure 3.13 summarizes the responses obtained.

I do not prescribe medicinal cannabis because the harm caused outweighs the benefit.

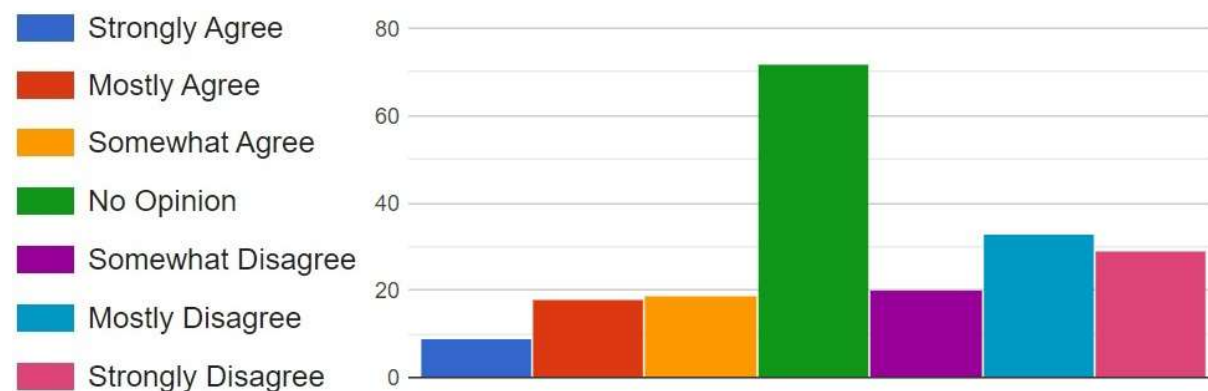


Figure 3.13. *Reservations in prescribing medicinal cannabis due to harm outweighing benefit.*

The fourth prescription-related question (I do not prescribe medicinal cannabis because the risk of abuse and dependence is higher than for conventional therapy) was also answered via the 'no opinion' option from the majority of pharmacists (n=68). The second most popular selection was 'mostly disagree' (n=33; 16.5%), followed by 'somewhat agree' (n=28; 14%) and 'somewhat disagree' (n=25; 12.5%). Figure 3.14 summarizes the responses received.

I do not prescribe medicinal cannabis because the risk of abuse and dependence is higher than for conventional therapy.

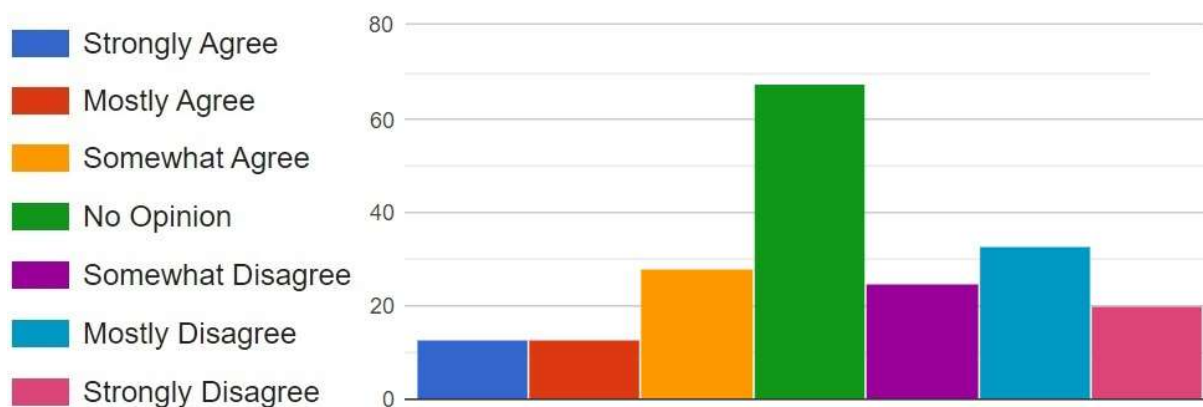


Figure 3.14. Reservations in prescribing medicinal cannabis due to risk of abuse and dependence being higher than for conventional therapy.

In relation to the statement 'I do not prescribe medicinal cannabis because the risk of side effects is higher than for conventional therapy' a total of 79 (39.5%) respondents chose 'no opinion'. From the remainder of the answers the more popular categories were 'somewhat disagree' (n=32; 16%), 'mostly disagree' (n=27; 13.5%) and 'somewhat agree' (n=24; 12%) Figure 3.15 illustrates the responses received.

I do not prescribe medicinal cannabis because the risk of side effects is higher than for conventional therapy.

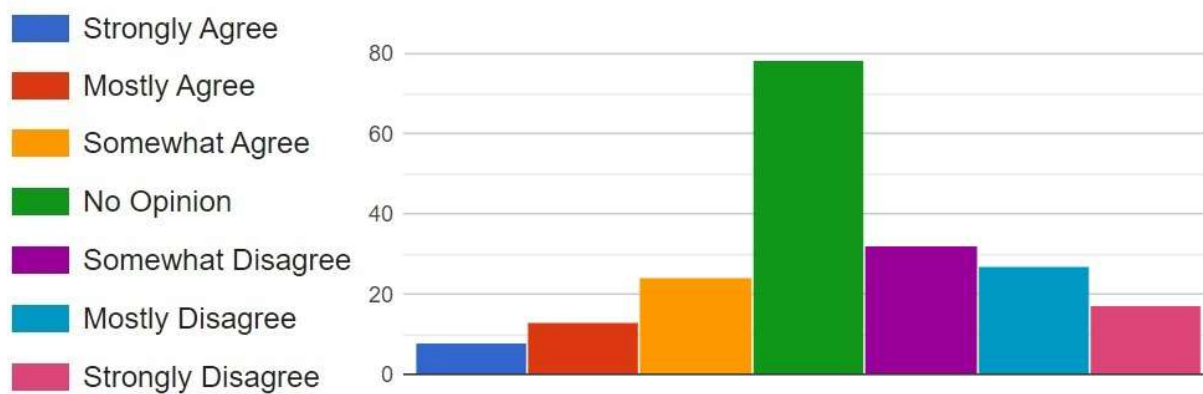


Figure 3.15. *Reservations in prescribing medicinal cannabis due to risk of side effects being higher than for conventional therapy.*

The sixth question focused on knowledge of the prescription process for medicinal cannabis therefore pharmacist respondents were able to express an opinion. The most prevalent answer to the statement 'I am knowledgeable about the modalities and indications for medicinal cannabis prescription' was 'somewhat agree' (n=53; 26.5%). The 'mostly agree' option gathered support from 41 participants (20.5%) and the 'somewhat disagree' was chosen by 33 healthcare professionals (16.5%). Figure 3.16 summarizes the responses.

I am knowledgeable about the modalities and indications for medicinal cannabis prescription.

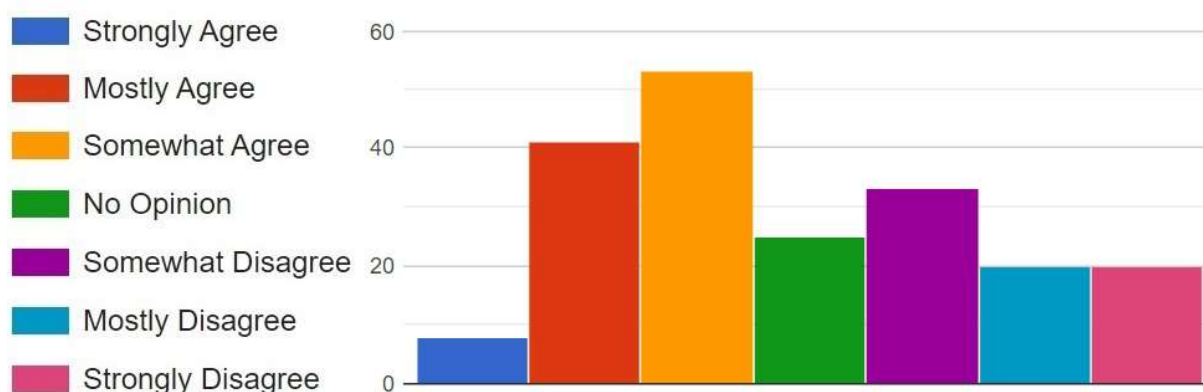


Figure 3.16. *Knowledge about modalities and indications of medicinal cannabis prescription.*

3.2.5. Clinical conditions and medicinal cannabis

When asked about which conditions should be treated with medicinal cannabis participants were able to tick more than one option, giving multiple responses to answer the question. One hundred and fifty-seven healthcare professionals (78.5%) chose 'chronic cancer pain'. The 'palliative care' option was indicated by 149 participants 74.5%. 'Neuropathic pain' was included by 120 respondents (60%), 'multiple sclerosis spasticity' by 116 (58%) and 'chronic non-cancer pain' by 113 (56.5%) participants. Ninety-six healthcare professionals (48%) indicated 'chemotherapy-induced nausea and vomiting' and 74 (37%) indicated 'epilepsy' as a condition that could be addressed by medicinal cannabis (Figure 3.17).

Medicinal cannabis should be used in addressing:

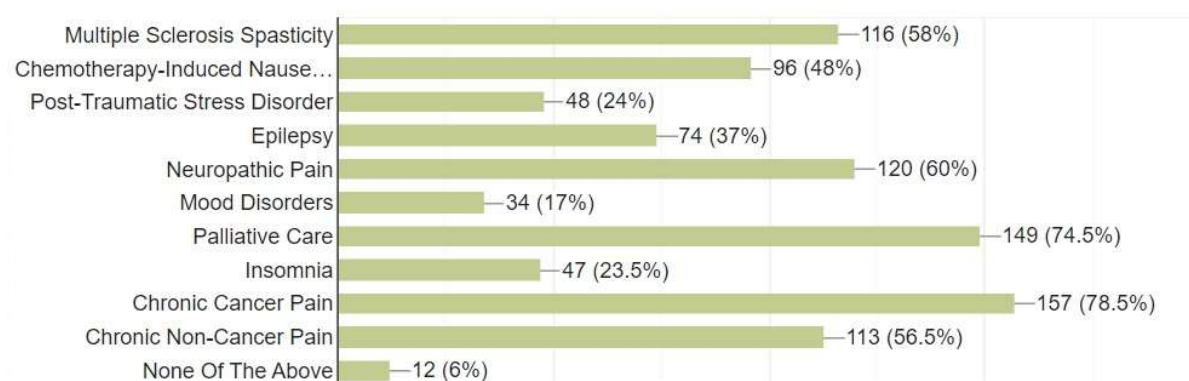


Figure 3.17. *Conditions that might be addressed using medicinal cannabis.*

3.2.6. Danger Levels of Medicinal Cannabis

The options for each of the seven categories presented for the statement ‘medicinal cannabis is less dangerous than’, were three: ‘agree’, ‘I don’t know’ and ‘disagree’. In the comparison of medicinal cannabis to anxiolytic drugs in terms of danger posed to the patient, the majority of respondents chose ‘I don’t know’ (n=78; 39%). 63 (31.5%) chose ‘disagree’ and 59 (29.5%) selected ‘agree’. The answers received were similar for anticonvulsant drugs, antidepressant drugs and antipsychotic drugs with the majority of respondents indicating ‘I don’t know’ as their preferred answer - 95 (47.5%), 84 (42%) and 87 (43.5%) respectively - followed by ‘disagree’ - 63 (31.5%), 73 (36.5%) and 62 (31%) respectively. The ‘agree’ option was less popular for these three drug classes, chosen by 42 (21%), 43 (21.5%) and 51 (25.5%) participants respectively. Figure 3.18 depicts responses received.

Medicinal cannabis is less dangerous than:

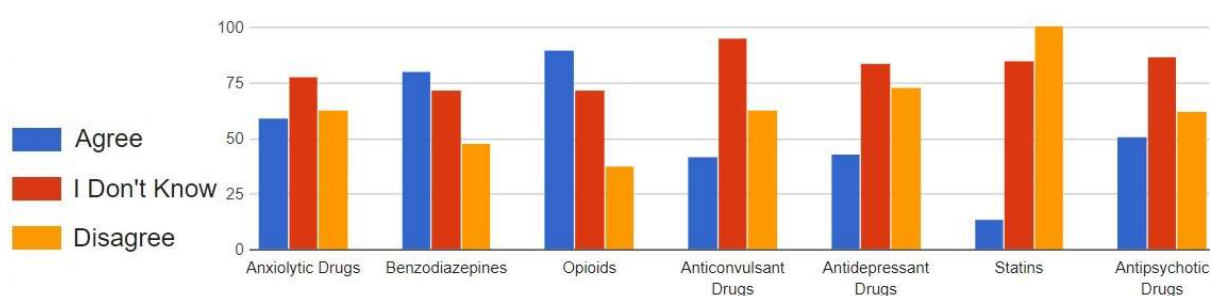


Figure 3.18. *Health professionals' perceptions about the danger levels of medicinal cannabis in comparison to other drug classes.*

The largest consensus was registered for statins with 101 (50.5%) participants disagreeing that they are more dangerous than medicinal cannabis. Eighty-five respondents (42.5%) claimed that they did not know. The two drug classes that the majority of respondents agreed are more dangerous than medicinal cannabis were benzodiazepines, where 80 participants (40%) chose 'agree', and opioids, with 90 participants (45%) agreeing. For benzodiazepines 48 respondents (24%) chose 'disagree' and for opioids 38 healthcare professionals (19%) opted for 'disagree'.

3.2.7. Education about medicinal cannabis

The questions in this section were associated with education on the subject of medicinal cannabis. There was significant agreement with the statement referring to knowledge of medicinal cannabis among the population (Among the general population there is little understanding of medicinal cannabis). One hundred and eighty-three healthcare professionals (91.5%) showed some level of agreement with the statement. The majority (n=78; 39%) indicated 'strongly agree' as their answer. Seventy respondents (35%) opted for 'mostly agree' and 35 (17.5%) chose 'somewhat agree' (Figure 3.19).

Among the general population there is little understanding of medicinal cannabis.

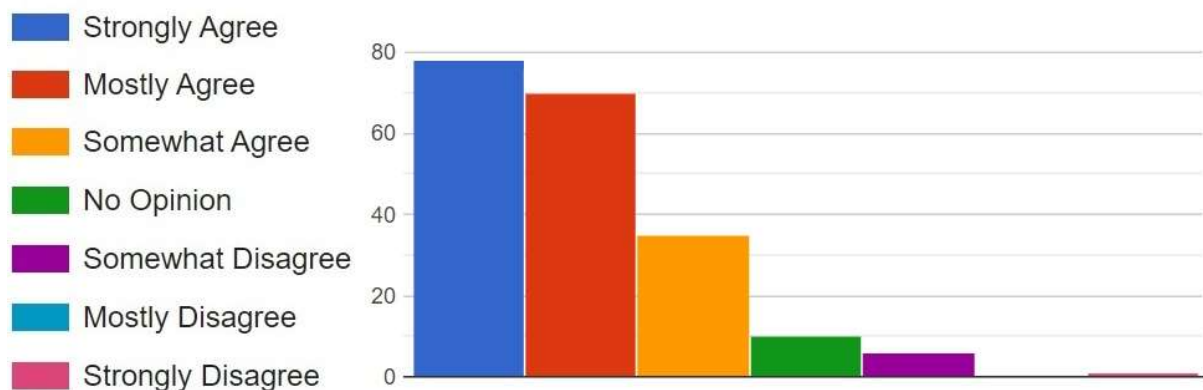


Figure 3.19. *Health professionals' perceptions about the general population's understanding of medicinal cannabis.*

In relation to the statement 'I agree that students of medicine and pharmacy should be required to learn about medicinal cannabis as part of their curriculum' 120 healthcare professionals (60%) chose 'strongly agree', 43 respondents (21.5%) chose 'mostly agree' and 24 (12%) participants chose 'somewhat agree' (Figure 3.20).

I agree that students of medicine and pharmacy should be required to learn about medicinal cannabis as part of their curriculum.

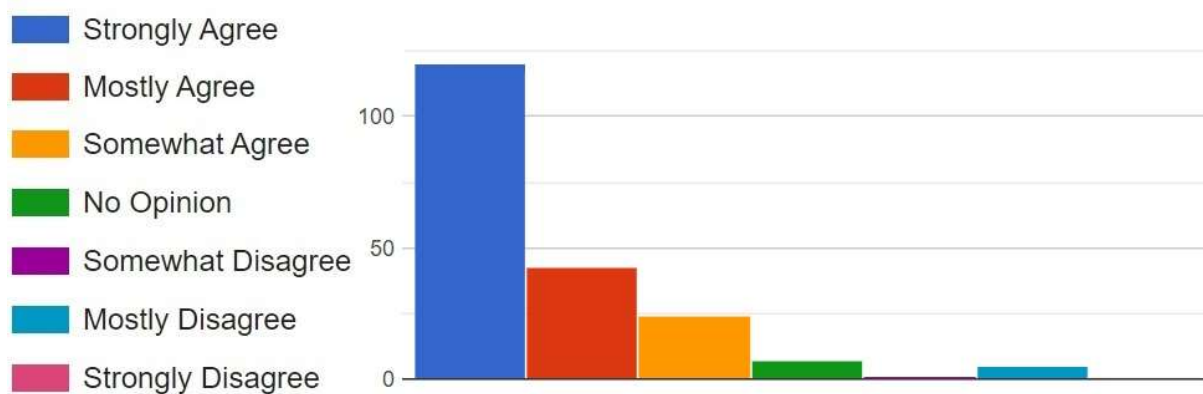


Figure 3.20. *Convictions about inclusion of medicinal cannabis in students' curricula.*

When asked to indicate the level of agreement to the statement 'I have received satisfactory formal education about medicinal cannabis' 80 respondents (40%) opted for the 'strongly disagree' option, 31 healthcare professionals (15.5%) answered 'mostly disagree' and another 31 individuals (15.5%) chose 'somewhat disagree'. In total, the number of participants who opted for a degree of disagreement with the statement was 142 (71%). Figure 3.21 captures the responses received.

I have received satisfactory formal education about medicinal cannabis.

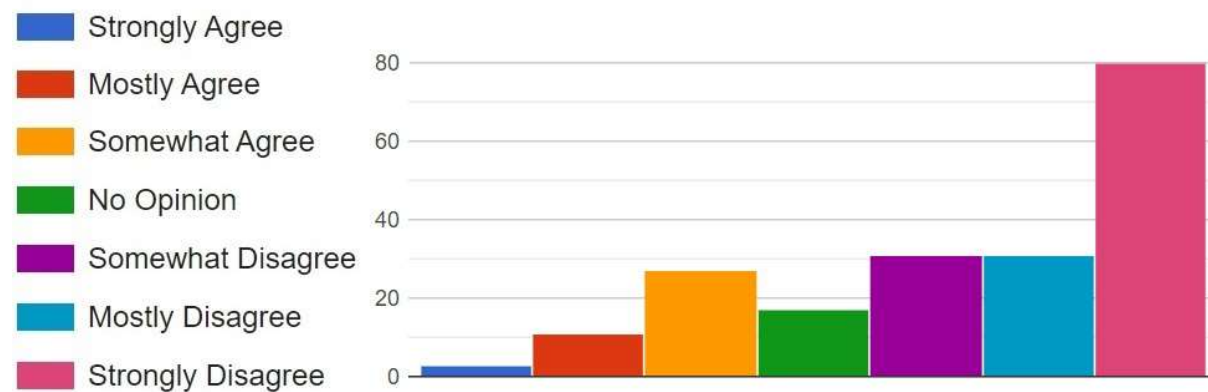


Figure 3.21. *Education received with regards to medicinal cannabis.*

The majority of participants indicated that they gained insight into medicinal cannabis after doing their own research, mostly via consultation of online resources and journal publications.

When asked whether they would be interested in educational activities about medicinal cannabis (I would be interested in attending educational activities to learn more about medicinal cannabis) 174 healthcare professionals (87%) expressed different levels of agreement. Most of them, 74 (37%) chose to 'strongly agree' with the statement. Fifty-three healthcare professionals (26.5%) selected 'mostly agree' and 47 participants (23.5%) selected 'somewhat agree'. Nineteen of the respondents (9.5%) had no opinion on the statement (Figure 3.22).

I would be interested in attending educational activities to learn more about medicinal cannabis.

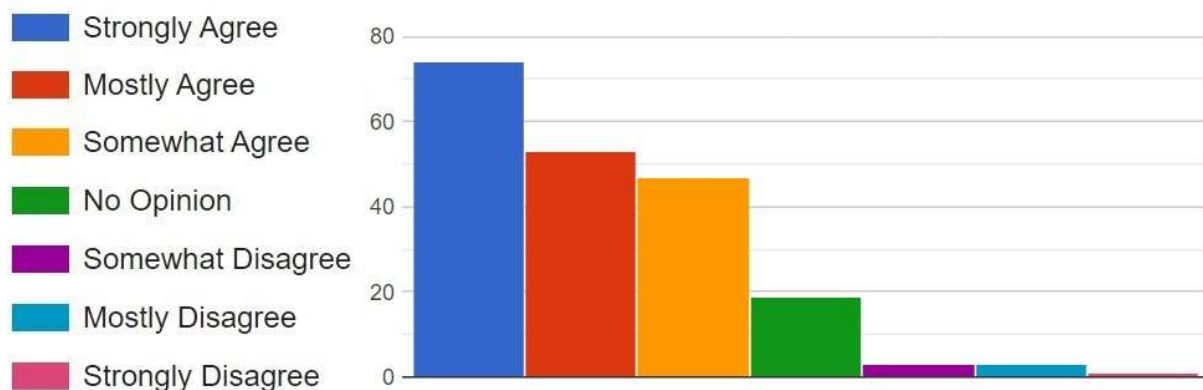


Figure 3.22. *Interest in attending educational activities about medicinal cannabis.*

In a related question to the latter, when specifically asked to choose which methods would be best for them to get more education on medicinal cannabis (What would be your preferred method/s for acquiring more knowledge about medicinal cannabis), with respondents able to choose more than one option, the two answers that gathered more than 100 selections were ‘webinars’ (n=135; 67.5%) and ‘expert-driven online lectures’ (n=101; 50.5%).

Other popular choices were ‘medical conference / symposium’ chosen by 69 healthcare professionals (34.5%), followed by ‘hybrid learning (face-to-face and online)’ which was opted for by a total of 64 respondents (32%), ‘face-to-face seminars’ selected by 51 respondents (25.5%) and ‘pharmaceutical company-organized webinar’ that was chosen by 42 healthcare professionals (21%). Figure 3.23 summarizes the data findings.

What would be your preferred method/s for acquiring more knowledge about medicinal cannabis?

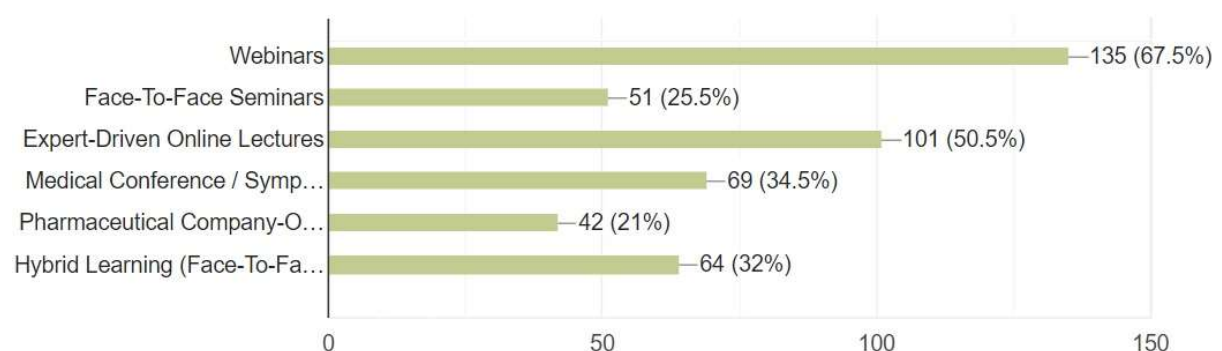


Figure 3.23. Preferred methods for receiving education on medicinal cannabis.

3.2.8. Comparison of results: pharmacists and doctors

The previous section reported findings for the full population sample, without differentiating between results for the pharmacist group and the physician group. For a more comprehensive analysis and to enhance interpretative depth, it is deemed valuable to present the results for each group separately, thereby providing a more granular understanding of the survey data.

The blue column in the subsequent bar graphs represents data for the two groups together. The red column represents results for the doctor group. and the yellow one for the pharmacist group. Trend lines in the respective colours have also been produced on these bar graphs for a more immediate analysis of results. Absence of a colour in any of the seven category selections indicates that for that group the total number of responses recorded was zero. The y axis represents percentage and not participant responses this time.

There are patients who could benefit from use of medicinal cannabis.

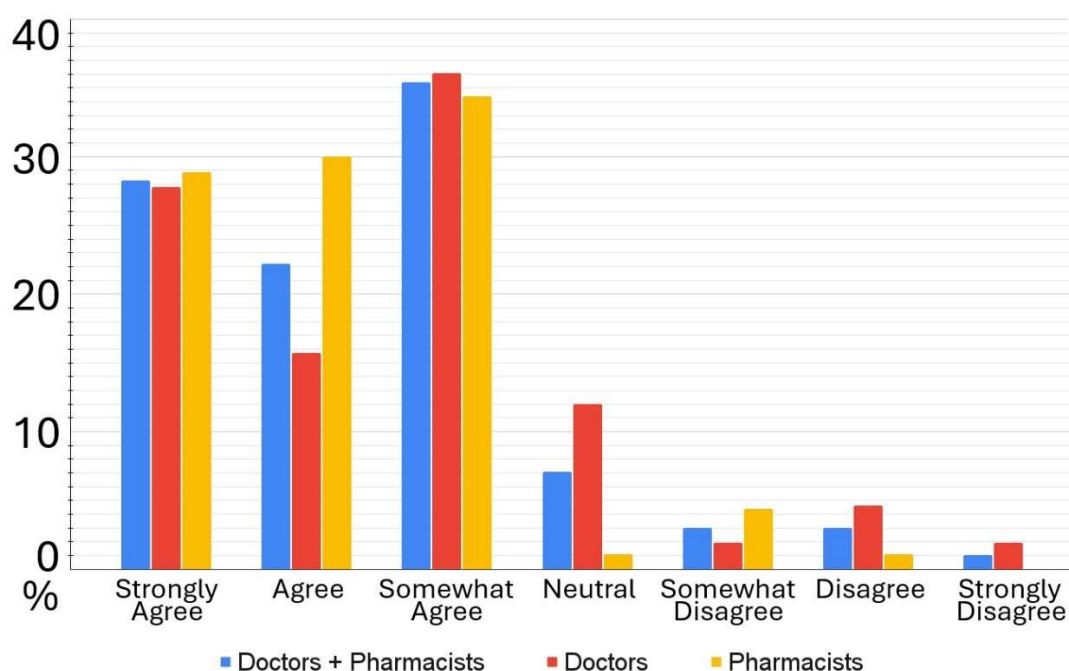


Figure 3.24. Patient benefit from medicinal cannabis: separate groups.

I am knowledgeable about which patients can derive beneficial effects from medicinal cannabis.

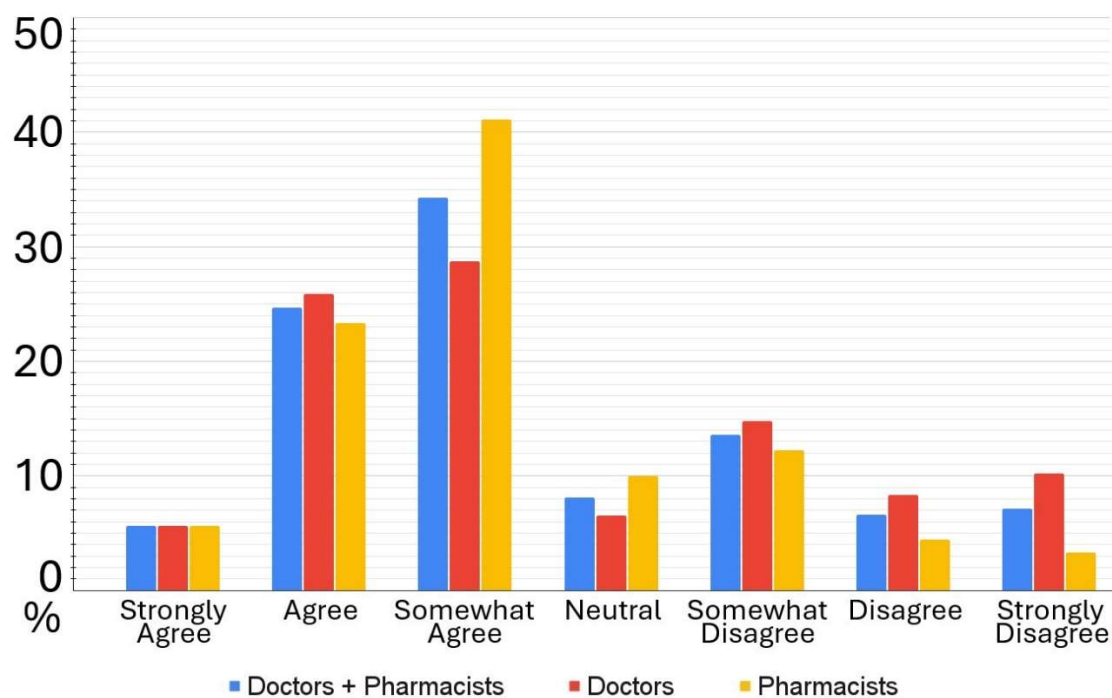


Figure 3.25. Aware of which patients benefit from medicinal cannabis: separate groups.

I feel comfortable discussing medicinal cannabis with patients.

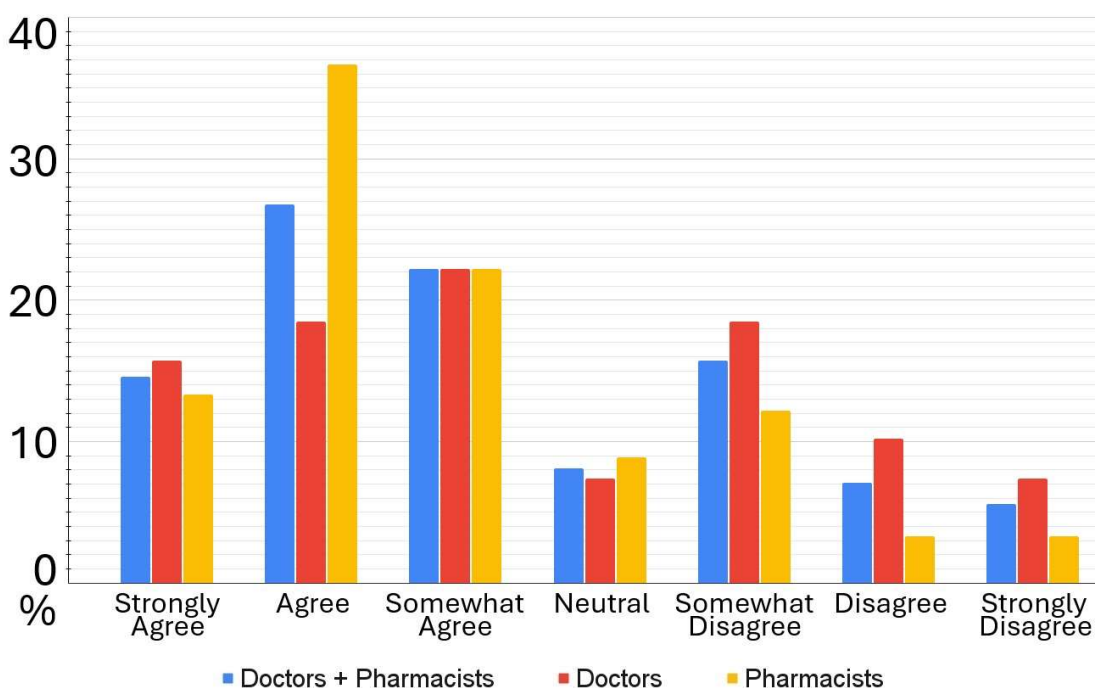


Figure 3.26. *Comfort in discussing medicinal cannabis with patients: separate groups.*

I am confident in answering questions put forward by patients on the use of medicinal cannabis.

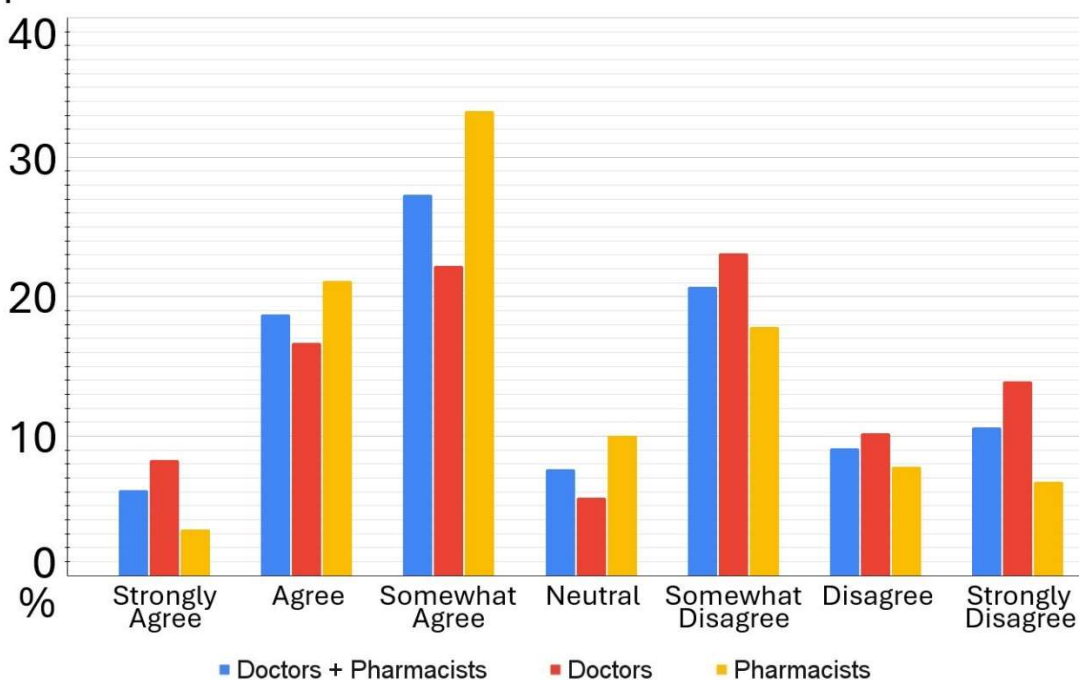


Figure 3.27. *Confident in answering medicinal cannabis patient questions: separate groups.*

I am knowledgeable about the therapeutic effects of medicinal cannabis.

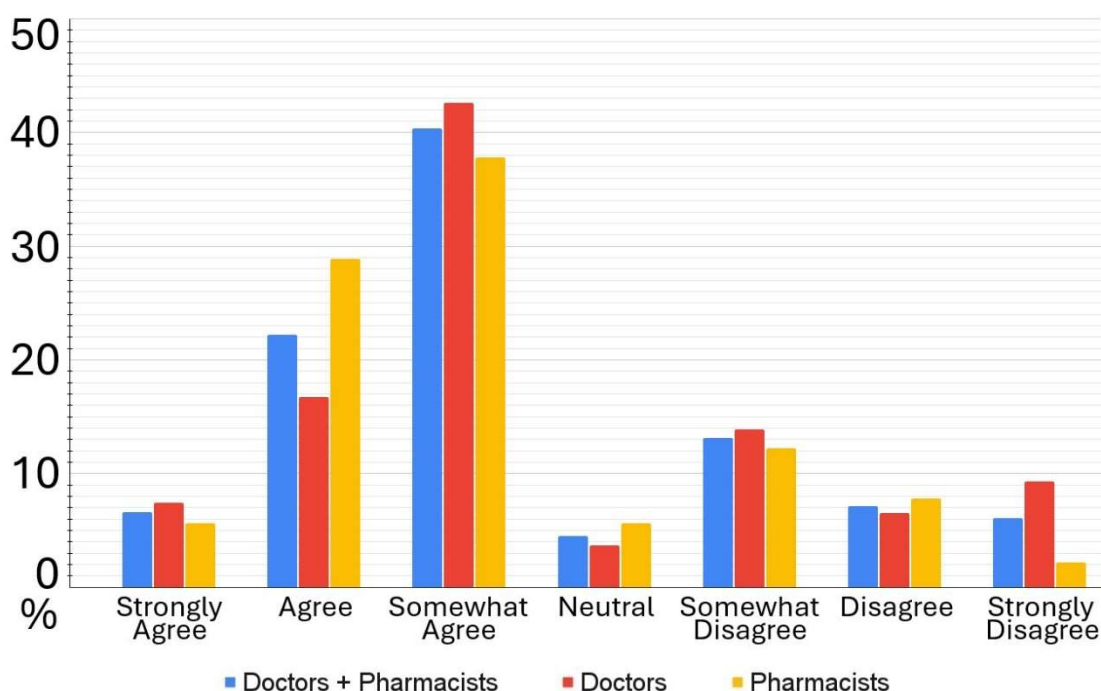


Figure 3.28. Knowledge of therapeutic effects of medicinal cannabis: separate groups.

I am knowledgeable about the side effects of medicinal cannabis.

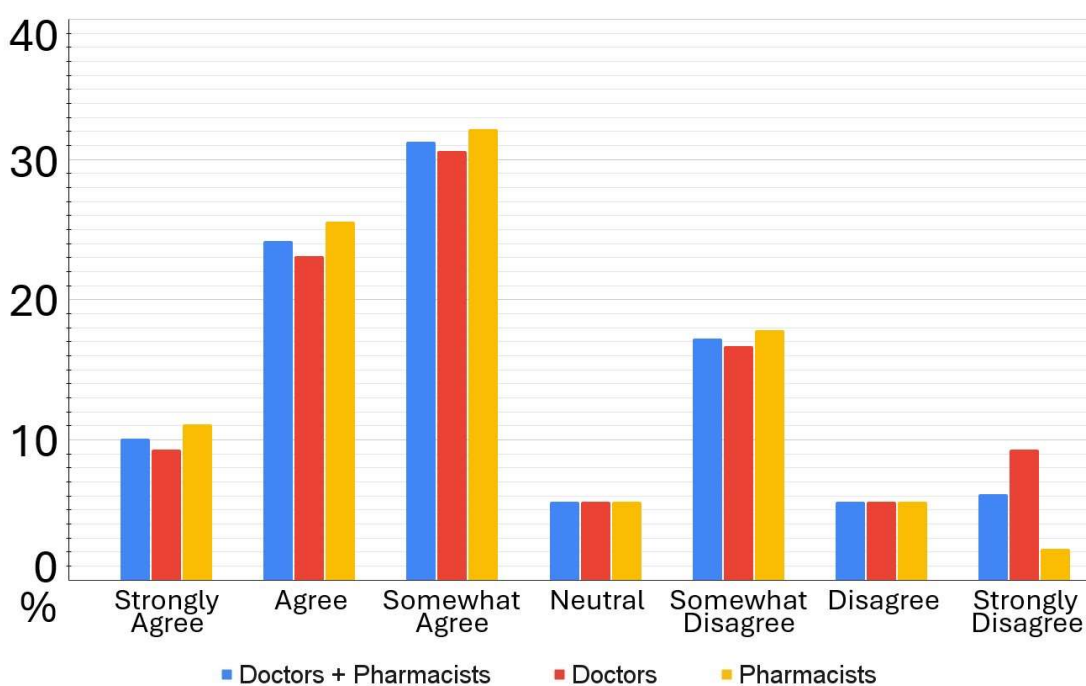


Figure 3.29. Knowledge of side effects of medicinal cannabis: separate groups.

I am confident in dealing with patients exhibiting side effects due to use of medicinal cannabis.

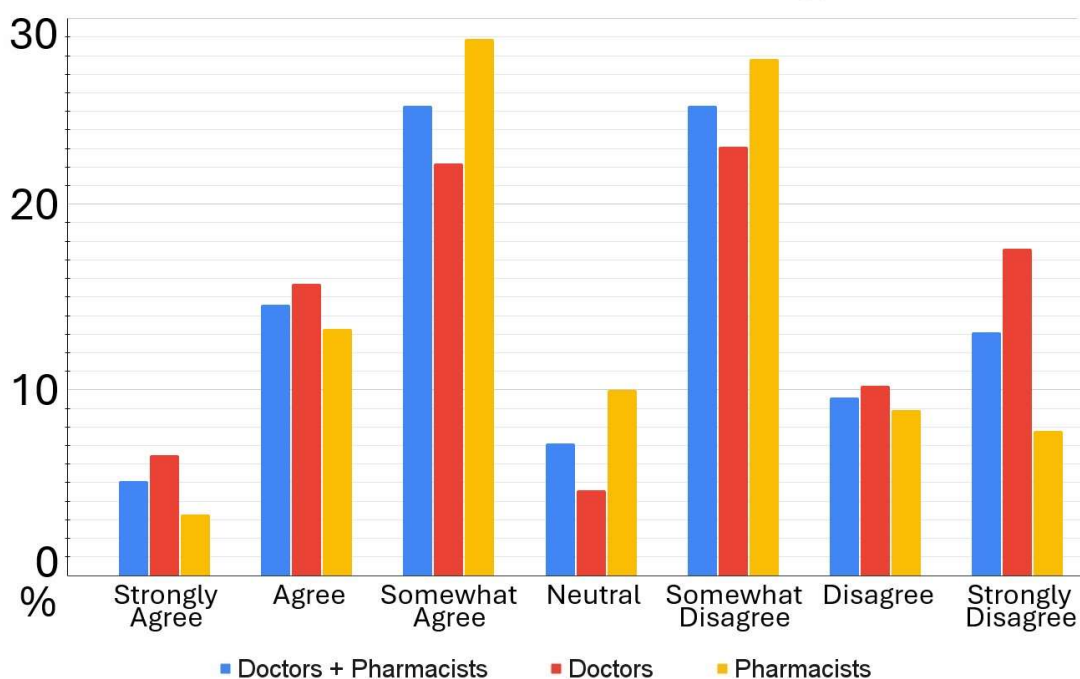


Figure 3.30. Confidence in dealing with side effects of medicinal cannabis: separate groups.

I am knowledgeable about the modalities for medicinal cannabis prescription.

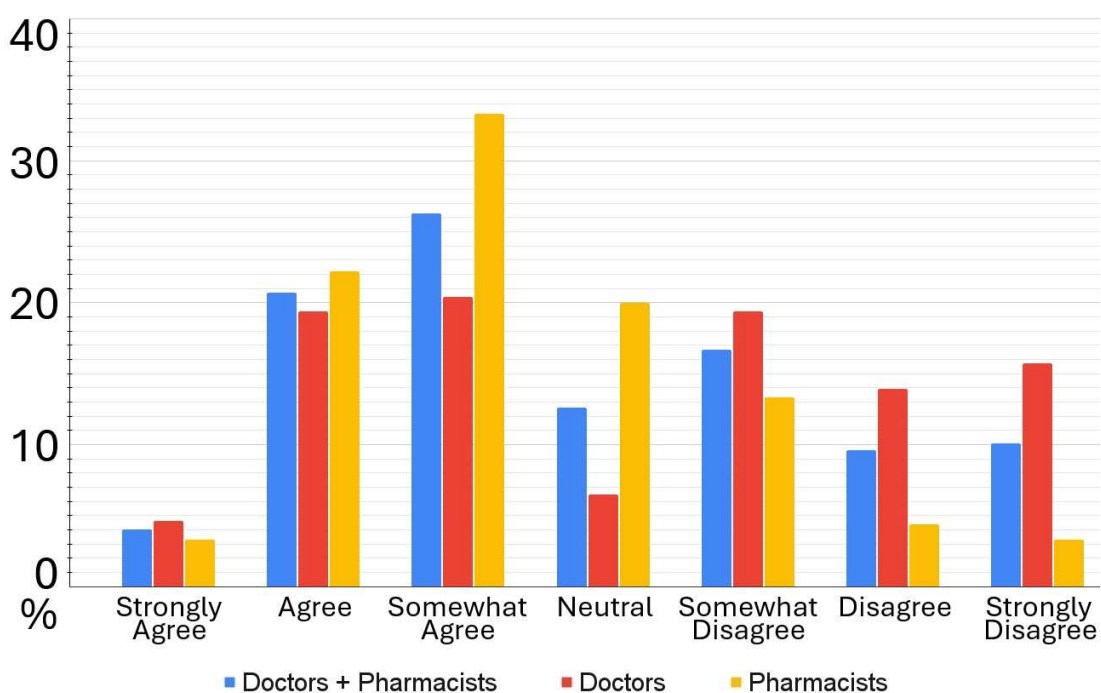


Figure 3.31. Knowledge on medicinal cannabis prescription modalities: separate groups.

Medicinal cannabis is less dangerous than:

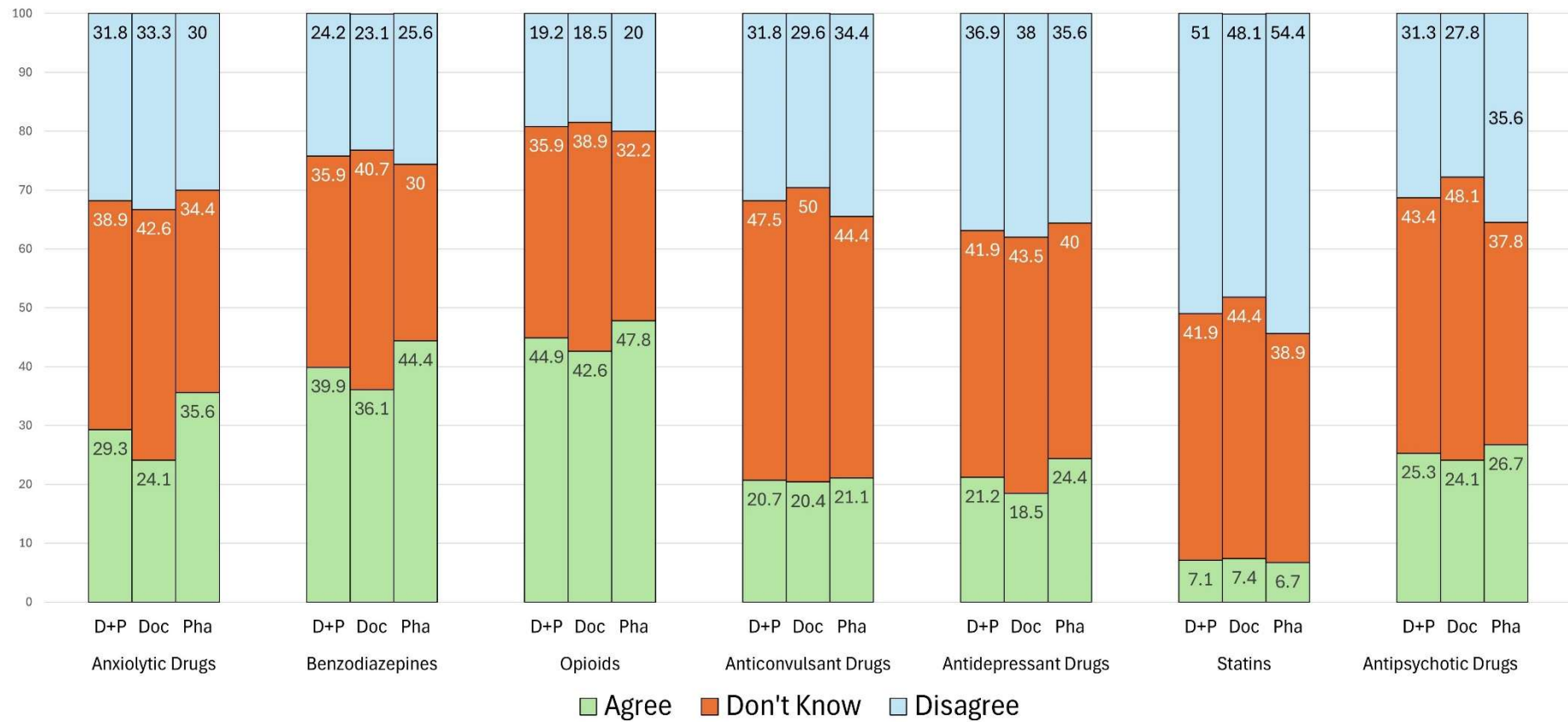


Figure 3.32. Perceived danger of medicinal cannabis in comparison to some conventional therapeutic drugs: separate groups.

Among the general population there is little understanding of medicinal cannabis.

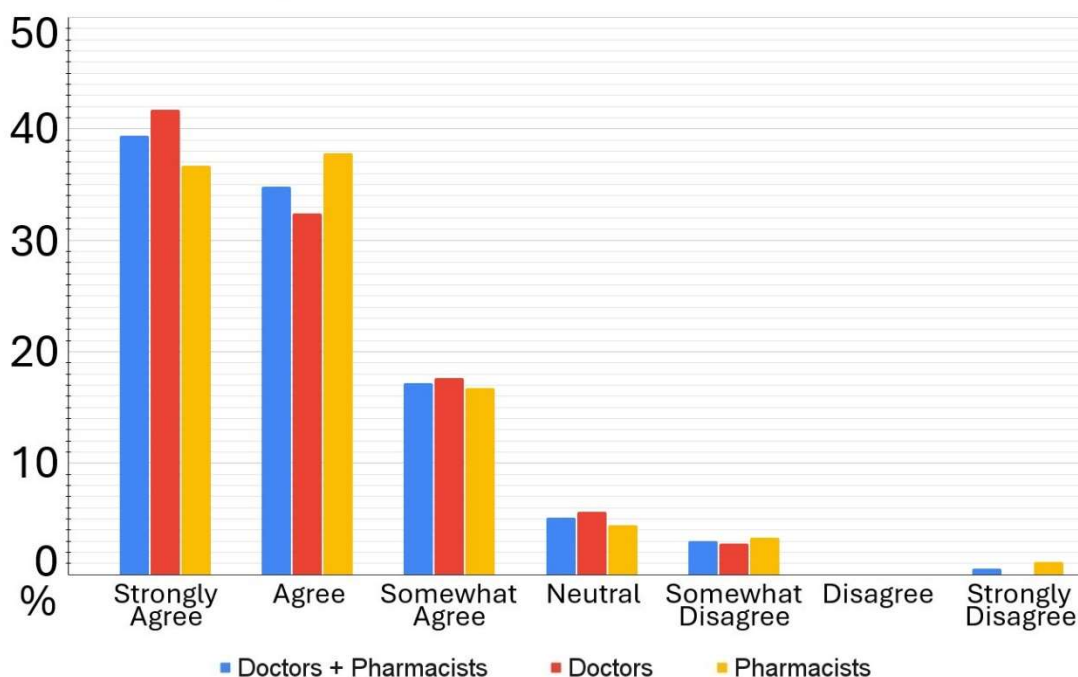


Figure 3.33. *Understanding of medicinal cannabis among population: separate groups.*

I agree that students of medicine and pharmacy should learn more about medicinal cannabis.

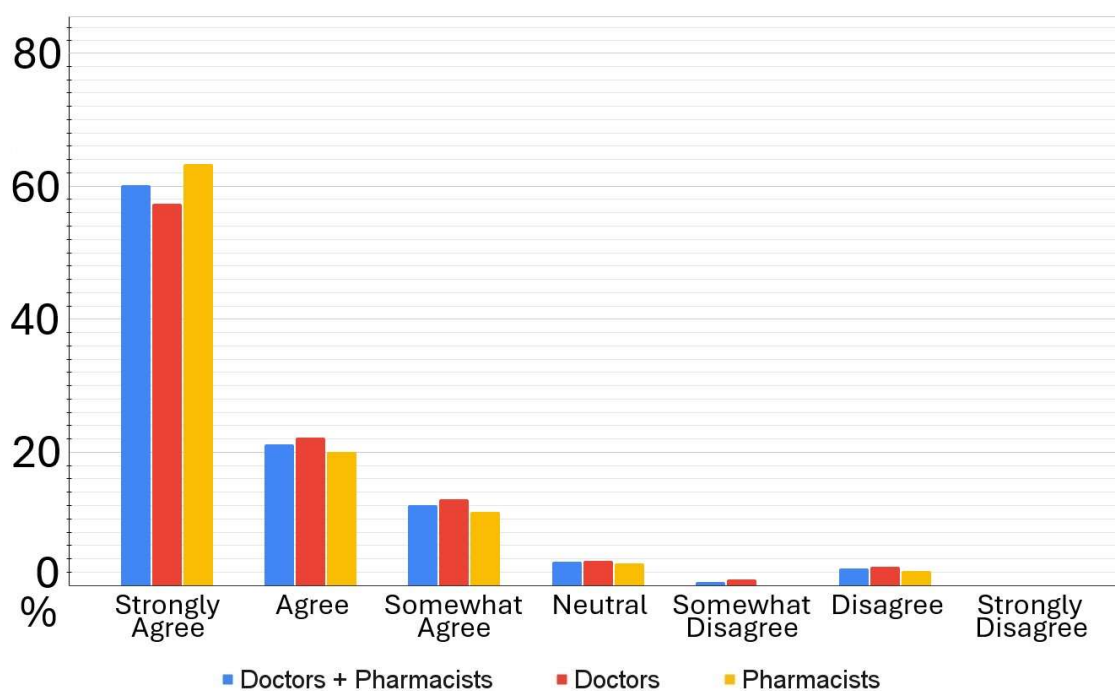


Figure 3.34. *Medicinal cannabis on students' curriculum: separate groups.*

I have received satisfactory formal education about medicinal cannabis.

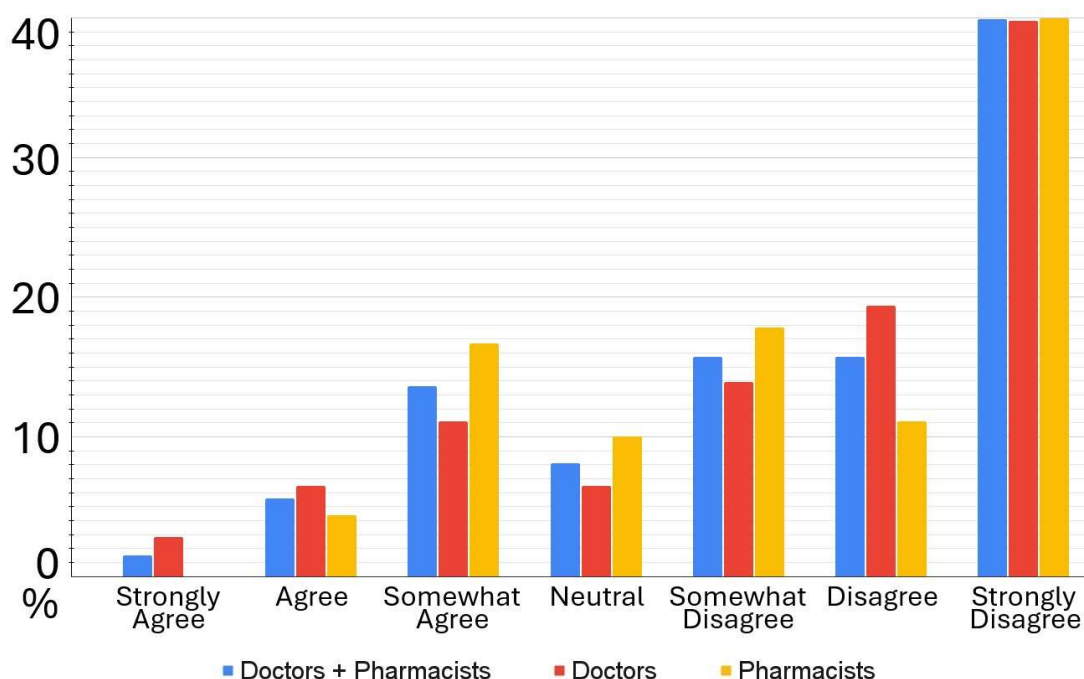


Figure 3.35. Formal education received on medicinal cannabis: separate groups.

I would be interested in attending educational activities to learn more about medicinal cannabis.

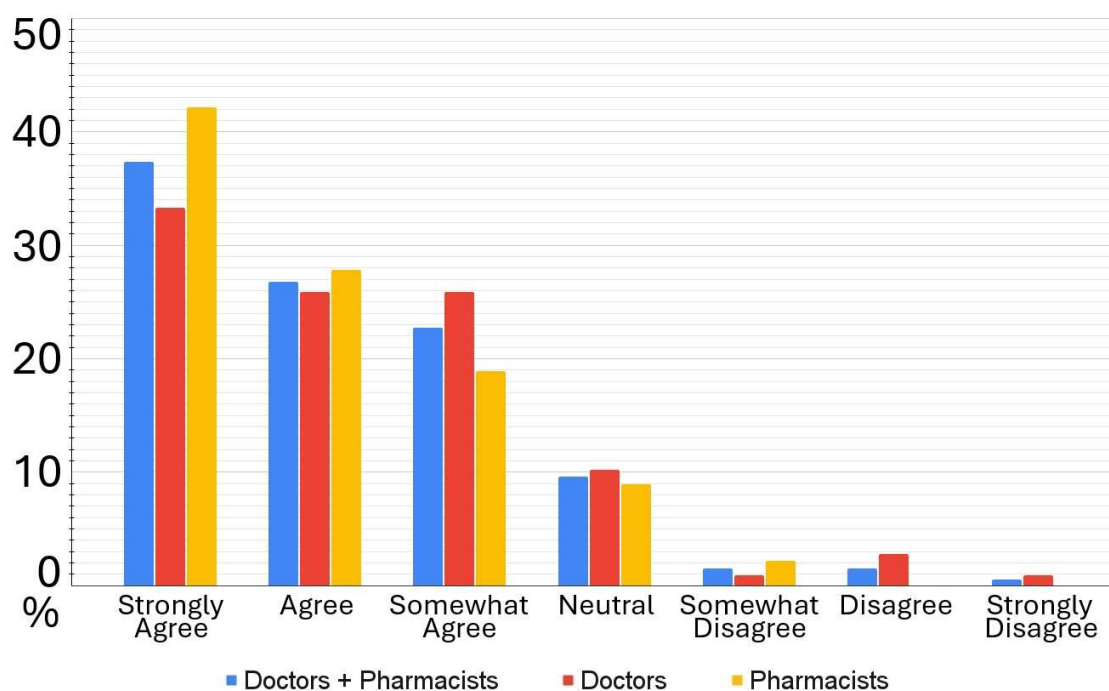


Figure 3.36. Interest in medicinal cannabis educational activities: separate groups.

I do not prescribe medicinal cannabis because it is not an ethical form of therapy.

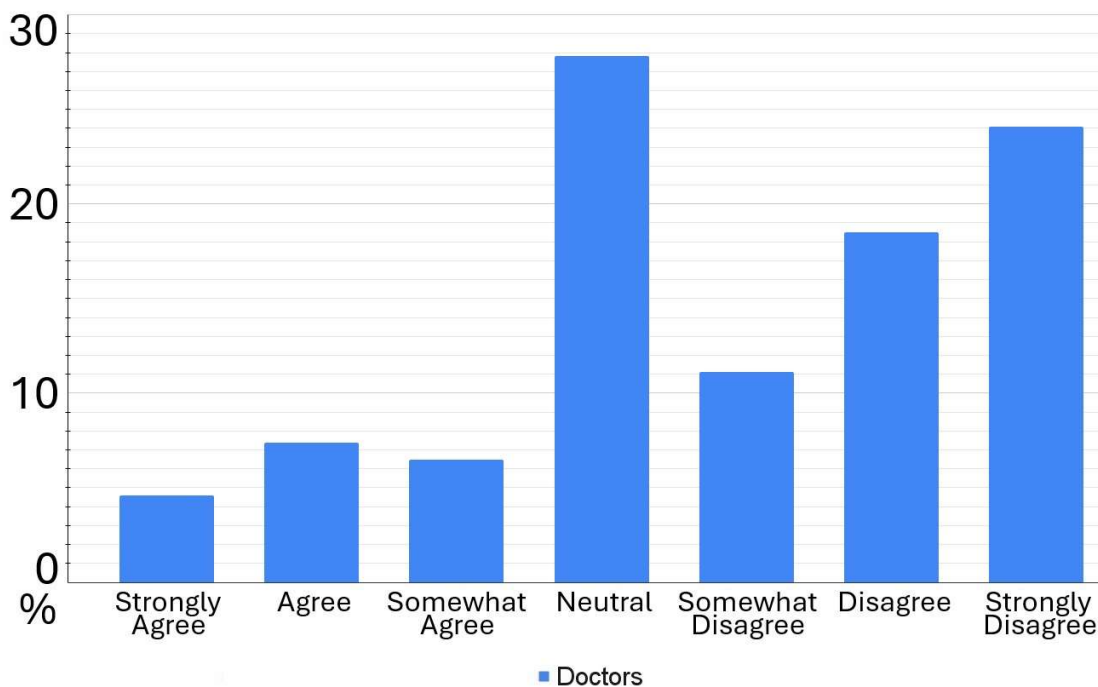


Figure 3.37. *Ethical considerations on medicinal cannabis: doctors only.*

I feel comfortable prescribing medicinal cannabis to patients.

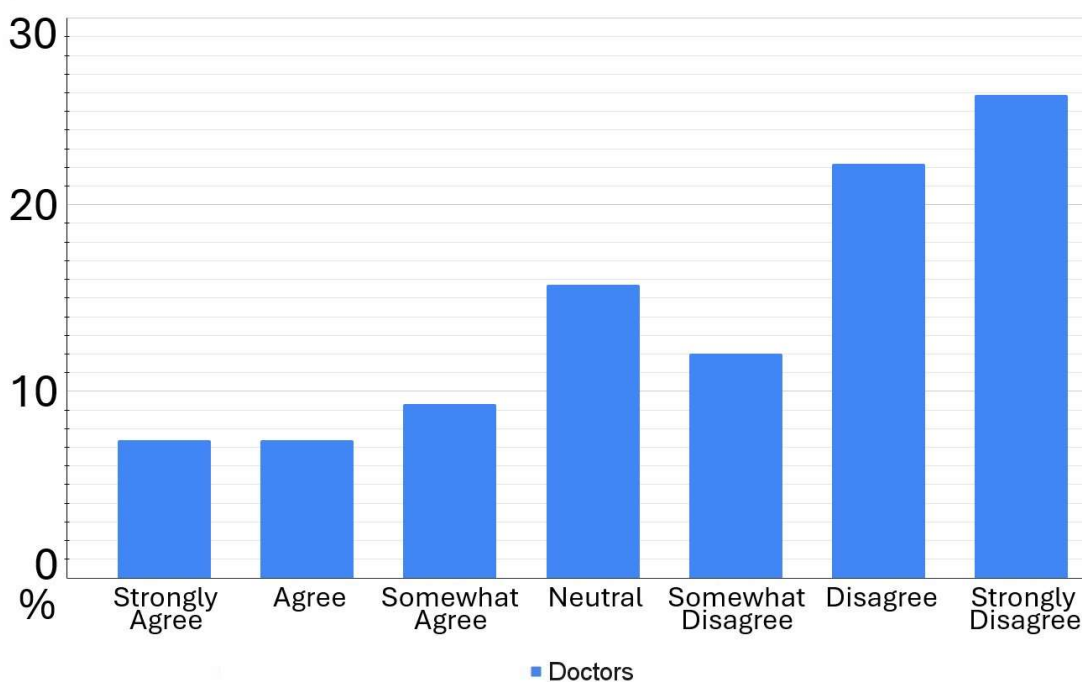


Figure 3.38. *Comfort in prescribing medicinal cannabis: doctors only.*

I do not prescribe medicinal cannabis because the harm caused outweighs the benefit.

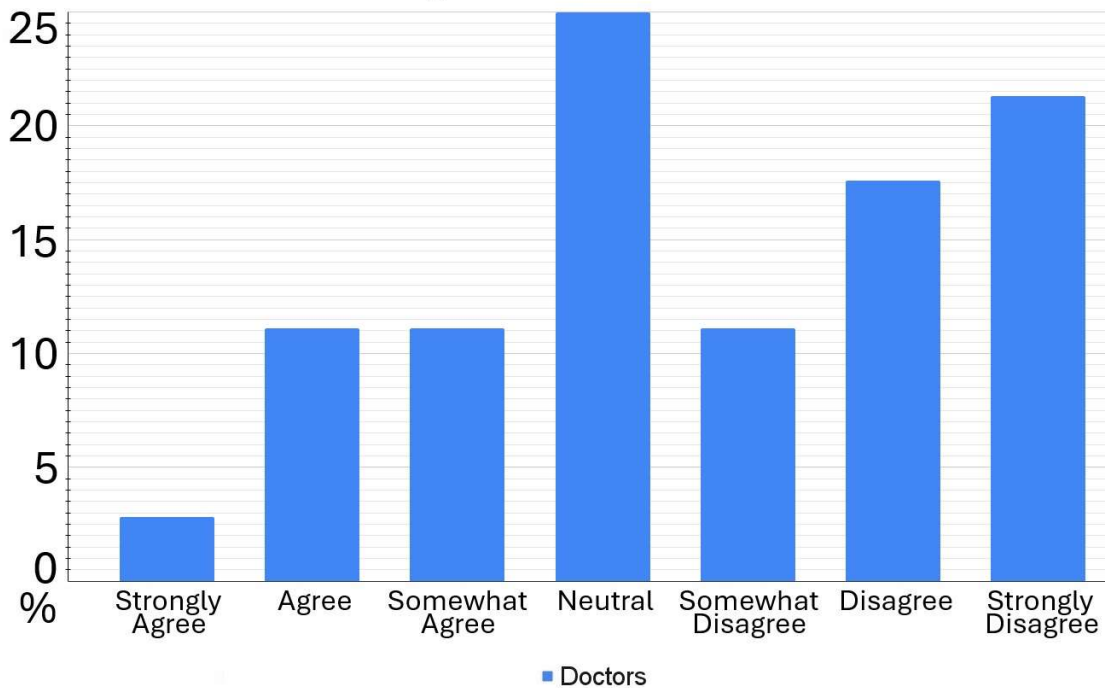


Figure 3.39. *Harm vs benefit in prescribing medicinal cannabis: doctors only.*

I do not prescribe medicinal cannabis because the risk of abuse is higher than for conservative therapy.

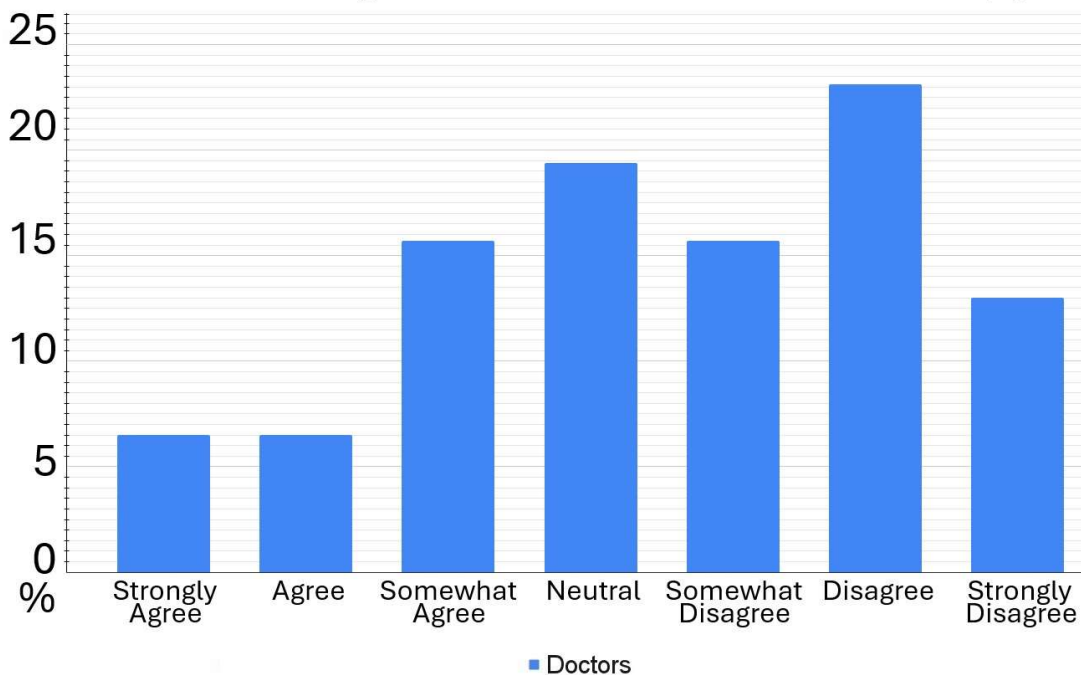


Figure 3.40. *Risk of abuse and dependence in prescribing medicinal cannabis: doctors only.*

I do not prescribe medicinal cannabis because the risk of side effects is higher than for conservative therapy.

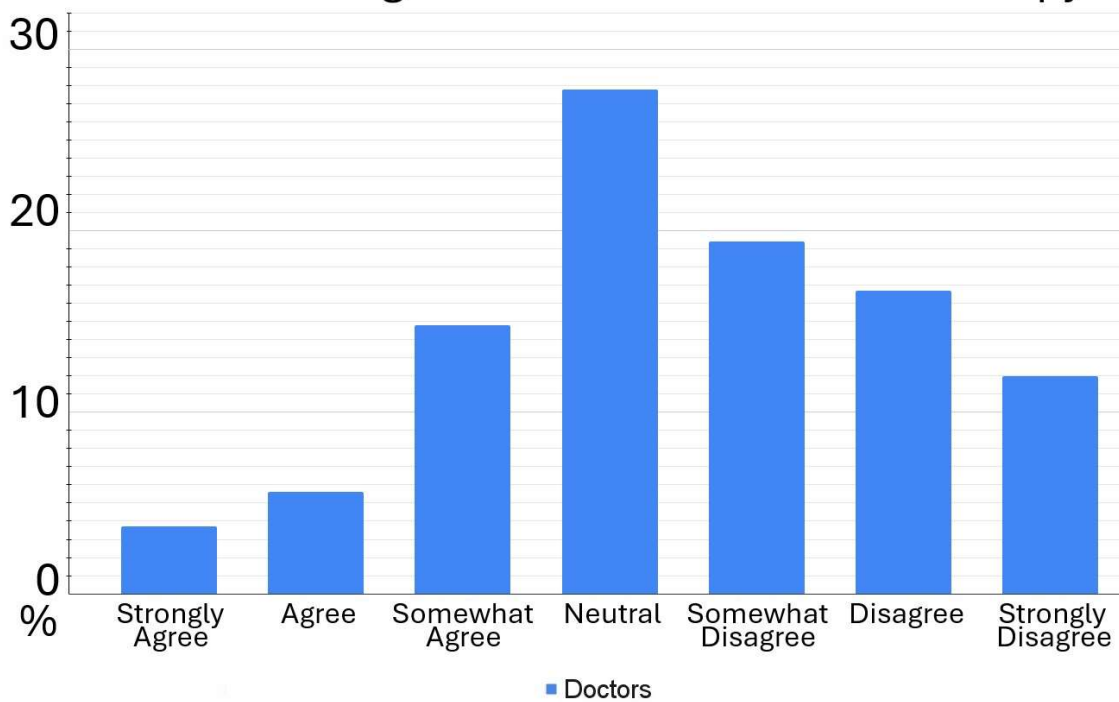


Figure 3.41. Risk of side effects when prescribing medicinal cannabis: doctors only.

3.2.9. Statistical analysis of questionnaire data collected

The questionnaire data were utilized to derive clearer data points and to elucidate any correlations that might shed light on key themes. These themes are considered potentially useful in understanding the current sentiments, beliefs, and attitudes of healthcare professionals in Malta regarding the clinical use of medicinal cannabis. Through rigorous analysis, the study aimed to uncover underlying patterns and associations within the responses, thereby providing insights into professional perspectives on this emerging clinical intervention.

A total of 200 responses were received, however, two records were excluded from the analysis due to incomplete data provision. Specifically, these records lacked age information, a variable considered relevant for the study's objectives. This exclusion ensured that the analytical integrity of the dataset was maintained, enabling more accurate statistical interpretations. The processed data were subjected to a series of robust statistical analyses. An independent samples t-test was employed to compare group means, while Pearson product moment correlation analysis was used to assess the strength and direction of linear relationships between variables. Additionally, hierarchical regression analysis was conducted to explore the predictive power of various factors on the observed outcomes. These analytical methods were chosen to comprehensively examine the interplay among the variables of interest. Below are the results obtained from these analyses, providing a structured overview of the statistical findings and their implications for understanding the clinical use of medicinal cannabis among healthcare professionals in Malta.

The questionnaire responses were separated into five distinct categories: safety, approach, knowledge, education, and prescription attitude. This design enabled

capturing a comprehensive picture of the various dimensions influencing both pharmacists' and doctors' perspectives on medicinal cannabis. Notably, while the safety category was initially included, the responses from both professional groups were so similar that they exhibited a high degree of parity. Consequently, this category was excluded from the detailed statistical analysis, allowing a focus solely on the Likert scale responses from the remaining areas of inquiry. The Approach category, consisting of question 1 and question 2 from the questionnaire (excluding demographic data capture questions), was devised to assess the initial attitude and overall stance toward medicinal cannabis in clinical practice. Meanwhile, the Knowledge category, which encompasses questions 3, 4, 5, 6, 8, and 13, was intended to evaluate the depth and breadth of understanding regarding the pharmacological and therapeutic aspects of medicinal cannabis. The Education category, derived from responses to questions 16, 17, 18, and 20, provided insight into the formal and informal educational experiences that shape the professional perspective on the clinical use of medicinal cannabis. The Prescription Attitude category, including questions 7, 9, 10, 11, and 12, focused on measuring the willingness and readiness of the professional to incorporate medicinal cannabis into clinical prescribing practices. This category could only be measured for doctors due to the inability of pharmacists to issue prescriptions themselves and was therefore only included in analysis reserved for physicians in the tables below. Scores for the category were also reverse scored to create coherence and reliable data outputs. By focusing exclusively on the approach, knowledge, education, and prescription attitude categories, the statistical analysis was able to generate distinct data points that allowed for a detailed comparison between professions. This approach provided valuable insights into how factors such as professional background, age, gender and

individual variable contributions influence the way healthcare professionals relate to and connect with the use of clinical cannabis. The analyses offered an understanding of these relationships, forming a robust basis for future initiatives aimed at aligning educational efforts and policy frameworks with clinical practice.

Although the survey data utilized Likert scales, which are ordinal in nature, parametric analyses including independent samples t-tests were deemed appropriate for this study. This decision was based on the composite nature of the derived scores and the robust sample sizes exceeding 30 participants per group, consistent with the Central Limit Theorem which supports the normality assumption for such distributions.

Furthermore, regarding the interpretation of the data presented in the subsequent tables, it is important to note the directionality of the scoring metrics. For the 'Approach' category, the scoring is inversely keyed. Consequently, higher mean scores are indicative of a less favourable or more negative attitude towards the clinical use of medicinal cannabis.

Variable	Pharmacists (n = 90)		Doctors (n = 108)		<i>t</i> (195.78)	<i>p</i>	95% <i>CI</i>		<i>Cohen's</i> <i>d</i>
	<i>M</i>	<i>SD</i>	<i>M</i>	<i>SD</i>			<i>LL</i>	<i>UL</i>	
Approach	5.19	2.26	6.20	2.88	-2.71	0.006	-1.735	-0.294	-0.4

Table 3.1. *Independent samples t-test for Approach to medicinal cannabis: pharmacists vs doctors.*

The independent samples t-test conducted to compare pharmacists' and doctors' responses regarding their Approach to the clinical use of medicinal cannabis revealed slight but statistically significant differences between the two groups. As illustrated in Table 3.1, the mean scores for doctors (*M*= 6.20, *SD*= 2.88) were marginally lower than those for pharmacists (*M*= 5.19, *SD*= 2.26), indicating that doctors held a less favourable approach toward the clinical use of medicinal cannabis compared to their pharmacist counterparts.

Variable	Pharmacists (n = 90)		Doctors (n = 108)		<i>t</i> (196)	<i>p</i>	95% <i>CI</i>		<i>Cohen's</i> <i>d</i>
	<i>M</i>	<i>SD</i>	<i>M</i>	<i>SD</i>			<i>LL</i>	<i>UL</i>	
Knowledge	24.28	9.06	23.21	9.78	0.79	0.431	-1.598	3.727	0.1

Table 3.2. *Independent samples t-test for Knowledge of medicinal cannabis: pharmacists vs doctors.*

The independent samples t-test conducted to compare pharmacists' and doctors' responses regarding their Knowledge of the clinical use of medicinal cannabis revealed no statistically significant differences between the two groups. As illustrated in Table 3.2, the mean scores for both pharmacists (*M*= 24.28, *SD*= 9.06) and doctors (*M*= 23.21, *SD*= 9.78) were comparable, indicating that both groups possess a similar level of knowledge regarding key aspects of medicinal cannabis, such as its indications, benefits, therapeutic effects, and potential side effects.

Variable	Female (n = 57)		Male (n = 33)		<i>t</i> (88)	<i>p</i>	95% <i>CI</i>		<i>Cohen's</i> <i>d</i>
	<i>M</i>	<i>SD</i>	<i>M</i>	<i>SD</i>			<i>LL</i>	<i>UL</i>	
Approach	5.63	2.21	4.42	2.15	2.51	0.014	0.253	2.160	0.5
Knowledge	25.70	8.73	21.82	9.22	1.99	0.049	0.009	7.758	0.4
Education	8.24	3.20	8.52	3.36	0.71	0.706	-1.684	1.145	-0.08

Table 3.3. *Independent samples t-test for pharmacists assessing gender differences in Approach, Knowledge and Education.*

The independent samples t-test (Table 3.3) conducted to assess gender differences in pharmacists' responses across the Approach, Knowledge, and Education categories indicated no significant differences in Education but revealed differences between male and female pharmacists in their Approach and Knowledge of medicinal cannabis. Male pharmacists demonstrated a more favourable approach toward the clinical use of medicinal cannabis compared to their female counterparts, and they also claimed higher levels of knowledge regarding medicinal cannabis.

Variable	Female (n = 50)		Male (n = 58)		<i>t</i> (106)	<i>p</i>	95% <i>CI</i>		<i>Cohen's d</i>
	<i>M</i>	<i>SD</i>	<i>M</i>	<i>SD</i>			<i>LL</i>	<i>UL</i>	
Approach	6.48	3.26	5.97	2.51	0.925	0.357	-0.588	1.617	0.2
Knowledge	24.08	9.69	22.47	9.88	0.854	0.395	-2.132	5.361	0.2
Education	8.64	3.55	8.64	3.46	0.003	0.998	-1.337	1.341	0.0
Presc. Attitude	18.32	7.39	18.28	7.12	0.032	0.975	-2.728	2.817	0.0

Table 3.4. *Independent samples t-test for doctors assessing gender differences in Approach, Knowledge, Education and Prescription Attitude.*

An independent samples t-test (Table 3.4) was performed to evaluate gender differences in doctors' responses across the Approach, Knowledge, Education, and Prescription Attitude categories, revealing no significant differences between male and female doctors in any of these areas.

(N= 90)

Variables	<i>M</i>	<i>SD</i>	<i>1</i>	<i>2</i>	<i>3</i>	<i>4</i>
1. Age	41.52	10.55	-	-0.07	0.01	-0.03
2. Approach	5.19	2.26		-	0.41***	0.05
3. Knowledge	24.28	9.06			-	-0.16
4. Education	8.34	3.24				-

Note. * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$.

Table 3.5. *Pearson product moment correlation analysis for pharmacists assessing relationship between age, Approach, Knowledge and Education.*

The Pearson product moment correlation analysis was conducted to examine the relationships between pharmacists' age, Approach, Knowledge, and Education in relation to their attitudes toward the clinical use of medicinal cannabis. The results, as presented in Table 3.5, reveal a statistically significant positive correlation between pharmacists' knowledge of medicinal cannabis and their attitude toward its clinical use ($r = 0.41$, $p < 0.001$). The analysis found no significant correlations between pharmacists' age, Approach, or Education and their attitudes toward the clinical use of medicinal cannabis.

(N= 90)

Variables	<i>Male</i>		<i>Female</i>		<i>1</i>	<i>2</i>	<i>3</i>	<i>4</i>
	<i>M</i>	<i>SD</i>	<i>M</i>	<i>SD</i>				
1. Age	42.55	11.14	40.93	10.26	-	-0.02	-0.06	-0.14
2. Approach	4.42	2.15	5.63	2.22	-0.07	-	0.39*	0.21
3. Knowledge	21.82	9.22	25.70	8.73	0.09	0.38**	-	0.24
4. Education	8.52	3.36	8.25	3.20	0.03	-0.01	- 0.40**	-

Note. * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$. Upper diagonal = Male, Lower diagonal = Female

Table 3.6. *Pearson product moment correlation analysis for pharmacists assessing relationship between age, Approach, Knowledge and Education: male vs female.*

A Pearson product moment correlation analysis was conducted to explore the relationships between age, Approach, Knowledge, and Education among male and female pharmacists, with a focus on their attitudes toward the clinical use of medicinal cannabis. As detailed in Table 3.6, the results reveal a significant positive correlation between pharmacists' knowledge of medicinal cannabis and their attitude toward its clinical use for both genders (males: $r=0.39$, $p<0.001$; females: $r=0.38$, $p<0.001$).

(N= 108)

Variables	M	SD	1	2	3	4	5
1. Age	48.69	13.53	-	0.03	-0.11	0.15	0.20*
2. Approach	6.20	2.88		-	0.57***	0.33***	0.68***
3. Knowledge	23.21	9.78			-	-0.23*	0.31**
4. Education	8.64	3.48				-	0.30**
5. Presc. Attitude	18.30	7.21					-

Note. * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$.

Table 3.7. *Pearson product moment correlation analysis for doctors assessing relationship between age, Approach, Knowledge, Education and Prescription Attitude.*

A Pearson product-moment correlation analysis (Table 3.7) was conducted to assess the relationships between age, Approach, Knowledge, and Education in doctors' responses regarding the clinical use of medicinal cannabis. The results revealed several significant correlations, providing valuable insights into the factors influencing doctors' attitudes and behaviours in this context.

A significant positive correlation was found between age and Prescription Attitude ($r = 0.20$, $p = 0.040$). This suggests that older doctors tend to hold less favourable attitudes toward the clinical use of medicinal cannabis. Doctors' Approach toward the clinical use of medicinal cannabis was significantly positively correlated with their Knowledge ($r = 0.57$, $p < 0.001$) and Education ($r = 0.33$, $p < 0.001$). This indicates that doctors with greater knowledge and more favourable educational experiences related to medicinal cannabis are more likely to adopt a positive approach toward its clinical use.

A strong positive correlation was observed between Approach and Prescription Attitude ($r = 0.68$, $p < 0.001$), suggesting that doctors who have a positive approach toward medicinal cannabis are significantly more likely to hold favourable attitudes toward prescribing it. Knowledge of medicinal cannabis was also significantly positively correlated with Prescription Attitude ($r = 0.31$, $p < 0.001$). Education was significantly positively correlated with Prescription Attitude ($r = 0.30$, $p < 0.002$). This indicates that doctors with more favourable educational outlooks regarding medicinal cannabis are more likely to support its clinical use.

($N = 108$)

Variables	<i>Male</i>		<i>Female</i>		<i>1</i>	<i>2</i>	<i>3</i>	<i>4</i>	<i>5</i>
	<i>M</i>	<i>SD</i>	<i>M</i>	<i>SD</i>					
1. Age	52.2	14.1	44.7	11.8	-	0.19	-0.01	0.12	0.34**
2. Approach	6.0	2.5	6.5	3.3	-0.08	-	0.66**	0.24	0.67**
3. Knowledge	22.5	9.9	24.1	9.7	-0.22	0.48***	-	-0.26*	0.32*
4. Education	8.6	3.5	8.6	3.5	0.20	0.42**	-0.18	-	0.29*
5. Presc. Attitude	18.3	7.1	18.3	7.4	0.03	0.71***	0.30*	0.32*	-

Note. * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$. Upper diagonal = Male, Lower diagonal = Female

Table 3.8. *Pearson product moment correlation analysis for doctors assessing relationship between age, Approach, Knowledge, Education and Prescription Attitude: male vs female.*

As presented in Table 3.8, among male doctors, age was found to be significantly positively correlated with Prescription Attitude ($r = 0.34$, $p = 0.009$), indicating that older male doctors tend to hold less favourable attitudes toward the clinical use of medicinal cannabis. This trend was not observed among female doctors, suggesting that age-related differences in attitudes may be more pronounced in male practitioners.

A strong positive correlation was found between Approach and Knowledge for both male ($r = 0.66$, $p < 0.001$) and female doctors ($r = 0.48$, $p < 0.001$). This indicates that, regardless of gender, doctors with greater knowledge about medicinal cannabis are more likely to adopt a positive approach toward its clinical use. Among female doctors, Approach was significantly positively correlated with Education ($r = 0.42$, $p < 0.003$). This suggests that female doctors with more favourable educational experiences or perspectives regarding medicinal cannabis are more likely to maintain a positive approach toward its use. Approach was strongly positively correlated with Prescription Attitude for both male ($r = 0.67$, $p < 0.001$) and female doctors ($r = 0.71$, $p < 0.001$). This underscores the critical role of a positive approach in influencing doctors' willingness to prescribe medicinal cannabis, regardless of gender.

Knowledge of medicinal cannabis was significantly positively correlated with Prescription Attitude for both male ($r = 0.32$, $p < 0.014$) and female doctors ($r = 0.30$, $p = 0.036$). This reinforces the importance of knowledge in fostering favourable attitudes toward the clinical use of medicinal cannabis, with both genders demonstrating a similar trend. Education was significantly positively correlated with Prescription Attitude for both male ($r = 0.29$, $p = 0.030$) and female doctors ($r = 0.32$, $p = 0.025$). This indicates that doctors with more favourable educational outlooks regarding medicinal cannabis are more likely to support its clinical use, regardless of gender. The slightly stronger correlation among female doctors suggests that education may have a marginally greater influence on their prescribing attitudes.

<i>Predictors</i>	<i>B</i>	<i>95% CI</i>		<i>SE B</i>	β	<i>R</i> ²	ΔR^2
		<i>LL</i>	<i>UL</i>				
Step1	-	-	-	-	-	0.04	0.04
Gender	-0.90	-3.738	1.935	1.43	-0.06		
Age	0.11	0.010	0.220	0.05	0.22*		
Step 2	-	-	-	-	-	0.46	0.50
Approach	1.77	1.256	2.281	0.26	0.71***		
Knowledge	-0.05	-0.194	0.099	0.07	-0.06		
Education	0.06	-0.299	0.418	0.18	0.03		

Table 3.9. *Hierarchical regression analysis predicting Prescription Attitude.*

A hierarchical regression analysis (Table 3.9) was carried out to find predictors of Prescription Attitude, Gender and age were added in step 1 as control variables, and Approach towards the clinical use of medicinal cannabis, Knowledge medicinal cannabis, and Education were added in step 2. The 1st model accounted for 4% of variance on Prescription Attitude with $F(2, 105) = 2.345$, $p = 0.101$. The results of the analysis showed that age was found to be a significant predictor of Prescription Attitude among doctors, albeit weak ($\beta = 0.22$, $p = 0.033$, $t = 2.17$). The 2nd model accounted for 46% of variance on Prescription Attitude with $F(5, 102) = 20.66$, $p < 0.001$. The results of the analysis showed that Approach towards the clinical use of medicinal cannabis was found to be a significant predictor of Prescription Attitude among doctors ($\beta = 0.71$, $p < 0.001$, $t = 6.84$). The overall model accounted for 50% of variance on Prescription Attitude.

3.3. Phase 3: Development and validation of educational initiatives

This section reports the findings in relation to the development and validation of the educational programme intended for health care professionals taking into consideration findings from ‘The Healthcare Professionals Questionnaire on use of medicinal cannabis’ and the development and validation of an information leaflet intended for patients on medicinal cannabis.

3.3.1. Educational programme for healthcare professionals

The educational programme developed consisted of 16 lectures aiming to navigate the multifaceted landscape of cannabis in medicine. The learning objectives of the educational programme are to:

- i) educate physicians about their responsibilities when prescribing medicinal cannabis as a therapeutic option
- ii) understand the importance of a judicious approach to enhance patient care.

The topics to be covered delve into the latest advancements in cannabis research, shedding light on the pharmacological properties of cannabis, its potential therapeutic applications, and the clinical evidence supporting its use for specific conditions. Lectures address critical ethical considerations, navigating the complexities of patient autonomy, informed consent, and the potential risks and benefits of cannabis therapy. Legal frameworks governing the use of medicinal cannabis are a focal point, providing physicians with the knowledge necessary to navigate the regulatory environment confidently.

The programme consists of five modules to be covered within the 16 lectures.

The healthcare professionals' educational programme is structured into five distinct modules, each comprising one-hour lectures that address specific aspects of the curriculum.

The modules are:

- A. Introduction to medicinal cannabis
- B. Clinical applications of cannabis
- C. Medical conditions and cannabis therapy
- D. Practical aspects of medicinal cannabis use
- E. Future directions and research

In total, the programme is delivered over 16 one-hour lectures, providing a comprehensive overview of the subject matter. Figure 3.42 details the components of each module, illustrating how the lectures are organized to cover the key topics effectively.

A. Introduction to Medicinal Cannabis

Lecture 1. Historical Context of Cannabis as Medicine

Lecture 2. Understanding the Cannabis Plant and its Components

Lecture 3. Mechanisms of Action in the Body and the Endocannabinoid System

Lecture 4. Adverse Effects and Risk Management

B. Clinical Applications of Cannabis

Lecture 5. Dosage Principles and Considerations

Lecture 6. Different Forms and Delivery Methods of Cannabis

Lecture 7. Overview of Cannabis Varieties and Their Medical Implications

C. Medical Conditions and Cannabis Therapy

Lecture 8. Discussion on Medical Conditions that Might Benefit from Cannabis Use.

Lecture 9. Case Studies and Clinical Evidence Supporting Cannabis Use

Lecture 10. Cannabis in Special Populations (Children, Pregnant Women, Elderly)

D. Practical Aspects of Medicinal Cannabis Use

Lecture 11. Legal and Ethical Considerations in Prescribing Cannabis

Lecture 12. Cannabis in the Workplace and Implications for Healthcare Professionals

Lecture 13. Patient Education and Safety Measures

E. Future Directions and Research

Lecture 14. Emerging Research on Cannabis and Its Compounds

Lecture 15. Integrative Approaches to Cannabis Therapy

Lecture 16. Challenges and Opportunities in Cannabis Medicine

Figure 3.42. *Healthcare professionals' educational programme.*

3.3.1.1. Learning objectives and rationale for each module

Section A. Introduction to Medicinal Cannabis

Lecture 1. Historical Context of Cannabis as Medicine

Rationale: Understanding the historical use of cannabis in various cultures can provide insight into its therapeutic potential and how perceptions of the plant have evolved over time. This context is crucial for appreciating the complexity of current debates around its medical use.

Learning Objectives:

- To explore the historical significance of cannabis in medicine across different cultures and eras.
- To understand the shift in perception of cannabis from a medicinal herb to a regulated substance.
- To recognize the impact of historical context on current medicinal cannabis research and legislation.

Lecture 2. Understanding the Cannabis Plant and its Components

Rationale: A thorough knowledge of the cannabis plant, including its chemical constituents such as cannabinoids and terpenes, is essential for understanding its therapeutic effects and potential medical applications.

Learning Objectives:

- To identify the main components of the cannabis plant, including THC, CBD, and other cannabinoids.
- To understand the roles of terpenes and flavonoids in the therapeutic effects of cannabis.
- To discuss the importance of the entourage effect and how different components interact to enhance medicinal benefits.

Lecture 3. Mechanisms of Action in the Body and the Endocannabinoid System

Rationale: The endocannabinoid system plays a crucial role in regulating various physiological processes. Understanding how cannabis interacts with this system is key to comprehending its therapeutic potential.

Learning Objectives:

- To outline the components of the endocannabinoid system and their functions in the human body.
- To examine how cannabinoids interact with the endocannabinoid system to produce therapeutic effects.
- To discuss the implications of these interactions for treating various medical conditions.

Lecture 4. Adverse Effects and Risk Management

Rationale: While cannabis has therapeutic potential, it is also associated with risks and adverse effects. Medical practitioners need to be aware of these to effectively manage patient care.

Learning Objectives:

- To identify common adverse effects associated with medicinal cannabis use.
- To understand patient risk factors and contraindications for cannabis therapy.
- To develop strategies for monitoring and managing adverse effects in patients using medicinal cannabis.

Section B. Clinical Applications of Cannabis

Lecture 5. Dosage Principles and Considerations

Rationale: Proper dosing is crucial in medicinal cannabis to maximize therapeutic benefits while minimizing adverse effects. Understanding dosing principles is essential for personalized patient care.

Learning Objectives:

- To understand the factors influencing cannabis dosing, including patient tolerance, condition severity, and cannabinoid profiles.
- To learn about titration methods and starting low and going slow.
- To discuss the challenges and strategies in dosing due to the variability of cannabis potency and patient response.

Lecture 6. Different Forms and Delivery Methods of Cannabis

Rationale: The effects of cannabis can vary significantly depending on the form and delivery method, influencing onset, duration, and intensity of effects.

Learning Objectives:

- To compare the pharmacokinetics and pharmacodynamics of different cannabis delivery methods (inhalation, oral, topical, etc.).
- To understand the implications of each delivery method for specific medical conditions.
- To evaluate the pros and cons of each method in clinical practice.

Lecture 7. Overview of Cannabis Varieties and Their Medical Implications

Rationale: Cannabis strains vary in their cannabinoid and terpene profiles, which can influence their therapeutic effects. Knowledge of these variations is important for selecting the appropriate strain for specific conditions.

Learning Objectives:

- To learn about the major cannabis strains (Indica, Sativa, Hybrid) and their general effects.
- To understand how different cannabinoid and terpene profiles can influence medical outcomes.
- To discuss the current evidence and limitations in strain-specific research for medical use.

Section C. Medical Conditions and Cannabis Therapy

Lecture 8. Discussion on Medical Conditions that Might Benefit from Cannabis Use

Rationale: A deep dive into specific conditions allows for a nuanced understanding of how cannabis may alleviate symptoms or affect disease progression, tailored to the complexities of each condition.

Learning Objectives:

- To examine the potential therapeutic effects of cannabis on neurological conditions, mental health disorders, oncological symptoms, and chronic pain.
- To review current research, including clinical trials and epidemiological studies, on cannabis use for these conditions.
- To discuss the limitations and gaps in current research and the need for future studies.

Lecture 9. Case Studies and Clinical Evidence Supporting Cannabis Use

Rationale: Real-world examples and clinical evidence can provide practical insights into the effectiveness of cannabis therapy and inform best practices in patient management.

Learning Objectives:

- To analyze case studies where cannabis has been used to manage symptoms of specific medical conditions.

- To evaluate the strength and implications of clinical evidence supporting cannabis use in treatment protocols.
- To discuss the role of healthcare professionals in monitoring and adjusting cannabis therapy based on patient outcomes.

Lecture 10. Cannabis in Special Populations (Children, Pregnant Women, Elderly)

Rationale: Special populations may have different physiological responses, risk profiles, and ethical considerations when using cannabis for therapeutic purposes.

Learning Objectives:

- To understand the considerations and contraindications of using cannabis in vulnerable populations such as children, pregnant women, and the elderly.
- To review the existing literature and guidelines on cannabis use in these groups.
- To discuss ethical considerations and the importance of informed consent in cannabis therapy for special populations.

Section D. Practical Aspects of Medicinal Cannabis Use

Lecture 11. Legal and Ethical Considerations in Prescribing Cannabis

Rationale: Navigating the legal landscape and ethical responsibilities is crucial for healthcare professionals prescribing cannabis, ensuring compliance and patient safety.

Learning Objectives:

- To understand the legal framework surrounding medicinal cannabis in various jurisdictions.
- To discuss ethical considerations in prescribing cannabis, including patient autonomy, informed consent, and non-maleficence.
- To explore the role of healthcare professionals in advocating for patient access and evidence-based cannabis policies.

Lecture 12. Cannabis in the Workplace and Implications for Healthcare Professionals

Rationale: Healthcare professionals must be aware of the implications of cannabis use in the workplace, including policy, patient care, and professional conduct.

Learning Objectives:

- To review workplace policies regarding medicinal cannabis use, particularly in healthcare settings.
- To discuss the implications of cannabis use for healthcare professionals, including issues related to impairment, confidentiality, and patient safety.
- To explore strategies for addressing cannabis use among healthcare staff and patients within legal and ethical guidelines.

Lecture 13. Patient Education and Safety Measures

Rationale: Effective patient education and safety measures are essential in mitigating risks associated with cannabis use and ensuring optimal therapeutic outcomes.

Learning Objectives:

- To identify key components of patient education on medicinal cannabis use, including dosing, administration, and side effects.
- To discuss strategies for monitoring and managing potential risks and adverse effects in patients using cannabis.
- To emphasize the importance of ongoing patient-provider communication and education in the context of medicinal cannabis therapy.

Section E. Future Directions and Research

Lecture 14. Emerging Research on Cannabis and Its Compounds

Rationale: Staying abreast of the latest research is essential for understanding the evolving landscape of cannabis medicine, including new therapeutic targets and compounds.

Learning Objectives:

- To explore recent discoveries in cannabis research, focusing on novel cannabinoids and their potential medical applications.
- To discuss advancements in understanding the mechanisms of action of cannabis and its components.
- To assess the impact of new research on clinical practice and drug development.

Lecture 15. Integrative Approaches to Cannabis Therapy

Rationale: An integrative approach to cannabis therapy considers the holistic use of cannabis in conjunction with other treatments to optimize patient outcomes.

Learning Objectives:

- To examine how cannabis can be integrated with conventional and alternative therapies for a comprehensive treatment plan.
- To discuss the principles of holistic health in the context of cannabis therapy, including lifestyle, nutrition, and psychological well-being.
- To evaluate the evidence and best practices for using cannabis as part of an integrative treatment approach.

Lecture 16. Challenges and Opportunities in Cannabis Medicine

Rationale: Recognizing the challenges and opportunities in cannabis medicine is crucial for advancing the field and improving patient care.

Learning Objectives:

- To identify the current challenges in cannabis research, regulation, and clinical application.
- To explore opportunities for innovation in cannabis therapeutics, including personalized medicine and technological advancements.
- To discuss the future of cannabis policy and its implications for healthcare professionals and patients.

3.3.1.2. Post-lecture assessment

Incorporating a short post-lecture assessment quiz (Appendix 5), consisting of 10 multiple-choice questions, at the end of each lecture is a strategic approach to enhancing the educational impact of the educational programme. This method serves several crucial functions in both reinforcing learning and ensuring the effective assimilation of knowledge.

The immediate application of acquired knowledge through a quiz helps solidify the information presented during the lecture. It encourages learners to engage with the material actively, promoting better retention of the key concepts and details. This active recall practice is not just about testing but also a powerful learning tool in itself. In addition, the post-lecture assessment serves as a valuable feedback mechanism for both the learners and the educators. For learners, it provides instant feedback on their understanding of the lecture content, helping them identify areas where they might need further review or clarification. This immediate assessment can guide their subsequent study efforts and encourage a more focused review of the lecture materials. For educators, the aggregated results of these quizzes offer insights into how effectively the lecture content is being absorbed by the audience. Patterns in the quiz results can highlight topics that may need to be presented more clearly or revisited in future sessions, ensuring that the lecture series continuously evolves to meet the learners' needs more effectively.

3.3.1.3. Educational programme validation form

The formulation of the educational feedback validation form (Appendix 4), containing carefully crafted evaluation statements, is a crucial step in ensuring the highest quality and effectiveness of a lecture series designed for physicians on the topic of medicinal cannabis. This form is intended for use by external observers, whose expert assessments will play a vital role in refining and validating the content of a hypothetical online lecture series.

The evaluation statements are structured to ascertain whether the lecture series successfully covers the designated topics in a comprehensive, engaging, and coherent manner. They are designed to assess the relevance of the content to current professional practices, the incorporation of recent advancements in the field, and evaluation of the lecture topics' ability to foster critical thinking and navigate the complex ethical and cultural dimensions of medicinal cannabis use.

This validation process, underpinned by the insights from external observers, is essential for ensuring that the lecture series not only meets educational standards but also effectively equips physicians with the knowledge and skills necessary for the judicious prescription of medicinal cannabis. This, in turn, will contribute to improved patient outcomes and the responsible integration of cannabis therapy into medical practice.

3.3.1.4. Educational programme validation feedback

The feedback received from the expert panel on the proposed educational lecture series reflects strong approval of the structure and content outlined. All expert responses received reflected unanimous agreement with each of the nine statements presented in the feedback form, signaling a positive reception of the program.

Firstly, the panel confirmed that the lecture series is well-organized, with a clear progression from introductory to advanced topics. This structured approach is crucial for facilitating understanding, especially in a complex field like medicinal cannabis where practitioners may have varying levels of prior knowledge. The clear progression ensures that foundational concepts are established before delving into more intricate subjects. The experts also agreed that the lecture series structure enhances learning and engagement. An engaging structure is vital for maintaining the attention of healthcare professionals, encouraging active participation, and promoting better retention of information. This positive feedback suggests that the series is designed to be interactive and thought-provoking, which can lead to more effective learning outcomes. Regarding content relevance, the panel found that the rationale delineated for each section is relevant and logical. This means that each part of the series is purposefully crafted to build upon the previous one, ensuring that the information is not only current but also pertinent to clinical practice. Logical sequencing of topics helps in reinforcing learning and aids in the practical application of knowledge.

The clarity and achievability of the learning objectives for each lecture were also affirmed. Clear objectives are essential for guiding learners through the educational process and providing measurable goals. The experts' agreement indicates that the objectives are well-defined and attainable, which can enhance the confidence of

healthcare professionals in integrating medicinal cannabis into their practice. An emphasis on ample coverage of background themes for gradual instructional development was appreciated by the panel. Thorough background information lays the groundwork for understanding more advanced concepts, ensuring that all participants, regardless of their initial familiarity with the subject, can benefit from the series. The series was commended for providing a comprehensive overview of the practical aspects of medicinal cannabis use. Practical knowledge is indispensable for healthcare professionals who will be making real-world decisions regarding patient care. The experts' approval suggests that the series effectively bridges the gap between theory and practice.

Prioritization of risk management and safety measures was another area where the series received unanimous support. Addressing potential risks and emphasizing patient safety are critical components of any medical education, particularly in areas involving controlled substances. This focus reassures that the series promotes responsible prescribing practices. The inclusion of ethical considerations in the use of medicinal cannabis was also positively noted. Ethical guidelines help practitioners navigate the moral complexities that can arise in clinical scenarios. By incorporating these discussions, the series demonstrates a commitment to holistic education that respects both legal frameworks and patient rights. The experts also agreed that the lectures contemplate future advancements in the field, discussing research and challenges. This forward-thinking approach prepares healthcare professionals to stay informed about emerging trends, new evidence, and potential obstacles in the evolving landscape of medicinal cannabis.

3.3.2. Patient information leaflet

The patient information leaflet (Appendix 6) was structured to provide a comprehensive overview of medicinal cannabis, ensuring that patients receive balanced, accurate, and easily digestible information. An introductory section familiarizes the reader with medicinal cannabis, providing a brief, targeted overview. Subsequent sections detail various administration modalities, informing patients about the different methods through which medicinal cannabis can be consumed. The leaflet also outlines the primary benefits of medicinal cannabis, specifically its common prescriptions for conditions like multiple sclerosis spasticity, chemotherapy-induced nausea and vomiting, appetite stimulation, epilepsy, and chronic pain. In addition, it highlights other potential therapeutic uses that are still under investigation, including its impact on sleep disorders, movement disorders, and anxiety. This dual focus on established and emerging evidence aims to provide a balanced view of the drug's therapeutic potential.

To ensure the safe use of medicinal cannabis, the leaflet emphasizes the correct approach to treatment. It advises that patients should first be assessed by a qualified medical professional, and, once a prescription is obtained, underscores the importance of proper administration and regular monitoring to assess the effectiveness of the therapy. This section aims to promote a cautious and systematic approach to treatment. The leaflet discusses potential risks and side effects. It addresses specific vulnerabilities, such as the heightened risk for individuals with psychological conditions, cardiovascular disease, or younger individuals whose brains are still developing. Side effects such as insomnia, drowsiness, reduced perception, impaired responsiveness, and anxiety are also clearly outlined, providing patients with essential

warnings regarding the safe use of medicinal cannabis. Special considerations are also covered, including the risks of dependency and addiction, issues related to driving, and concerns during pregnancy. This section is designed to inform patients about the broader implications of using medicinal cannabis beyond its primary therapeutic effects. The patient information leaflet also emphasizes the importance of obtaining medicinal cannabis from reliable sources. It cautions patients against unverified online sources and emphasizes the necessity of seeking professional medical advice. The leaflet advises patients to remain critical of online information due to the potential for misinformation and commercial biases. It also stresses the ongoing nature of research in this field, reminding patients to monitor any changes in their condition and to seek immediate medical attention if adverse effects occur.

The patient information brochure has been meticulously conceived and developed, adhering to the principles of the Baker Able Leaflet Design (BALD) criteria. This comprehensive approach ensures that the brochure is not only informative but also accessible and user-friendly for its intended audience. The BALD criteria, a cornerstone in the design of effective health communication materials, emphasizes key elements such as clarity of language, engaging layout, and the thoughtful use of visual aids to enhance understanding.

By employing the BALD criteria, the ease of readability and the overall aesthetic appeal of the brochure were prioritized, ensuring that critical health information is conveyed in a manner that is both engaging and easy to comprehend. This methodological approach encompasses a careful consideration of factors such as the length of text lines, the spacing between lines, the size and type of fonts used, and the

strategic use of white space to create a visually appealing and reader-friendly document.

Furthermore, the BALD criteria guide the selection of paper quality and the overall design characteristics, ensuring that the physical attributes of the brochure contribute positively to the user's experience. The patient information brochure should be a commitment to responsible patient care providing information that is not only informative but also empowering, enabling readers to make informed health decisions with confidence. The objective of the brochure is to bridge the gap between complex medical information and patient understanding, facilitating a better healthcare experience for all.

3.3.2.1. Patient information leaflet validation form

The validation process undertaken by the expert panel aimed at assessing the leaflet's content, design and overall effectiveness in terms of clarity and relevance for its intended audience, the patients. The inclusion of the evaluation statements in the patient information leaflet validation form (Appendix 6) is grounded in the principle that effective patient communication is paramount in healthcare. A well-designed patient information leaflet not only delivers essential information but also empowers patients to make informed decisions about their health. Therefore, the feedback gathered through this form played a pivotal role in identifying areas of strength and opportunities for improvement.

3.3.2.2. Patient information leaflet validation feedback

The expert panel's feedback on the patient information brochure designed to educate patients about the judicious and responsible use of prescribed medicinal cannabis was overwhelmingly positive. All expert opinions received were unanimous in agreeing with each of the 13 statements presented in the feedback form, indicating strong approval of the brochure's content, design, and overall effectiveness.

The panel confirmed that the leaflet clearly identifies its target audience and that its purpose is clearly stated and easy to understand. This suggests that the brochure effectively communicates its intent and is tailored appropriately for patients who may benefit from medicinal cannabis. The clarity in audience identification and purpose is crucial for ensuring that the information reaches and resonates with the intended readers. The experts agreed that the language and terminology used are appropriate for the intended audience, avoiding medical jargon and explaining any terms that might be unfamiliar to the general public. This accessibility in language ensures that patients of varying educational backgrounds can comprehend the information, which is essential for promoting responsible use and adherence to medical guidance. Accuracy and relevance of health information were also affirmed by the panel, highlighting that the brochure provides trustworthy content consistent with current best practices and guidelines in healthcare. The logical and coherent order of information presentation facilitates understanding, allowing patients to follow the content smoothly from one section to the next.

Key messages and instructions are highlighted effectively, which is important for emphasizing critical points such as possible side effects, potential risks, and the necessity for monitoring by a medical professional. The use of visual aids was also

commended, as they enhance understanding and can make complex information more digestible for readers. In terms of design elements, the experts noted that the font size and style are easy to read, with sufficient contrast between the text and background. The layout, including the use of white space, headings, and bullet points, facilitates easy navigation through the content. These design choices contribute to the overall readability of the brochure, ensuring that patients can easily find and focus on the information most relevant to them. The presence of a clear call-to-action encourages readers to seek further advice from healthcare professionals. This is a critical component, as it promotes ongoing dialogue between patients and providers, ensuring that patients remain informed and supported throughout their treatment.

3.4. Phase 4: Medicinal Cannabis in Clinical Trials

Protocols for the clinical use of a medication serve as comprehensive guides that outline the standards for prescribing, administering, and managing a therapeutic regimen. Specifically for medicinal cannabis, these protocols encompass detailed instructions regarding dosage, delivery methods, potential interactions with other medications, monitoring and reporting of outcomes, and adjustments based on patient responses. They are meticulously developed based on rigorous research, clinical trials, and consensus among medical experts, ensuring that they are grounded in the most current scientific evidence and best practices.

The necessity for such protocols stems from several critical considerations. First and foremost, they provide a foundational layer of safety for patients by standardizing treatment approaches to minimize risks and optimize benefits. Given the complex nature of medicinal cannabis, which involves multiple active compounds with varying

effects, precise guidelines help in tailoring treatments to individual patient needs while ensuring safety and efficacy.

For medical practitioners, these protocols serve as essential tools that support clinical decision-making. They offer evidence-based recommendations that guide physicians in choosing the appropriate formulation, dosage, and administration route for medicinal cannabis, tailored to the specific therapeutic needs and medical history of each patient. This is particularly crucial given the diverse array of cannabis-based products and the broad spectrum of conditions for which they may be prescribed.

Moreover, well-defined protocols facilitate consistency in treatment approaches across different healthcare providers and settings, ensuring that patients receive uniform care standards regardless of where they are treated. This consistency is vital for maintaining the quality of care and for the systematic evaluation of treatment outcomes, contributing to the broader body of medical knowledge on the efficacy and safety of medicinal cannabis.

Additionally, for stakeholders such as policymakers, insurers, and regulatory bodies, these protocols provide a clear framework that informs policy development, coverage decisions, and regulatory oversight. By aligning clinical practices with current evidence and regulatory standards, protocols help in navigating the complex legal and ethical landscape surrounding medicinal cannabis, ensuring that patient care is not only effective and safe but also compliant with legal requirements.

3.4.1. Rationale for Guidelines

The rationale for researching, compiling, and validating protocols for the clinical use of medicinal cannabis is multifaceted and grounded in the compound's complex pharmacology, its therapeutic potential, and the imperatives of ensuring patient safety, navigating regulatory environments, and achieving standardization in medical practice. This comprehensive approach is essential for harnessing the medicinal properties of cannabis within a framework that prioritizes efficacy, safety, and regulatory compliance.

3.4.1.1. Biochemical composition

The intricate nature of cannabis, with its array of over 500 distinct molecules, including roughly a hundred that fall within the cannabinoid category, underscores the plant's complex pharmacological landscape. Predominant among these are THC and CBD, both of which have garnered significant attention for their potential therapeutic properties. THC is renowned for its psychoactive effects, contributing to the "high" associated with cannabis use, while CBD is non-psychoactive and has been studied for its potential in treating conditions such as anxiety, epilepsy, and inflammation.

This molecular diversity is at the heart of cannabis's therapeutic versatility but also presents considerable challenges. The effects of cannabinoids are not straightforward; they can vary dramatically depending on their concentration, the presence of other compounds, and the individual's unique physiology. For instance, minor variations in the molecular structure of cannabinoids can alter their affinity for cannabinoid receptors in the body, leading to significantly different pharmacological effects. This highlights the necessity for thorough research to delineate the pharmacodynamics (the

effects of the drug on the body) and pharmacokinetics (the body's effect on the drug, including absorption, distribution, metabolism, and excretion) of these compounds.

Understanding the pharmacodynamics of cannabinoids is crucial for unravelling how they interact with the endocannabinoid system. Cannabinoids like THC and CBD can mimic or influence the behaviour of endogenous cannabinoids, potentially modulating a wide range of physiological and cognitive processes, including pain sensation, mood, appetite, and memory. Pharmacokinetics, on the other hand, sheds light on the optimal routes of administration, dosing, and the potential for drug interactions. For instance, the bioavailability of THC and CBD can vary significantly depending on whether the cannabis product is ingested, inhaled, or applied topically, impacting the onset, intensity, and duration of effects. Furthermore, factors like the metabolism of cannabinoids in the liver and their interaction with other medications can profoundly influence their efficacy and safety profile.

Given these complexities, rigorous scientific research is essential to establish evidence-based guidelines for the clinical use of cannabis. Such research not only aids in maximizing the therapeutic potential of cannabis but also in mitigating risks, ensuring patient safety, and informing regulatory policies. The goal is to harness the medicinal properties of cannabis within a framework that prioritizes efficacy, safety, and patient well-being, navigating the intricacies of its molecular diversity with precision and care.

3.4.1.2. Therapeutic potential of medicinal cannabis

Historically, cannabis has been used for its medicinal properties, with records dating back to ancient China (Russo, 2004; Russo, 2007). Modern science has begun to uncover its potential for treating a variety of conditions, such as chronic pain, epilepsy, and multiple sclerosis, among others. The expanding body of evidence supporting the medicinal use of cannabis underscores the urgent need for standardized clinical protocols. These protocols are crucial for guiding healthcare providers in the responsible prescription of medicinal cannabis, ensuring that patients receive safe, effective, and evidence-based treatments. By formalizing these guidelines, the medical community can offer consistent care, optimizing therapeutic outcomes while minimizing risks associated with cannabis use.

3.4.1.3. Drug safety and efficacy

The imperative to balance the safety and efficacy of cannabis use in medicinal contexts arises from its associated adverse effects, which can range from mild symptoms like sedation and dizziness to more concerning ones such as anxiety and cognitive dysfunction. These potential side effects highlight the necessity for meticulously crafted dosing guidelines that aim to harness the therapeutic advantages of cannabis while curtailing its risks.

The development of personalized dosage escalation regimens is a cornerstone of these efforts. Such regimens are tailored to the individual, taking into account not only the patient's specific health condition but also the type and formulation of the cannabis product being used. This personalized approach is pivotal because it acknowledges

the variability in how individuals metabolize and respond to cannabis, thereby optimizing therapeutic outcomes and minimizing adverse effects.

Moreover, the establishment and validation of clinical protocols for cannabis administration play a crucial role in providing healthcare professionals with a structured framework to guide their practice. These protocols are built on a foundation of scientific evidence and clinical expertise, offering clear guidelines on starting dosages, titration schedules, and monitoring parameters. They also provide insights into selecting the appropriate formulation and route of administration based on the patient's condition, preferences, and treatment goals.

Such guidelines are vital for clinicians, as they navigate the complexities of prescribing medicinal cannabis in a landscape where the therapeutic benefits must be weighed carefully against the potential for harm. By adhering to these evidence-based protocols, healthcare providers can ensure a consistent and rational approach to cannabis use in the clinical setting, thereby safeguarding patient welfare and optimizing the medicinal potential of cannabis.

3.4.1.4. Regulatory considerations

The legal landscape surrounding medicinal cannabis varies widely across different countries and jurisdictions, directly impacting both the clinical application and research into cannabis-based therapies. In some regions, medicinal cannabis is fully legal and integrated into healthcare systems, while in others, it remains heavily restricted or outright prohibited. This variability presents significant challenges for healthcare providers, researchers, and patients.

For healthcare providers, navigating these legal frameworks is crucial to ensure that their prescriptions of medicinal cannabis comply with local laws and regulations. This compliance is not only a matter of legal necessity but also crucial for maintaining professional integrity and patient trust. Providers must stay informed about the legal status of various cannabis products in their jurisdiction, including which forms of cannabis are permitted for medical use, the conditions for which it can be prescribed, and the required documentation and approvals.

For researchers, legal constraints can significantly influence the scope of clinical studies on cannabis. In regions where medicinal cannabis is heavily regulated or illegal, conducting rigorous clinical trials can be fraught with hurdles, from obtaining the necessary licenses to recruit participants and secure funding. These legal barriers can stymie the advancement of knowledge around cannabis, limiting our understanding of its efficacy, safety, and potential therapeutic applications.

The compilation and validation of clinical protocols within the framework of these legal boundaries are therefore essential. Such protocols serve not only as a guide for best practices in the clinical use of cannabis but also as a tool for aligning medical practices with the law. They provide a structured approach to prescribing and administering cannabis, ensuring that healthcare professionals can offer this treatment option to patients safely and legally.

Furthermore, standardized clinical protocols can support advocacy for policy changes by providing evidence-based practices that demonstrate the safe and effective use of medicinal cannabis. By showcasing the potential benefits and minimized risks through well-structured protocols, stakeholders can influence policymakers to reconsider

restrictive regulations and their stipulated local legislation, potentially expanding access to medicinal cannabis for patients in need.

3.4.1.5. Quality assurance

The diversity within the realm of medicinal cannabis, characterized by a broad spectrum of strains, product formulations, and modes of administration, presents substantial challenges in achieving standardization and ensuring quality control. This diversity stems from the plant's complex biochemistry, which gives rise to various cannabinoids and terpenes, each with unique effects and potential therapeutic benefits. Consequently, medicinal cannabis products can vary widely in their composition and potency, leading to inconsistencies in patient responses and treatment outcomes.

The establishment of validated clinical protocols is a pivotal step toward addressing these challenges. Such protocols serve as a cornerstone for setting industry-wide benchmarks for product quality, ensuring that all medicinal cannabis products meet stringent standards for purity, consistency, and cannabinoid composition. This not only safeguards patients from substandard products but also provides a foundation for clinicians to base their prescribing decisions on.

Moreover, standardized dosing guidelines are integral to these protocols, offering precise recommendations for the administration of medicinal cannabis. Given the variable potency and effects of different cannabis strains and products, these guidelines play a crucial role in mitigating risks associated with overdosing or underdosing, thereby enhancing the safety and efficacy of treatments.

The mode of administration is another critical aspect covered by these protocols. Medicinal cannabis can be consumed in various forms, including but not limited to oral, inhalation, topical, and sublingual routes. Each method has its own pharmacokinetic profiles, influencing the onset, duration, and intensity of the therapeutic effects. Protocols provide clarity on the most appropriate administration routes for specific conditions and patient needs, taking into account factors such as the desired speed of onset and the potential for side effects.

The rigorous standardization facilitated by validated protocols is not only beneficial for patient care but also vital for advancing clinical research. Consistent treatment methodologies allow for the collection of reliable data across studies, enhancing the robustness of clinical trials. This, in turn, contributes to a more comprehensive understanding of the therapeutic potential of medicinal cannabis, paving the way for its integration into mainstream healthcare.

In essence, the development and adherence to validated clinical protocols in medicinal cannabis use are indispensable for ensuring that patients receive high-quality, effective, and safe treatments. These protocols act as a blueprint for harmonizing practices across the medicinal cannabis industry, healthcare providers, and research institutions, ultimately contributing to the optimization of therapeutic outcomes and the broader acceptance of medicinal cannabis within the healthcare ecosystem.

3.4.2. Conditions and dosing

In clinical settings, determining the optimal dosing of cannabis is complex and is influenced by individual patient factors including body weight, the specific condition being treated, the presence of other medications, and individual tolerance and response to cannabis. The variability in cannabis plant composition and the lack of standardization in cannabinoid concentrations further complicate dosing considerations. The aim is to provide a critical overview of both the potential benefits and the challenges associated with the therapeutic use of cannabis, including the safety profiles, potential for adverse effects, and the impact of long-term use. Through a detailed analysis of current and historical research in the field, exploring clinical trials which have investigated the efficacy of cannabis in managing psychiatric disorders like PTSD, OCD and mood disorders such as anxiety and depression; neurodegenerative diseases including Alzheimer's disease, Huntington's disease, multiple sclerosis, amyotrophic lateral sclerosis ALS, and Parkinson's disease; as well as inflammatory bowel disease (IBD), palliative care, sleep disorders, epilepsy, cancer and eating disorders, it will be easier to get a panorama of the variety of dosages and approaches used in different contexts to manage such conditions.

3.4.2.1. Chemotherapy-induced nausea and vomiting

Chemotherapy-induced nausea and vomiting (CINV) remain among the most distressing and common side effects faced by cancer patients undergoing chemotherapy. The management of these symptoms is critical not only for the comfort but also for the overall health and treatment compliance of patients. Recent advances in pharmacological therapies have led to the development of various antiemetics which

have significantly improved the control of these symptoms. However, not all patients achieve full relief with standard treatments. This has propelled interest in alternative treatments, among which medicinal cannabis has emerged as a potential adjunct therapy. This introduction aims to explore the relevance and potential clinical uses of medicinal cannabis in managing chemotherapy-induced nausea and vomiting, drawing on a range of scientific studies and clinical trials.

Several clinical trials and studies have evaluated the efficacy of cannabis and its derivatives for treating CINV. A seminal study by Badoeski (2017) found that cannabinoids could be more effective than conventional dopamine receptor antagonists when used as adjunctive treatment (Badoeski, 2017). Similarly, an analysis presented by Bodine and Kemp (2024) demonstrated that patients receiving cannabinoids experienced a significant reduction in nausea and vomiting compared to those who were administered a placebo (Bodine & Kemp, 2024).

Mersiades et al. (2017) explored the outcomes of 30 randomized comparisons involving 2,960 participants. This review concluded that all but one of these trials showed a preference for cannabinoids over conventional antiemetics. However, the authors cautioned about the variability in trial outcomes, suggesting a need for more standardized and well-controlled studies. Grimison et al. (2020) compared different strains of medicinal cannabis and their effects on CINV. It was found that strains higher in CBD content were particularly effective in reducing symptoms without the psychoactive effects associated with THC. The comparative effectiveness of cannabinoids has also been a subject of research. Shah et al. (2021) discuss a trial where patients were administered either cannabinoids or ondansetron, a well-established antiemetic. The results indicated that cannabinoids were as effective as

ondansetron in preventing nausea and vomiting among patients with no prior experience with either treatment (Shah et al., 2021).

The management of Chemotherapy-Induced Nausea and Vomiting (CINV) is pivotal in maintaining the quality of life and treatment adherence in cancer patients. While traditional medications have been the cornerstone of treatment, recent explorations into the effectiveness of medicinal cannabis present a potential alternative or adjunct therapy.

3.4.2.1.1. Recommended dosages in current literature

The management of chemotherapy-induced nausea and vomiting remains a significant challenge in clinical oncology. Medicinal cannabis has been identified as a potential alternative to conventional antiemetics, with various studies suggesting different efficacies and dosages (Table 3.10). Appropriate dosing of medicinal cannabis is crucial to maximizing its efficacy and minimizing potential side effects in the treatment of chemotherapy-induced nausea and vomiting.

Machado Rocha et al. (2008) provided a thorough review of randomized clinical trials involving various cannabinoids. The studies typically employed doses of dronabinol around 10 mg/m² to combat nausea and vomiting, revealing that this dosage could effectively reduce symptoms when compared to placebo and various neuroleptics. Similarly, nabilone was often administered in doses ranging from 1 to 2 mg, which were found to be effective in several trials included in their meta-analysis. Less commonly, Levonantradol was used at doses between 0.5 mg to 1.0 mg and was part of the broader examination into its comparative effectiveness against neuroleptics. In

their systematic review, Tramèr et al. (2001) focused on quantifying the antiemetic efficacy and side effects associated with cannabis. They included data from studies using oral forms of nabilone and dronabinol, alongside intramuscular Levonantradol. Their findings supported the use of these cannabinoids, with dosages of dronabinol typically ranging from 5 mg to 10 mg, administered up to three times daily depending on the specifics of the chemotherapy protocol. For nabilone, a standard regimen involved 1 mg to 2 mg taken twice daily. Levonantradol, though used less frequently, was effective at doses of approximately 0.5 mg to 3 mg administered intramuscularly. Both sets of researchers found that cannabinoids could be more effective than conventional antiemetics in some cases. The studies reviewed by Machado Rocha et al. showed that cannabinoids generally had a higher efficacy in controlling CINV than placebo and could perform better than some traditional drugs under certain conditions. Tramèr et al. also noted significant efficacy of cannabinoids, with the added benefit that many patients preferred these treatments for future chemotherapy cycles due to better overall management of symptoms and fewer adverse effects compared to other antiemetics.

Smith et al. (2015) carried out a systematic review focusing on randomized controlled trials that compared cannabis-based medications against traditional antiemetics or a placebo. The review covered various dosages of nabilone and dronabinol used in clinical settings. nabilone was often administered at doses of 1-2 mg twice daily. dronabinol dosage varied more significantly, but a common regimen was 5 mg/m² to 15 mg/m², administered multiple times per day depending on the chemotherapy protocol. This review highlighted that cannabis-based medications generally provided better control of nausea and vomiting than placebos and were favoured by patients despite some experiencing notable side effects such as dizziness and a sensation of

feeling high. This preference suggests that patients might prioritize effective nausea control over the potential discomfort caused by side effects. In 2018, Mersiades et al. described the use of a THC/CBD cannabis extract in oral capsule form. Patients participating in the study were given capsules containing equal parts of THC and CBD, each component at 2.5 mg, administered three times a day. This regimen started one day before and continued until five days after the chemotherapy sessions. This study's findings supported the efficacy of this balanced THC/CBD approach in reducing episodes of nausea and vomiting, potentially offering a more favourable side effect profile compared to treatments with higher concentrations of THC alone. Grimison et al. (2020) further explored the THC:CBD ratio in a crossover study involving 72 patients who were already receiving standard antiemetic therapy. Each patient received capsules containing 2.5 mg of THC and 2.5 mg of CBD, taken three times daily from the day before to five days after chemotherapy. This regimen notably improved the control of nausea and vomiting, highlighting the therapeutic potential of combining THC and CBD in equal measures to mitigate CINV effectively while keeping adverse effects to a minimum.

According to Todaro (2012), nabilone is typically administered as 1 mg orally, taken twice daily, with dosages ranging from 1 to 2 mg. It's recommended that the first dose be administered one to three hours before chemotherapy to minimize nausea and vomiting, possibly extending up to 48 hours post-chemotherapy. The maximum daily dosage suggested is 2 mg to prevent excessive side effects. Dronabinol's administration involves more flexibility in dosing, ranging from 5 mg/m² to a maximum of 15 mg/m², depending on patient response and side effect profile. The initial dose should ideally be administered after a 10-hour fast and at least 30 minutes before any

Authors	Study	Pts	Age	Dose	Delivery	Follow-up	Outcomes
Sallan et al. (1975)	Randomized cross-over	22	18-76	15mg 1 st ; 10mg/m ² / 4 hours (3 doses)	Oral (dronabinol)	Chemo cycle duration	THC significantly reduced nausea and vomiting compared to placebo; side effects included euphoria and dizziness.
Chang et al. (1979)	Randomized cross-over	15	15-49	10mg/m ² / 3 hours (5 doses); 17.4mg THC (inhalation) if vomiting	Oral (dronabinol); Inhalation (THC)	Chemo cycle duration	THC significantly reduced the number of vomiting and retching episodes, the degree and duration of nausea, and the volume of emesis compared to placebo.
Ekert et al. (1979)	Randomized cross-over	19	-	Unspecified	Oral (THC)	-	THC was superior to metoclopramide for nausea control but caused dizziness and mild euphoria.
Frytak et al. (1979)	RCT	116	61 $\bar{x}$	15mg TDS	Oral (dronabinol)	Chemo cycle duration	THC showed superior antiemetic activity compared to placebo but was not more effective than prochlorperazine. Central nervous system side effects, such as sedation and euphoria, were significantly more frequent with THC.
Herman et al. (1979)	Randomized cross-over	152	15-74	2mg TDS	Oral (nabilone)	Chemo cycle duration	Nabilone demonstrated higher antiemetic efficacy compared to prochlorperazine. However, side effects were more frequent.
Kluin-Neleman et al. (1979)	Randomized cross-over	11	21-53	10 mg/m ²	Oral (dronabinol)	Chemo cycle duration	THC showed significant antiemetic effects, but the side effects were severe enough that most patients preferred to endure the nausea and vomiting rather than use THC.
Steele et al. (1980)	Randomized cross-over	55	19-65	2mg BD (3-5 total doses)	Oral (nabilone)	Chemo cycle duration	nabilone was more effective than prochlorperazine for patients receiving chemotherapy agents other than high-dose cisplatin, achieving a complete or partial elimination of symptoms in 18 patients. Side effects of nabilone included frequent drowsiness and dizziness, which were dose-limiting in 25% of patients.
Chang et al. (1981)	Randomized cross-over	8	17-58	10mg/m ² / 3 hours (5 doses); 17.4mg THC (inhalation) if vomiting	Oral (dronabinol); Inhalation (THC)	Chemo cycle duration	THC did not significantly reduce the number of vomiting episodes, volume of emesis, or degree and duration of nausea compared to placebo, indicating that its antiemetic properties may be limited to specific chemotherapy agents.
Einhorn et al. (1981)	Randomized cross-over	100	15-74	2mg QDS	Oral (nabilone)	Chemo cycle duration	Nabilone significantly reduced the severity of nausea and the frequency of vomiting compared to prochlorperazine.
Neidhart et al. (1981)	Randomized cross-over	52	41 $\bar{x}$	10mg / 3-4 hours (max. 8 doses)	Oral (capsules containing THC)	Chemo cycle duration	THC was as effective as haloperidol in controlling nausea and vomiting, though side effect were more common with THC. About 10% of patients achieved complete control of vomiting, and a third had fewer than five episodes.

Authors	Study	Pts	Age	Dose	Delivery	Follow-up	Outcomes
Orr et al. (1981)	Randomized cross-over	79	22-71	7mg/m ² / 4 hours (4 doses)	Oral (dronabinol)	Chemo cycle duration	Significantly reduced nausea compared to prochlorperazine and placebo, with 40 out of 55 patients who completed the study, experiencing no nausea on THC. An elevated "high", sedation, and transient loss of physical control were reported.
Johansson et al. (1982)	Randomized cross-over	27	28-70	2mg BD	Oral (nabilone)	Chemo cycle duration	Nabilone was found to be more effective than prochlorperazine in reducing nausea and vomiting episodes.
Jones et al. (1982)	Randomized cross-over	54	20- >58	2mg BD	Oral (nabilone)	Chemo cycle duration	Nabilone showed superior antiemetic effects compared to placebo.
Levitt et al. (1982)	Randomized cross-over	58	17-78	-	Oral (nabilone)	Chemo cycle duration	nabilone significantly reduced the severity of nausea and the frequency of vomiting compared to placebo. 78% preferred nabilone despite side effects such as vertigo, drowsiness, and depersonalization.
Ungerleider et al. (1982)	Randomized cross-over	214	18-82	7.5-12.5mg	Oral (dronabinol)	Chemo cycle duration	THC and prochlorperazine showed similar efficacy in reducing nausea and vomiting, but THC had more side effects, including dizziness and sedation. Patient preference was not significantly affected by the side effects.
Wada et al. (1982)	Randomized cross-over	114	18-81	2mg BD	Oral (nabilone)	Chemo cycle duration	Demonstrated a significant reduction in nausea and vomiting for patients receiving THC compared to placebo. 70% of patients preferred nabilone over placebo despite side effects.
Ahmedzai et al. (1983)	Randomized cross-over	34	58 $\bar{x}$	2mg BD	Oral (nabilone)	Chemo cycle duration	Nabilone significantly improved nausea, retching, and vomiting scores compared to prochlorperazine, with fewer vomiting episodes and no need for additional anti-emetics.
George et al. (1983)	Randomized cross-over	20	54.1 $\bar{x}$	1mg TDS	Oral (nabilone)	Chemo cycle duration	Nabilone was not more effective than chlorpromazine in reducing vomiting episodes. Similar side effects. Patient preferences were mixed, with slightly more favouring nabilone.
Hutcheon et al. (1983)	RCT	108	48.7-53.0 $\bar{x}$	0.5-1mg QDS	IM (Levonantradol)	1 day	Levonantradol was a significantly more effective anti-emetic than chlorpromazine (25 mg), but its use is not recommended due to a high incidence of unacceptable CNS side effects.
Kleinman et al. (1983)	Randomized cross-over	16	18-53	15mg BD	Oral (dronabinol)	Chemo cycle duration	No significant difference in the occurrence of vomiting between placebo and THC, though 3 patients vomited only with placebo. Two patients experienced dissociative reactions with THC. Not other side effects. The combination of prochlorperazine and THC was deemed safe and potentially beneficial.

Authors	Study	Pts	Age	Dose	Delivery	Follow-up	Outcomes
Gralla et al. (1984)	RCT	31	58 x̄	10mg/m ² / 3 hours (5 doses)	Oral (dronabinol)	Chemo cycle duration	Findings indicated antiemetic effectiveness.
Stambaugh et al. (1984)	RCT	20	-	0.5-2mg QDS	IM (Levonantradol)	1 day	All doses of levonantradol showed significant anti-emetic activity compared to placebo, but no dose-response effect was observed.
Niiranen & Mattson (1985)	Randomized cross-over	32	48-78	1mg BD	Oral (nabilone)	Chemo cycle duration	nabilone was significantly more effective than prochlorperazine in reducing vomiting episodes. Side effects in almost half the population, leading to three withdrawals. Two-thirds of patients preferred nabilone despite its side effects.
Crawford et al. (1986)	Randomized cross-over	32	15-74	1mg TDS	Oral (nabilone)	Chemo cycle duration	No significant difference in antiemetic efficacy between nabilone and metoclopramide; side effects were consistent with the known pharmacology of the drugs.
Niederle et al. (1986)	Randomized cross-over	20	25 x̄	2mg BD	Oral (nabilone)	Chemo cycle duration	Nabilone was significantly more effective than alizapride in reducing the frequency and duration of nausea and vomiting. More side effects with nabilone yet 50% preferred nabilone.
Pomeroy et al. (1986)	RCT	38	21-66	1mg TDS	Oral (nabilone)	Chemo cycle duration	Nabilone was significantly more effective than domperidone in reducing vomiting episodes, with fewer vomiting episodes observed during both cycles. Side effects were more common with nabilone.
McCabe et al. (1988)	Randomized cross-over	36	18-69	15mg/m ² / 4 hours	Oral (dronabinol)	Chemo cycle duration	THC reduced nausea and vomiting in 64% of patients compared to prochlorperazine, with all patients experiencing transient sensory changes such as euphoria or dysphoria.
Lane et al. (1991)	RCT	62	20-68	10mg QDS	Oral (dronabinol)	Chemo cycle duration	The combination of dronabinol and prochlorperazine showed better control of nausea and vomiting compared to either agent alone. dronabinol had a higher incidence of CNS-related side effects like dizziness and somnolence.
Plasse et al. (1991)	Open label pilot	42	-	2.5-10mg	Oral (dronabinol)	6 weeks	Dronabinol provided better control of CINV than prochlorperazine (51% vs. 83%). A significant reduction in weight loss rate (-0.93 before vs +0.54 after therapy) particularly at 2.5mg BD.
Jhangiani et al. (2005)	RCT	64		2.5mg day1; 10mg day 2; 10-20mg days 3-5	Oral (dronabinol)	Chemo cycle duration (5 days)	Adding dronabinol to the standard antiemetic regimen significantly improved nausea control and reduced nausea intensity. CNS-related side effects were more common in the combination group.

Authors	Study	Pts	Age	Dose	Delivery	Follow-up	Outcomes
Meiri et al. (2007)	RCT	64	24-81	2.5-20mg	Oral (dronabinol)	5 days	Dronabinol showed comparable efficacy to ondansetron for CINV, with a 54% total response rate versus 20% for placebo. The combination of dronabinol and ondansetron did not show additional benefits over individual treatments. Active treatments were generally well tolerated.
Duran et al. (2010)	RCT	16	34-76	4.8 x sprays/day (12.9mgTHC + 12mgCBD)	Oromucosal spray (nabiximols)	5 days	71.4% of patients in the cannabis group achieved a complete response in controlling delayed CINV, compared to 22.2% in the placebo group.
Polito et al. (2018)	Retrospective cohort	110	14 x	5.0–38.8 µg/kg BD	Oral (nabilone)	1 month	Complete control of vomiting achieved in 52.3% of patients. Adverse effects were common (34%) but mild, with sedation (20%) and dizziness (10%) being most frequent.
Grimison et al. (2020)	RCT	81	29-80	2.5mg THC + 2.5mg CBD per capsule; 1-4 capsules TDS	Oral (capsules containing THC + CBD)	Chemo cycle duration	Improvement in complete response rate from 14% to 25% with THC, with side effects such as sedation and dizziness noted. Improved quality of life scores and reduced number of vomiting episodes compared to placebo.
Sukpiriyagul et al. (2023)	Randomized cross-over	54	54.4 x	0.25mg-0.4mg [2.75mg THC + 2.5mg CBD per mL of CX oil]	Oral (THC:CBD extract oil 1:1)	Chemo cycle duration	Reduced nausea scores in the THC group compared to placebo, especially on days 1, 2 and 5. Dizziness and sedation were common side effects.
Grimison et al. (2024)	RCT	147	25-80	2.5mg THC + 2.5mg CBD per capsule; 1-4 capsules TDS	Oral (capsules containing THC + CBD)	42 days	Complete response (no vomiting or use of rescue medications) was achieved in 24% of the cannabis group vs. 8% in the placebo group (absolute difference: 16%; p = .01)

Table 3.10. *Studies evaluating use of medicinal cannabis for chemotherapy-induced nausea and vomiting.*

meal to optimize absorption and efficacy, with subsequent doses spread out every 2 to 4 hours, totalling 4 to 6 doses per day. The recent study by Sukpiriyagul et al. (2023) introduces an innovative THC:CBD oil administered sublingually, which provided significant relief from CINV. The oil, containing a balanced 1:1 ratio of THC to CBD, was given in a controlled regimen starting with one drop each in the morning and evening on the first three days of chemotherapy. This was adjusted to one drop three times a day on subsequent days to enhance efficacy as the treatment progressed. The formulation was effective in reducing nausea scores significantly compared to placebo, with common side effects being dizziness and sedation, which were reported as manageable. Both the THC:CBD oil study and the dosage guidelines for nabilone and dronabinol reflect a growing preference for cannabis-based treatments over traditional antiemetics, particularly in patients who experience side effects from standard CINV medications. The detailed regimen provided by Sukpiriyagul et al. (2023) offers a structured protocol that could be adapted for broader clinical use, ensuring both efficacy in symptom control and a favourable side effect profile.

In a comparative study between nabilone and Metoclopramide, Crawford & Buckman (1986) explored the effectiveness of these drugs in preventing CINV. The study used a double-blind, randomized control trial design where nabilone was administered as 1 mg oral capsules every 8 hours (three times a day). This dosing regimen was evaluated alongside Metoclopramide dosed at 1 mg per kg of body weight every 3 hours via intravenous infusion. The study assessed the control of vomiting and side effects such as drowsiness and diarrhoea between the two treatments. Despite similar effectiveness in controlling vomiting, nabilone was favoured for its less drowsy side effects compared to Metoclopramide. This finding highlights the importance of considering side effect profiles alongside efficacy in choosing an antiemetic treatment,

suggesting that nabilone could be preferred in scenarios where minimizing drowsiness is crucial. Sallan et al. (1975) conducted pioneering work in the use of THC for CINV through a randomized, double-blind, placebo-controlled trial. Patients received THC at a dosage of 15 mg/m² orally, administered every 3 to 5 hours, with a focus on reducing the frequency and severity of nausea and vomiting induced by chemotherapy. The study was groundbreaking in its demonstration that THC could significantly outperform placebos in managing these debilitating side effects of chemotherapy. The trial initially planned doses of 15 mg every 4 hours but adapted to 10 mg/m² per dose due to variability in patient response, emphasizing the need for flexible dosing strategies in clinical practice to accommodate individual tolerance and reaction to cannabis-based medication.

Both Frytak et al. (1979) and Chang et al. (1979, 1981) conducted randomized, double-blind trials that primarily explored the effectiveness of oral THC in managing CINV. Frytak et al. (1979) administered THC at 10 mg/m² every 3 hours for five doses starting on the first day of chemotherapy. Their findings indicated that THC was more effective than both a placebo and prochlorperazine, a standard antiemetic, in controlling nausea and vomiting. Chang's studies further supported these findings with similar dosage regimens. In 1979 and 1981, Chang et al. provided patients with THC at 10 mg/m² orally, structured in the same five-dose regimen. The 1981 study also included a comparison with smoked THC, demonstrating that both administration methods were effective but providing a preferential insight into oral consumption due to its ease of dose standardization and patient compliance. Niederle et al. (1986) conducted their research with a slightly lower dosage of THC, administering 7 mg orally every 2.5 hours on the first day of chemotherapy. Despite the lower dose, their results mirrored those of the aforementioned studies, with THC significantly reducing

episodes of vomiting when compared to placebo. This suggests that lower doses of THC might still be effective for some patients, offering a valuable alternative for individuals who might be sensitive to higher doses of cannabinoids. The findings from these studies emphasize THC's efficacy as an antiemetic that surpasses traditional treatments like prochlorperazine in certain cases. The typical effective oral dosage identified across these trials was approximately 10 mg/m², administered several times throughout the first day of chemotherapy. This regimen appears to optimize nausea and vomiting control without excessive side effects. However, the studies also highlight the need for flexibility in dosing, reducing the dosage in response to dysphoric reactions or other adverse effects, as noted in Chang's 1979 study.

Meiri et al. (2007) tested the efficacy of dronabinol, a synthetic THC, administered at 5 mg orally, twice daily from the first to the fifth day of chemotherapy. Their findings demonstrated a significant reduction in vomiting and the need for rescue medication in comparison to a control group. This regimen suggests that a consistent, moderate dosage of dronabinol throughout the chemotherapy cycle can effectively manage CINV. Cunningham et al. (1988) conducted a study comparing the effectiveness of nabilone and Prochlorperazine, each administered orally, against an intravenous regimen of Metoclopramide and Dexamethasone. Nabilone was given at 1 mg twice on the first day of chemotherapy, paired with Prochlorperazine at 5 mg every 12 hours for up to four doses. The results indicated that this combination was as effective as the intravenous regimen in controlling nausea and vomiting, with some patients preferring the oral medications due to their ease of use and fewer side effects. Duran et al. (1991) explored the use of Sativex®, an oromucosal spray containing a balanced mix of THC and CBD (2.7 mg THC and 2.5 mg CBD per spray). The study reported significant relief from CINV compared to a placebo group. This form of administration

allows for quick relief and easy dose adjustment, highlighting the potential of THC/CBD sprays in managing acute symptoms of nausea and vomiting effectively. Duran et al. (2010) explored the use of Sativex®, an oromucosal spray containing a balanced mix of THC and CBD (2.7 mg THC and 2.5 mg CBD per spray). The study reported significant relief from CINV compared to a placebo group. This form of administration allows for quick relief and easy dose adjustment, highlighting the potential of THC/CBD sprays in managing acute symptoms of nausea and vomiting effectively.

Lane's study (Lane, 1990) involved administering dronabinol at a dose of 10 mg every 6 hours, both as a standalone treatment and in combination with Prochlorperazine at the same dosage. The results indicated a notable decrease in vomiting frequency and an overall improvement in well-being when these medications were used together. This suggests that a combination of dronabinol and Prochlorperazine could be particularly effective for patients with severe symptoms of CINV, providing both symptom control and enhanced quality of life. McCabe et al. (1988) focused on the use of oral THC at a dosage of 15 mg/m², identifying it as more effective than placebo in reducing nausea and vomiting. This high dosage regimen highlights the potential for THC to be used effectively in a targeted manner for patients experiencing intense or refractory symptoms of CINV, especially when lower doses might not be sufficient. Crawford et al. (1986) conducted a study comparing nabilone, administered orally at 1 mg every 8 hours, with Metoclopramide for controlling nausea and vomiting due to cisplatin-based chemotherapy. While specific results were not detailed, the consistent dosing of nabilone in this regimen provides a basis for its use in clinical settings, particularly in comparison to traditional antiemetics like Metoclopramide. Pomeroy et al. (1986) compared the effects of nabilone and domperidone on CINV, using nabilone dosed at 1 mg in white capsules. Although the specific outcomes were

not detailed in the available summary, the inclusion of nabilone in this trial underscores its utility as part of comparative studies with other antiemetics, suggesting its effectiveness in managing emesis induced by cytotoxic therapy. The varying dosages and combinations used across these trials demonstrate the flexibility of cannabis-based treatments in addressing the needs of different patient populations facing CINV. For clinicians considering the incorporation of cannabis into CINV treatment regimes, these findings suggest multiple approaches. Combination therapies: Using dronabinol in conjunction with Prochlorperazine could enhance patient outcomes, especially in severe cases. High-dose options: THC at higher doses (e.g., 15 mg/m²) may be beneficial for patients with particularly severe symptoms. Standardized comparisons: Ongoing comparisons of nabilone with other antiemetics can refine its use, ensuring it is selected when most appropriate for patient care.

In a phase II trial, Stambaugh Jr et al. (1984) tested Levonantradol at varying doses (0.5mg, 1mg, 1.5mg, and 2mg) under a double-blind placebo-controlled randomized crossover design specifically targeting patients who were refractory to conventional antiemetic treatments. This approach aimed to evaluate Levonantradol's effectiveness in a difficult-to-treat patient population, suggesting its potential as a second-line treatment for those not responding to standard protocols. Hutcheon et al. (1983) conducted a multicentre single-blind study comparing Levonantradol at doses of 0.5mg, 0.75mg, and 1mg against Chlorpromazine. The results suggested that while both treatments were effective, Levonantradol was associated with a higher incidence of side effects. This study underscores the need to balance efficacy with tolerability when considering Levonantradol for managing CINV. Kleinman et al. (1983) assessed the use of THC (15mg) combined with Prochlorperazine as an adjunct treatment to control chemotherapy-induced vomiting. Their findings indicated that THC significantly

enhances the antiemetic efficacy of Prochlorperazine, providing strong support for the combined use of these drugs to reduce vomiting episodes more effectively than using Prochlorperazine alone. Niiranen & Mattson (1985) focused on comparing the efficacy of nabilone (1mg dosage) with Prochlorperazine for treating emesis induced by cancer chemotherapy in a cross-over study design. While specific outcomes regarding their comparative efficacy were not detailed, the study highlights the use of nabilone as a viable option against traditional antiemetics, potentially offering alternative benefits not captured by Prochlorperazine.

Ahmedzai et al. (1983) explored the use of nabilone, a synthetic cannabinoid, administering 2 mg at strategic times: the night before chemotherapy and then twice daily during the following three days. This regimen significantly reduced the frequency and severity of nausea and vomiting, demonstrating nabilone's potential as a robust antiemetic option in CINV management with manageable side effects. Levitt's (1982) research further supports the use of nabilone in chemotherapy settings, although specific dosage details were not provided in the available summary. His findings that nabilone outperformed placebo in reducing nausea and vomiting reinforce the cannabinoid's value as an effective antiemetic. The study conducted by Wada et al. (1982) assessed the effects of oral THC, confirming its substantial antiemetic benefits, especially on the first day of chemotherapy. The dosage used was 2 mg, aligning with effective dose ranges identified in other research, highlighting THC's capability to improve patient outcomes significantly when compared to placebo. Ungerleider et al. (1982) provided a more tailored approach to THC dosing, varying according to the patient's body surface area (BSA). The doses were adjusted as follows: 7.5 mg for BSA less than 1.4 m², 10 mg for BSA between 1.4 m² and 1.8 m², and 12.5 mg for BSA over 1.8 m². This method considers individual patient differences, potentially

optimizing efficacy and minimizing side effects by aligning the dose more closely with the patient's physical characteristics.

Orr et al.'s (1981) research focused on the use of THC dosed at 7 mg/m², comparing its antiemetic effects against Compazine (Prochlorperazine) and placebo. The study concluded that THC is an effective antiemetic that could significantly benefit patients undergoing chemotherapy, providing a viable option for those experiencing CINV. Neidhart et al. (1981) evaluated THC encapsulated in gelatin capsules (10 mg THC in 0.12 ml sesame oil) and compared its effectiveness with Haloperidol. The findings indicated that THC was superior in controlling nausea and vomiting induced by chemotherapy, highlighting its potential as a preferred antiemetic agent in oncology. In a randomized crossover trial, Johansson et al. (1982) compared nabilone and Prochlorperazine in patients who had previously not responded well to conventional antiemetics. Nabilone was dosed at 2 mg twice daily, which was found to be effective in managing refractory emesis. This study reinforces the role of nabilone as a potent alternative in cases where traditional antiemetics fail to provide relief. Jones et al. (1982) conducted a double-blind, placebo-controlled trial assessing the antiemetic effectiveness of nabilone, administered at 2 mg. Their findings highlighted nabilone's capability to control CINV effectively, suggesting that a moderate dosage of this cannabinoid provides a significant reduction in nausea and vomiting compared to placebo.

Herman et al. (1979) compared nabilone with Prochlorperazine in a comparative trial to evaluate their antiemetic effects during chemotherapy. Nabilone was administered at either 2 mg every 8 hours, starting with two doses before chemotherapy, or at 2 mg every 6 hours, beginning 30 minutes before chemotherapy. The results from this trial

demonstrated that nabilone was superior in controlling nausea and vomiting compared to Prochlorperazine, providing valuable insights into flexible dosing schedules that could be tailored to the severity of CINV and the timing of chemotherapy sessions. Kluin-Neleman's (1979) double-blind, crossover trial against placebo utilized THC at a dosage of 10 mg/m². This study highlighted the substantial antiemetic potential of THC, demonstrating better control of nausea and vomiting than placebo. This suggests that dosing based on body surface area (BSA) can be an effective strategy for administering THC in a clinical setting. Colls et al. (1980) conducted a randomized trial where Tetrahydrocannabinol (THC) was compared against metoclopramide and thiethylperazine. The dosage used for nabilone in this trial was 2 mg twice daily (BD). The findings revealed that THC could control nausea and vomiting more effectively than the compared traditional antiemetics, suggesting that a regular dosage schedule of 2 mg twice daily could be beneficial for patients experiencing CINV. Einhorn's (1981) randomized controlled trial tested nabilone at a dosage of 2 mg and confirmed its effectiveness as an antiemetic in patients undergoing cancer chemotherapy. The study underscored nabilone's ability to significantly reduce nausea and vomiting, indicating that a 2 mg dosage is effective for managing these chemotherapy side effects.

While the clinical utility of medicinal cannabis is supported by its efficacy in symptom control and patient preference, it is crucial to consider these potential side effects. Proper dosing remains essential to optimize benefits and minimize risks, and further research is needed to refine these recommendations and fully integrate cannabis-based treatments into CINV management protocols.

A review of the studies identifies nabilone and dronabinol as the primary cannabinoid agents investigated for the treatment of CINV. The dosing regimens utilized in these trials typically employed nabilone at dosages of 1 mg to 2 mg, administered twice daily, often initiating the evening prior to or 1-3 hours before chemotherapy. Dronabinol was frequently administered based on body surface area (5 mg/m² to 15 mg/m²) or in fixed doses ranging from 2.5 mg to 10 mg, given every 4 to 6 hours. However, it is imperative to interpret these recommendations within their historical context. The majority of the cited studies were conducted prior to the advent of modern guideline-consistent antiemetic therapies. Specifically, the introduction of 5-HT₃ receptor antagonists such as ondansetron, and NK₁ receptor antagonists such as aprepitant. Consequently, the efficacy of cannabinoids in these trials was established primarily against placebo or older, less effective agents such as prochlorperazine or metoclopramide. Current clinical evidence suggests that newer-generation non-cannabinoid agents offer superior efficacy and a more favourable side effect profile compared to the older comparators, such as chlorpromazine and prochlorperazine. Chow et al. (2020) indicate that while cannabinoids demonstrate superior efficacy to placebo, they are associated with a significantly higher incidence of CNS adverse events compared to standard agents. Furthermore, modern guideline-concordant regimens, typically combining 5-HT₃ receptor antagonists such as ondansetron, NK₁ receptor antagonists such as aprepitant, and dexamethasone, have established acute CINV control rates exceeding 90% in highly emetogenic settings, a standard that cannabinoids have not demonstrated (Hesketh et al., 2020). Therefore, while the dosages listed above reflect the historical evidence base, cannabinoids are now largely reserved for refractory cases where standard modern prophylaxis has failed, rather than as a first-line alternative.

3.4.2.1.2. Challenges and limitations in research

While the potential of medicinal cannabis to alleviate chemotherapy-induced nausea and vomiting (CINV) has been increasingly recognized, significant challenges and limitations persist in the research landscape. Insights from various studies reveal a complex array of issues that complicate the understanding and clinical application of cannabis-based therapies for CINV. One of the primary challenges in cannabis research is the inherent variability in cannabis preparations. The concentration of active cannabinoids such as tetrahydrocannabinol (THC) and cannabidiol (CBD) can vary dramatically between different strains and products (Mersiades et al., 2018 ; Grimison et al., 2020). This variability makes it difficult to standardize treatment protocols and compare results across different studies. Without consistent product formulations, drawing reliable conclusions about dosage, efficacy, and safety is challenging, which hampers the development of standardized treatment guidelines. The legal status of cannabis and its derivatives varies significantly by country and, in some cases, within regions of the same country. These discrepancies can restrict the availability of cannabis for research purposes and create a challenging environment for conducting large-scale clinical trials. Legal hurdles not only limit the accessibility of necessary research materials but also deter academic and medical institutions from engaging in cannabis research due to potential legal ramifications (Bathula & Maciver, 2023).

Despite its potential benefits, the use of medicinal cannabis is not without risks. Sukpiriyagul et al. (2023) and Todaro (2012) discuss the potential adverse effects associated with cannabis use, which include but are not limited to cognitive impairments, psychiatric symptoms, and dependency issues. The ethical implications

of exposing patients to these risks are a significant concern, particularly in vulnerable populations such as those undergoing chemotherapy. Furthermore, there is a lack of comprehensive data on the long-term effects of medicinal cannabis use, which poses additional safety concerns. CINV is a highly individual experience, with significant variability in how patients respond to both chemotherapy and antiemetic treatments, including cannabis-based therapies (Schussel et al., 2018; Michel et al., 2023).

Although the antiemetic properties of cannabinoids are well-documented, the precise mechanisms by which they alleviate symptoms of CINV remain poorly understood. The involvement of the endocannabinoid system and specific cannabinoid receptors is suggested however, detailed mechanistic insights are still lacking (Tafelski et al., 2016; Grimison et al., 2020). This incomplete understanding can hinder the optimization of treatment protocols and the development of more targeted therapies. The quality of research on medicinal cannabis varies widely, with many studies suffering from small sample sizes, lack of control groups, or potential biases in study design. These factors can skew results and lead to misleading conclusions about the effectiveness and safety of cannabis-based interventions (Chow et al., 2020; Alderman et al., 2022).

Addressing these challenges requires a concerted effort from the scientific community, regulatory bodies, and healthcare providers. Enhancing research methodologies, improving regulatory frameworks, and increasing funding for high-quality trials are crucial for advancing the understanding and clinical application of cannabis in the treatment of CINV. Only through rigorous, well-controlled studies can we hope to overcome the current limitations and fully realize the therapeutic potential of medicinal cannabis in oncology.

3.4.2.2. Sleeping disorders

Insomnia is a prevalent sleep disorder characterized by difficulty in initiating or maintaining sleep, which significantly affects daytime functionality and overall quality of life. Its impacts range from decreased work productivity to increased risk of serious medical conditions such as hypertension, diabetes, and depression, posing substantial public health challenges. Conventional treatments for insomnia include behavioural therapies and pharmacological interventions such as benzodiazepines and non-benzodiazepine sedatives. However, these solutions often come with limitations including dependency risks, tolerance development, and side effects like daytime drowsiness and cognitive impairment, highlighting a critical need for alternative treatments (Suraev et al., 2020; Spanagel & Bilbao, 2021).

Insomnia involves a persistent difficulty with sleep initiation, duration, consolidation, or quality despite adequate opportunity for sleep, occurring at least three times per week and for at least three months, as defined by the American Academy of Sleep Medicine. It is a major public health issue affecting approximately 10-30% of adults globally. Chronic insomnia is associated with various negative health outcomes, including increased risks for cardiovascular diseases, mental health disorders, and impaired immune function (Choi et al., 2020; Sarris et al., 2020).

The most commonly prescribed treatments for insomnia are pharmacological interventions, including benzodiazepines and non-benzodiazepine hypnotics like zolpidem and eszopiclone. These medications are effective in the short-term management of insomnia but are often associated with side effects such as morning grogginess, dizziness, and potential for abuse and dependence. Cognitive behavioural therapy for Insomnia (CBT-I), another standard treatment, although effective, is not

widely available due to a shortage of trained clinicians and high costs (Kaul et al., 2021; Velzeboer et al., 2022, Vivek et al., 2024).

3.4.2.2.1. Recommended dosages in current literature

The exploration of medicinal cannabis for treating insomnia and related sleep disorders has generated diverse recommendations regarding optimal dosages, reflecting varying study designs, cannabinoid compositions, and patient demographics (Table 3.11). An insightful review of recent scholarly articles reveals a spectrum of dosages aimed at maximizing therapeutic benefits while minimizing potential side effects.

The scientific discourse around the appropriate use of medicinal cannabis to treat insomnia and related sleep disorders includes a detailed examination of dosages and therapeutic outcomes. One pivotal study by Nicholson et al., (2004) investigates the effects of varying doses of THC and CBD on sleep parameters. They employed a carefully controlled design administering doses ranging from a combined 2.5 mg of THC with 2.5 mg of CBD to a combination of 15 mg each, aiming to optimize sleep efficiency without significant adverse effects. This research underlines how different cannabinoid profiles, such as THC and CBD, can distinctly influence sleep architecture. For instance, lower doses were associated with improvements in falling asleep but did not significantly alter sleep duration, while higher doses appeared to enhance overall sleep quality. Such findings are critical for clinicians aiming to tailor cannabinoid-based treatments to individual patient needs, highlighting the importance of precise dosing to balance efficacy and safety in sleep disorder management.

Two seminal studies that contribute significantly to this field are those conducted by Cousens and DiMascio (1973) and Ware et al., (2010), each offering unique insights into cannabinoid dosing. Cousens and DiMascio (1973), explored the hypnotic effects of THC on sleep. In their controlled study, dosages varied significantly, with an effective hypnotic dose identified at approximately 50 mg of THC taken orally. This high dosage was noted to reduce sleep latency effectively, highlighting the potent sedative properties of THC when used at higher concentrations. Conversely, the study by Ware et al., (2010), examined the use of the synthetic cannabinoid nabilone for managing pain and sleep disturbances in fibromyalgia patients. Initial dosages started at 0.5 mg, potentially doubled to 1 mg depending on patient tolerance, showcased nabilone's capacity to improve sleep and reduce pain. This study provides crucial data on using lower dosages of a synthetic cannabinoid to achieve therapeutic effects with minimal side effects.

The study conducted by Shannon & Opila-Lehman (2016) focused on the use of CBD oil for paediatric anxiety and insomnia related to posttraumatic stress disorder. In this case report, the child was administered 25 mg of CBD oil at bedtime, and doses up to 6-12 mg of sublingual spray as needed during the day depending on the anxiety levels observed. This flexible dosing approach was found to significantly reduce insomnia symptoms and improve sleep quality without noticeable side effects. Tringale & Jensen's study in 2011 discussed the effects of various forms of cannabis on sleep latency and overall sleep quality. They highlighted a significant decrease in sleep onset latency with the use of cannabis, suggesting its potential as a therapeutic agent for insomnia. However, the specific dosages used in this retrospective analysis were not standardized due to the varied forms of cannabis consumed by participants,

Authors	Study	Pts	Age	Dose	Delivery	Follow-up	Outcomes
Cousens & DiMascio (1973)	Randomized cross-over	9	21-40	10-30mg	Oral (95% THC liquid)	one-time	Decreased sleep latency across all doses. THC significantly reduced sleep onset times compared to placebo.
Carlini et al. (1981)	Randomized cross-over	15	-	40-160mg	Oral (CBD)	one-time	Participants reported reduced dream recall with all doses, and the 160 mg dose significantly increased sleep duration.
Nicholson et al. (2004)	Randomized cross-over	8	21-34	15mg THC, 5mg THC + 5mg CBD, 15mg THC + 15mg CBD	Oromucosal spray	-	THC improved sedative effects; combinations with CBD impacted cognitive performance and mood.
Ware et al. (2010)	Randomized cross-over	32	26-76	0.5-1mg	Oral (nabilone)	10 weeks / phase; 2-week wash-out	Both treatments improved sleep, with nabilone showing a greater effect on sleep quality compared to amitriptyline. Side effects were more frequent with nabilone, including dizziness and dry mouth.
Tringale & Jensen (2011)	Retrospective cohort	147	-	-	-	-	Cannabis use was associated with a reduction in time to sleep onset across both groups.
Prasad et al. (2013)	Open label trial	17	51.6 $\bar{x}$	10mg	Oral (dronabinol)	3 weeks	A significant reduction in AHI at 3 weeks from baseline, with an average decrease of 14.1 AHI units.
Chagas et al. (2014)	Case series	4	63.5 $\bar{x}$	75mg (3 pts); 300mg (1 pt)	Oral (CBD)	6 weeks	Substantial and consistent reduction in REM Sleep Behaviour Disorder events.
Farabi et al. (2014)	Cross-sectional	15	51.7 $\bar{x}$	2.5-10mg	Oral (dronabinol)	3 weeks	Dronabinol was associated with EEG changes suggesting improved restorative sleep, though individual variability in responses was noted.
Zalai et al. (2015)	Randomized cross-over	11	-	-	Oral (nabilone)	4 weeks / phase	Improvements in sleep parameters including a 3.8% increase in sleep efficiency and a significant increase in sleep onset latency.
Shannon & Opila-Lehman (2016)	Case report	1	10	25mg / day (oil); 6-12mg PRN (sublingual)	Oral (CBD)	5 months	Improved sleep quality and reduction in anxiety; the patient was able to sleep alone and manage daily activities.
Megelin & Ghorayeb (2017)	Case series	6	43.2 $\bar{x}$	-	Oral (CBD), Inhalation	-	All patients reported immediate relief from Restless Legs Syndrome symptoms.
Carley et al. (2018)	RCT	73	53.6 $\bar{x}$	2.5-10mg	Oral (dronabinol)	6 weeks	Dose-dependent reduction of AHI compared to placebo. Improvements in subjective sleepiness and overall treatment satisfaction, but without improvement in sleep architecture.

Authors	Study	Pts	Age	Dose	Delivery	Follow-up	Outcomes
Casarett et al. (2019)	Retrospective cohort	869	18-76	95% THC / 5% CBD	Inhalation	-	Reported significant improvement in sleep quality across treatment sessions, with 93% reporting reduced insomnia symptoms.
Shannon et al. (2019)	Retrospective case series	72	18-72	25-175mg	Oral (CBD capsules)	3 months	CBD treatment was associated with decreased anxiety scores over time, with mild improvement in sleep scores; well-tolerated with minimal side effects.
Aungsumart et al. (2021)	Case study	5	39-60	max. 27mg THC + 25mg CBD / day	Oromucosal spray	12 weeks	Reported moderate improvement in sleep disturbances as a secondary benefit of treatment, although primary focus was on MS-related symptoms.
De Almeida et al. (2021)	RCT	33	57 x̄	75mg (wk1), 150mg (wk2), 300mg (wk3-14)	Oral (CBD capsules)	14 weeks	CBD did not reduce REM sleep behaviour disorder events compared to placebo, although a transient improvement in sleep satisfaction was observed.

Table 3.11. *Studies evaluating use of medicinal cannabis to address sleep disorders.*

illustrating the challenges in quantifying exact dosage recommendations from observational studies.

In the research conducted by Jumpertz et al. (2010) the focus was not directly on sleep but on the role of endocannabinoids like oleoylethanolamide (OEA) in sleep apnoea, a condition closely associated with sleep quality. The study did not administer cannabinoids directly but measured natural levels of endocannabinoids such as oleoylethanolamide (OEA), AEA, and 2-arachidonoylglycerol (2-AG) in patients. Jumpertz et al. (2010) found that patients with sleep apnoea had significantly higher levels of OEA compared to controls, suggesting an adaptive increase in response to sleep disturbance. Although specific dosages of cannabinoids were not administered in this observational study, the natural variations in endocannabinoid levels pointed to potential therapeutic targets for cannabinoid-based interventions.

The study by Shannon et al. (2019) investigated the impact of Cannabidiol (CBD) on sleep and anxiety. The research was structured as a large case series and provided comprehensive dosage details that help illuminate the therapeutic potential of CBD for insomnia linked with anxiety disorders. Participants were initially given 25 mg of CBD each day, in capsule form, to manage sleep disorders and anxiety. Depending on the observed efficacy and reported patient outcomes, the dose was incrementally increased to a maximum of 175 mg per day. This gradual increase allowed for a detailed assessment of the dosage needed to achieve optimal results while monitoring for any potential side effects. Carley et al. (2018) focus on the use of dronabinol, a synthetic form of THC, to manage obstructive sleep apnoea. The researchers employed a tiered dosing strategy starting at a low dose of 2.5 mg, increasing to 5 mg, and a maximum of 10 mg based on patient tolerance and therapeutic need. This

approach was designed to evaluate the drug's efficacy in reducing the apnoea-hypopnea index, an important measure of apnoea severity, with findings suggesting significant improvements at higher dosages. In a related study by Prasad et al. (2013) the therapeutic potential of dronabinol was again examined but with a focus on a fixed dosage of 2.5 mg. This study further confirms the beneficial effects of dronabinol in sleep apnoea, particularly in reducing nighttime disturbances and improving overall sleep quality. Farabi et al. (2014) explored the use of dronabinol at dosages similar to those used by Prasad et al. (2013), to investigate its impact on sleep architecture in sleep apnoea patients. They explored the effects of dronabinol on sleep, specifically its impact on EEG power distributions in patients with OSA. Their methodology included a dose escalation protocol starting at 2.5 mg per day, increasing to 5 mg and possibly to 10 mg depending on tolerance. This study found that higher doses might enhance the restorative aspects of sleep by altering EEG power towards delta and theta frequencies, which are typically associated with deeper sleep stages. It highlights how varying levels of dronabinol dosage can influence sleep parameters, including shifts in EEG power spectra towards delta and theta waves, which are indicative of deeper and more restorative sleep.

In their study, de Almeida and colleagues focused on the use of cannabidiol (CBD) to treat Rapid Eye Movement (REM) Sleep Behaviour Disorder in patients with Parkinson's Disease, a demographic often troubled by this sleep disorder. The study meticulously explored the impact of CBD at different dosages, administering a progressive dosing regimen that began with 75 mg daily and was increased to 300 mg by the end of the 12-week study period. The primary objective was to assess if higher dosages of CBD could effectively reduce the symptoms associated with REM Sleep Behaviour Disorder. Interestingly, while the study did not find a significant reduction in

the primary disorder symptoms at these dosages, it did note an improvement in sleep satisfaction among participants during the mid-phase of the trial (weeks 4 to 8). This transient benefit highlights the potential subjective improvement in sleep quality with CBD use, even if the primary diagnostic outcomes remain unchanged. This study's approach to dosing, starting at a lower dose and gradually increasing, provides a critical framework for the clinical administration of CBD in sleep medicine. It emphasizes the necessity of tailoring dosages to individual patient responses and conditions to optimize therapeutic outcomes while minimizing potential side effects such as sedation or cognitive disturbances.

Aungsumart et al. (2021) conducted an observational prospective pilot study to evaluate the efficacy and safety of a standardized cannabis extract (THC:CBD 1:1 ratio) produced by the Government Pharmaceutical Organization (GPO) in Thailand. While the study's primary endpoint was the reduction of spasticity in patients with Multiple Sclerosis who had failed standard treatments, it provides relevant secondary data regarding sleep outcomes. Participants received the GPO Cannabis Extract (GPOCE) via oromucosal administration. As part of the secondary outcome measures, the researchers utilized a Numerical Rating Scale to assess various symptoms, including sleep disturbance. The results indicated a trend towards improvement, with patients reporting a reduction in sleep disturbance scores post-treatment. However, unlike the primary outcome for spasticity (which showed statistically significant improvement), the changes in sleep scores did not reach statistical significance ($p=0.109$).

In the context of sleep disorder research, this study highlights a common theme in cannabinoid therapeutics. Subjective improvements in sleep are often reported as

secondary benefits in trials targeting other conditions, such as pain or spasticity, even when the study is not powered to detect them as a primary endpoint. The authors noted that the extract was generally well-tolerated, contributing to the safety data for 1:1 THC:CBD formulations. However, the study's observational nature, small sample size, and lack of a control group limit the ability to draw definitive conclusions about efficacy for insomnia. It serves primarily to support the safety profile of these agents and suggests a signal of potential benefit that justifies further investigation in dedicated, powered sleep trials.

The CANSLEEP trial designed by Suraev et al., (2020) was meant to assess the effects of medicinal cannabis on chronic insomnia disorder. The trial utilized a pharmaceutical-grade oral oil solution, labelled ETC120, containing 10 mg of Δ^9 -tetrahydrocannabinol (THC) and 200 mg of cannabidiol (CBD). This combination was chosen to explore the synergistic effects of THC and CBD on sleep quality and daytime function without causing significant intoxication or cognitive impairment. The study's single-dose design aimed to provide a preliminary indication of the efficacy and safety of these cannabinoid ratios for improving sleep in individuals diagnosed with chronic insomnia. Lavender et al., (2023) focused specifically on the effects of cannabinol (CBN) on sleep quality and next-day cognitive function. Their study employed two distinct dosages of CBN, 30 mg and 300 mg, to evaluate its sedative properties compared to placebo. This trial represents one of the first to rigorously test high doses of CBN in a controlled setting, providing valuable data on its potential as a sleep aid for those with insomnia disorder. The use of such high dosages of CBN is particularly significant, as it helps to define therapeutic thresholds and safety parameters for new and less-studied cannabinoids in the treatment of sleep disorders.

3.4.2.2.2. Research and Clinical Practice

The evolving landscape of using medicinal cannabis for insomnia and related sleep disorders offers a complex yet promising frontier for modern medicine. As seen across numerous studies, medicinal cannabis has significant potential to enhance sleep quality and decrease sleep disturbances across a variety of conditions. Medicinal cannabis has been shown to provide therapeutic benefits for conditions such as sleep apnoea, as detailed in the studies by Carley et al., (2018) and insomnia as explored by Nicholson et al., (2004). These studies and others like them provide strong empirical support for the efficacy of cannabis in treating sleep-related issues, suggesting that it could be integrated into treatment regimens for patients suffering from these disorders. However, the integration of cannabis into clinical practice must be approached with caution due to its complex safety profile. For instance, studies such as those by Farabi et al., (2014) and Shannon et al., (2019) have highlighted potential side effects like cognitive impairment, which are of particular concern. These adverse effects underscore the need for careful patient selection and monitoring, ensuring that cannabis is prescribed only when the potential therapeutic benefits outweigh the risks. Another critical aspect of integrating cannabis into medical practice is dosage optimization. Effective dosage management is essential to maximize therapeutic efficacy while minimizing side effects, a balance that is not always easy to achieve. For example, the work by Suraev et al., (2020) suggests that even small variations in the ratio of THC to CBD can significantly affect outcomes. Therefore, clinicians need to be well-versed in the pharmacodynamics of cannabis and its effects on sleep to tailor treatments to individual patient needs.

3.4.2.3. Multiple Sclerosis Spasticity

Multiple sclerosis (MS) is a chronic, potentially debilitating disease that affects the central nervous system (CNS), leading to various neurological symptoms. Among the most challenging symptoms that significantly impair quality of life are muscle spasticity and associated symptoms like pain, bladder issues, and mobility restrictions (Maayah et al., 2020). Spasticity in MS is characterized by feelings of stiffness and a range of involuntary muscle spasms; it is not only painful but can also contribute to the complexity of daily activities (Markovà et al., 2019; de Fátima Dos Santos Sampaio, 2024).

The management of MS spasticity primarily involves the use of muscle relaxants, anti-spasticity agents such as baclofen and tizanidine, and physical therapy. While these treatments can be effective for some patients, they often come with side effects like fatigue, weakness, and dizziness, which may further limit functionality and quality of life (Arroyo González, 2018). Moreover, a significant number of MS patients experience refractory spasticity, which does not adequately respond to traditional medications (Furgieuele et al., 2021).

Clinical trials and observational studies have provided supporting evidence that THC/CBD oromucosal spray (Sativex®) significantly reduces spasticity scores and improves associated symptoms such as pain and bladder control in a substantial proportion of MS patients (Abd-Nikfarjam et al., 2023). For instance, a multicentre study by Patti et al. (2020) reported that 70.5% of patients achieved a meaningful improvement in spasticity as measured by the Numerical Rating Scale (NRS), with over 40% also reporting improvements in one or more associated symptoms. Moreover, Gustavsen et al. (2021) discussed the use of low-dose medical cannabis

oil, highlighting its safety and efficacy in reducing pain and spasticity in MS, offering a well-tolerated alternative to traditional treatments. Hansen et al. (2023) also emphasized the non-inferiority of cannabis-based treatments in managing neuropathic pain and spasticity compared to placebo, suggesting a broad potential for symptom control.

While the use of medicinal cannabis in MS management is promising, it is not without challenges. The variability in response, concerns about the long-term effects, and the need for precise dosing call for more comprehensive studies and clinical trials. The integration of medicinal cannabis into clinical practice for MS spasticity management should be approached cautiously, with a focus on personalized medicine to optimize outcomes and minimize adverse effects. As research progresses, medicinal cannabis could potentially be considered a mainstream treatment modality alongside or in place of current pharmacological options, provided that its benefits consistently outweigh the risks (Garde & Heibel, 2024).

3.4.2.3.1. Recommended Dosages in Current Literature

Effective management of MS symptoms and spasticity requires not only the right choice of medication but also the correct dosing strategy to optimize efficacy while minimizing adverse effects. The introduction of medicinal cannabis, particularly cannabinoid-based therapies like THC (tetrahydrocannabinol) and CBD (cannabidiol), has provided new avenues for the treatment of MS spasticity and associated symptoms. This section explores the recommended dosages as reported in current literature, focusing on their clinical relevance and potential in routine care (Table 3.12). In recent years, several studies have rigorously evaluated the dosage parameters of

cannabis-based products to achieve the best therapeutic outcomes in MS treatment. Nabiximols (Sativex®), an oromucosal spray containing equal proportions of THC and CBD, is among the most well-documented in this regard. Clinical trials have typically started patients on lower doses, with gradual increases until symptom relief is achieved or side effects become pronounced. Dosage recommendations for cannabis oil and other cannabinoid products vary widely and are influenced by the concentration of active ingredients, the formulation of the product, and individual patient factors such as disease severity and concurrent medications.

The study by Zajicek et al. (2003) was pioneering in its exploration of the effects of Cannador, a cannabis extract, on spasticity and other symptoms associated with multiple sclerosis (MS). Utilizing a randomized, placebo-controlled design with a significant cohort of 630 patients, this research aimed to comprehensively evaluate the therapeutic potential of cannabis extracts in alleviating key MS symptoms such as spasticity, spasms, pain, and sleep quality over a 15-week period (Zajicek et al., 2003). The participants received a substantial daily dose, with 10 capsules of Cannador, equating to a maximum THC dose of 25 mg/kg/day. This methodical dosage aimed to balance efficacy with safety, seeking to minimize psychoactive side effects while alleviating physical symptoms. The study's outcomes highlighted that, while the Ashworth score did not show significant changes in spasticity, patient-reported outcomes did indicate improvements in pain and spasticity, suggesting a potential discrepancy between clinical measurements and patient experiences. Following up in 2005, Zajicek et al. (2005) continued their investigation into the long-term use of Cannador in the same patient group from the initial CAMS trial. This follow-up study was crucial for understanding the prolonged effects of medicinal cannabis, with a consistent dosage of 10 capsules per day extended over an additional year (Zajicek

et al., 2005). This extended study reinforced the initial findings, demonstrating sustained improvements in spasticity, spasms, pain, and tiredness without significant safety concerns. The consistent positive outcomes across an extended period provided compelling evidence supporting the long-term safety and efficacy of cannabis-based treatments for MS. In 2012, Zajicek et al. (2012) built upon their previous work with the MUSEC trial, which introduced a fast dose titration method aiming to maximize therapeutic efficacy by rapidly reaching the maximum tolerated dose. This trial, involving 279 patients, focused particularly on muscle stiffness, pain, and sleep quality and utilized a more aggressive dosing strategy to potentially enhance benefits (Zajicek et al., 2012). The outcomes from the MUSEC trial underscored the effectiveness of Cannador in significantly improving muscle stiffness and pain. The use of a rapid titration schedule was pivotal in achieving these results, highlighting the importance of dosing strategies in maximizing the therapeutic potential of cannabis extracts.

Marková et al. (2019) conducted a comprehensive randomized, double-blind, placebo-controlled clinical trial to evaluate the effectiveness of THC:CBD spray as an add-on therapy compared to optimized first-line antispastics alone. Their study was methodically divided into two phases, ensuring rigorous assessment of both immediate and extended outcomes. In the initial phase, patients self-titrated up to a maximum of 12 sprays per day, with 70.5% of participants exhibiting over 20% improvement in the spasticity numerical rating scale (NRS). These responders then moved to the second phase, where they were randomized to continue with THC:CBD spray or switch to a placebo. Significant improvements were observed in spasticity NRS, modified Ashworth scale (MAS), and pain NRS scores compared to those on

Authors	Study	Pts	Age	Dose	Delivery	Follow-up	Outcomes
Killestein et al. (2002)	Randomized cross-over	16	46 $\bar{x}$	5-10mg	Oral (THC)	4 weeks / phase; 4-week wash-out	No significant reduction in spasticity.
Wade et al. (2003)	Randomized cross-over	24	48 $\bar{x}$	max. 120mg (2.5mg THC:CBD 1:1)	Sublingual spray	2 weeks / phase	Improvement in symptoms such as pain, bladder control, spasms, and spasticity. Adverse effects included transient hypotension and intoxication.
Zajicek et al. (2003)	RCT	630	-	max. 25mg (THC:CBD extract)	Oral (capsule)	12 months	Mixed results with no significant reduction in objective spasticity measures using the Ashworth scale, but improvements in subjective VAS scores for spasticity (60% vs 46% placebo).
Fox et al. (2004)	Randomized cross-over	14	45 $\bar{x}$	2.5mg THC	Oral (THC as Cannador)	2 weeks / phase	No significant improvement in tremor index; some patients reported subjective relief, but no objective change.
Vaney et al. (2004)	Randomized cross-over	57	-	max. 30mg (THC:CBD)	Oral (THC)	2 weeks	Significant reduction in spasticity scores on the Ashworth scale. Some minor adverse effects.
Wade et al. (2004)	RCT	154	-	max. 120mg (2.5mg THC:CBD 1:1)	Sublingual spray	6 weeks	Improvement in patient-reported spasticity and symptom relief. Adverse effects were minimal and included mild sedation and dizziness.
Collin et al. (2007)	RCT	184	-	max. 25mg (THC:CBD)	Oral (THC)	6 weeks	Moderate reduction in spasticity symptoms. Adverse effects were generally mild and included dizziness and nausea.
Collin et al. (2010)	RCT	337	48 $\bar{x}$	8.5 $\bar{x}$ sprays / day (2.7mgTHC + 2.5mgCBD)	Oromucosal spray (nabiximols)	15 weeks	Significant improvement in spasticity (0-10 Numerical Rating Scale, NRS) in the per-protocol population, with 36% achieving $\geq 30\%$ improvement versus 24% for placebo.
Notcutt et al. (2011)	RCT	36	57 $\bar{x}$	8 $\bar{x}$ sprays / day (2.7mgTHC + 2.5mgCBD)	Oromucosal spray (nabiximols)	16 weeks	Longer time to treatment failure than placebo (28 days vs 1.5 days). Patient- and caregiver-reported improvements in symptom control and overall functional status.
Novotna et al. (2011)	RCT	241	23-76	8.3 $\bar{x}$ sprays / day (2.7mgTHC + 2.5mgCBD)	Oromucosal spray (nabiximols)	18 weeks	Notable reduction in spasticity (0.84 mean reduction in NRS score compared to placebo). Improved spasm frequency and sleep quality. Most adverse effects were mild to moderate.
Corey-Bloom et al. (2012)	Randomized cross-over	30	51 $\bar{x}$	4 puffs / day (4% THC)	Inhalation	3 days / phase; 11-day wash-out	Significant reduction in spasticity (Modified Ashworth Scale) and pain (visual analogue scale), with no significant effect on timed walk; cognitive function decreased during treatment.
Serpell et al. (2012)	Open label	146	20-69	7.3 $\bar{x}$ sprays / day (2.7mgTHC + 2.5mgCBD)	Oromucosal spray (nabiximols)	801 days	Patients reported stable symptom relief over time, with no evidence of tolerance. Only 14% withdrew due to adverse effects. No withdrawal syndrome observed on cessation.
Zajicek et al. (2012)	RCT	279	50 $\bar{x}$	max. 25mg (THC:CBD extract)	Oral (extract)	12 weeks	Improved muscle stiffness (OR: 2.26). Patient-reported improvement in muscle spasms (30.8% vs 13.4%, body pain (28% vs 18.7%), and sleep quality (33.6% vs 19.4%).

Authors	Study	Pts	Age	Dose	Delivery	Follow-up	Outcomes
Koehler et al. (2014)	Retrospective cohort	166	49 $\bar{x}$	4 $\bar{x}$ sprays / day (THC:CBD 1:1)	Oromucosal spray	9 months	57% reduction in spasticity with a 72% response rate. Common adverse effects were dizziness, fatigue, and oral discomfort.
Ferre et al. (2015)	Retrospective cohort	144		6.5-7.7 $\bar{x}$ sprays / day	Oromucosal (nabiximols)	48 weeks	Significant improvement in spasticity and pain (numerical rating scale). Low drop-out rate and manageable side effects.
Leocani et al. (2015)	Randomized cross-over	34	48 $\bar{x}$	8 $\bar{x}$ (max.12) sprays / day (2.7mgTHC + 2.5mgCBD)	Oromucosal spray (nabiximols)	4 weeks / phase; 2-week wash-out	Sativex® resulted in a significant improvement in spasticity (measured by Modified Ashworth Scale) compared to placebo (50% vs. 23.5% response rate). No significant differences in neurophysiological measures of spasticity.
Haupts et al. (2016)	RCT	241	49 $\bar{x}$	4 $\bar{x}$ sprays / day (THC:CBD 1:1)	Oromucosal spray (nabiximols)	16 weeks	Reduction in spasticity on NRS vs placebo. Improved associated symptoms like sleep disruption and timed 10-meter walk. Some adverse events noted (dizziness and nausea).
van Amerongen et al. (2017)	Randomized cross-over	24	54.3 $\bar{x}$	max. 24mg	Oral (THC)	4 weeks	Pain and spasticity were reduced. No significant effect was observed in the objective measures (H/M ratio) vs placebo.
Marková et al. (2019)	RCT	106	51.3 $\bar{x}$	7.3-8.5 $\bar{x}$ sprays / day	Oromucosal (nabiximols)	16 weeks	Reduced spasticity (77.4% responders with $\geq 30\%$ improvement in NRS spasticity score vs to 32.1% in placebo).
Meuth et al. (2020)	RCT	106	51.3 $\bar{x}$	-	Oromucosal spray (nabiximols)	16 weeks	Reduced spasticity and pain (0-10 NRS) in active treatment group across various subgroups. Consistent therapeutic response observed across disability and spasticity subgroups.
Patti et al. (2020)	Retrospective cohort	1615	-	-	Oromucosal spray (nabiximols)	4 weeks	At 4 weeks, 70.5% a $\geq 20\%$ reduction on NRS. 43.8% reported improvements in spasticity-related symptom: cramps, nocturnal spasms, bladder dysfunction, pain, and sleep disturbances.
Guger et al. (2023)	Prospective cohort	55	52.5 $\bar{x}$	7.2 $\bar{x}$ sprays / day (2.7mgTHC + 2.5mgCBD)	Oromucosal spray (nabiximols)	3 months	Reduced spasticity (39%), sleep impairment (47.2%), fatigue, pain (40.4%), and urinary incontinence episodes.
Hansen et al. (2023)	RCT	134	21-84	22.5mg THC, 45mg CBD, or combination	Oral (capsule)	7 weeks	No significant difference with placebo for pain intensity or spasticity levels.
Rainka et al. (2023)	Retrospective cohort	141	51 $\bar{x}$	Varied	Oral, inhalation	340 $\bar{x}$ days	48% decreased spasticity. 72% pain relief, 40% improved sleep. 22% discontinued opioids and 32% reduced dosage.
Garde and Heibel (2024)	Case series	12	26-75	8 $\bar{x}$ sprays / day (2.7mgTHC + 2.5mgCBD)	Oromucosal spray (nabiximols)	9 years	Significant improvements in spasticity severity for 11 patients, with 8 achieving $\geq 30\%$ reduction in NRS scores. Additional improvements were observed in related symptoms.
Haupts et al. (2024)	Prospective cohort	51	51.4 $\bar{x}$	5.3-5.9 $\bar{x}$ sprays / day	Oromucosal (nabiximols)	12 weeks	Meaningful reductions in spasticity, pain, sleep quality, and bladder dysfunction. Over 60% of treatment goals achieved.

Table 3.12. *Studies evaluating use of medicinal cannabis for multiple sclerosis spasticity.*

placebo, highlighting the spray's potential in enhancing patient outcomes over standard treatments (Markovà et al., 2019). In a series of studies reviewed by Arroyo Gonzalez (2018), THC:CBD spray was consistently shown to improve spasticity-related symptoms and enhance walking abilities in MS patients. Notably, the use of THC:CBD spray as an add-on therapy significantly bettered performance in timed 10-meter walk tests and was associated with positive changes in various gait analysis parameters. These findings underscore the spray's role not only in alleviating spasticity but also in improving overall motor function and quality of life for those affected by MS. Notcutt et al. (2012) multicentre study further supports the long-term efficacy of THC:CBD sprays in symptom management for MS. Over a 12-week period, patients treated with Sativex® showed sustained symptomatic improvement, which was maintained beyond the treatment duration. This study contributes to the growing body of evidence that THC:CBD can be a viable long-term treatment option for managing chronic symptoms of MS (Notcutt et al., 2012). Langford et al. (2013) focused on the response of MS patients to THC:CBD spray concerning central neuropathic pain. Their findings revealed a high response rate at week 10 of the treatment; however, this was not maintained by week 14. Interestingly, withdrawal of the THC:CBD spray led to significant deterioration in pain scores among the placebo group, suggesting that continuous treatment might be necessary to sustain symptom relief. This study highlights the complexities associated with timing and dosage in the effective management of pain in MS using cannabinoid therapies (Langford et al., 2013). The randomized, double-blind, placebo-controlled study by Haupts et al. (2016) investigated the efficacy and tolerability of THC:CBD spray in 241 MS patients over 12 weeks. Results indicated significant relief from MS spasticity symptoms across diverse patient groups, irrespective of their prior anti-spasticity medication history,

highlighting the broad applicability of THC:CBD spray as a therapeutic option in MS spasticity management.

Messina et al. (2017) conducted a multicentre, open-label study involving 1,597 patients to evaluate the practicality of THC:CBD spray over 24 weeks. One key finding was that the initial six weeks of treatment could effectively identify patients who would benefit from continued therapy, thus potentially reducing the costs associated with prolonged ineffective treatments. Two studies by Wade et al. (2004) (2006) provided early evidence of the efficacy and safety of CBD and THC in a 1:1 ratio, administered in dosages ranging from 2.5 to 120 mg/day. The 2004 study documented a significant reduction in the Visual Analogue Scale (VAS) for pain, with minimal adverse effects. The follow-up 2006 study reinforced these findings and further noted that benefits from CBD and THC were sustained beyond the acute treatment phase without significant withdrawal symptoms, underscoring the potential for long-term use. Collin et al. (2007) (2010) also explored the impact of CBD and THC sprays on spasticity in MS patients in studies conducted in 2007 and 2010. The first study used an average dosage of 23.5 mg/day and reported improvements in Numeric Rating Scale (NRS) spasticity scores and general health impression with mild to moderate side effects. The latter study expanded on these findings, employing a dosage range from 2.5 to 55 mg/day and confirmed ongoing improvements in spasticity management without escalating adverse effects. Novotna and colleagues conducted a pivotal study that assessed the impact of a THC:CBD spray on spasticity in MS patients, using an average of 8.3 sprays per day which corresponds to about 20.75 mg/day. The study reported notable reductions in the Numeric Rating Scale (NRS) for spasticity, frequency of spasms, and disturbances in sleep, all while maintaining a good tolerability profile (Novotna et al., 2011). These outcomes emphasize the potential of THC:CBD to significantly improve

quality of life factors for MS patients with minimal adverse effects. Flachenecker's study further corroborated the benefits of THC:CBD sprays, documenting reductions in resistant MS spasticity and improvements in sleep disturbances across a dosage range of 2.5–40 mg/day. Importantly, the study highlighted the absence of serious safety concerns, presenting the therapy as a viable option for long-term management of MS symptoms (Flachenecker et al., 2014). Trojano et al. provided additional evidence supporting the efficacy of THC:CBD in reducing spasticity as measured by the NRS and the modified Ashworth score. Although the study indicated a generally safe profile with dosages up to 30 mg/day, it also noted severe adverse effects in two patients, including mental impairment and suicidal ideation, underscoring the need for careful patient monitoring (Trojano et al., 2015). In a more recent investigation, Doohan and associates examined the effects of THC:CBD spray within the same dosage range (2.5–30 mg/day) and documented improvements in the EuroQoL visual analogue scale alongside the spasticity NRS. The mild to moderate nature of observed adverse effects suggests that the therapy is generally well-tolerated, although the range of potential reactions should be carefully considered in clinical settings (Doohan et al., 2021). Hansen et al. embarked on a comprehensive national multicentre trial to explore the effects of cannabis-based medicine on neuropathic pain and spasticity in individuals with MS and SCI. This double-blinded, placebo-controlled trial is distinguished by its rigorous methodology and its inclusion of a pharmacokinetic sub-study, which aims to provide deeper insights into the metabolic and operational pathways of THC and CBD in the human body. Preliminary findings suggest significant potential for symptom relief across several domains, including quality of life and pain management (Hansen et al., 2021).

The post hoc analysis by Meuth et al. (2020) from the SAVANT study further validated the efficacy of THC:CBD spray (nabiximols) in a large cohort of MS patients. This study distinguished itself by initially screening for responsiveness to the treatment in a single-blind setup before proceeding to a double-blind phase. It was found that nabiximols significantly reduced spasticity and pain scores, particularly in patients with severe symptoms at baseline. This suggests that nabiximols can be an effective adjunct therapy for patients who have not responded adequately to other medications. Importantly, the treatment exhibited a manageable safety profile with no serious adverse effects reported, reinforcing its potential as a sustainable option for long-term management of MS symptoms (Meuth et al., 2020).

van Amerongen's (2017) study provided a comprehensive analysis of the effects of a synthetic THC formulation (ECP002A) on spasticity and pain in 24 progressive MS patients. This accelerated proof-of-concept study included a dose-finding phase followed by a randomized, placebo-controlled treatment phase, highlighting the importance of precise dosing in achieving optimal therapeutic outcomes. While the study showed significant reductions in spasticity and pain immediately following administration, the variability in pain assessment underscored the complex nature of MS symptom management. The research also emphasized the necessity of personalized medicine approaches to minimize adverse effects while maximizing benefits (van Amerongen et al., 2017).

In a non-interventional study conducted across various neurological departments in Austria, Guger et al. (2023) explored the use of nabiximols as an add-on therapy in 55 MS patients suffering from spasticity. The study reported significant improvements in spasticity-associated symptoms such as pain, spasms, and sleep disruptions, with an average usage of 7 sprays per day. Patient satisfaction and reduced impairment in daily activities further underscored the therapeutic potential of nabiximols in enhancing

quality of life for MS patients. Notably, the treatment was well-tolerated, with mostly mild to moderate adverse effects reported, indicating a favourable safety profile (Guger et al., 2023).

Leocani et al. (2015) conducted a randomized, double-blind, placebo-controlled crossover study focusing on patients with progressive MS and lower limb spasticity. The primary aim was to explore the neurophysiological impact of Sativex® (nabiximols) on spasticity, assessed through the H/M ratio and other corticospinal excitability measures. Despite not observing significant changes in the primary neurophysiological outcomes, there was a notable improvement in clinical measures of spasticity using the modified Ashworth scale (MAS). Approximately 50% of Sativex®-treated patients reported significant symptom relief compared to 23.5% in the placebo group, suggesting that while the neurophysiological mechanisms might not fully explain the clinical benefits, the subjective improvements are meaningful to patients (Leocani et al., 2015). Fox et al. (2004) aimed to determine the efficacy of Cannador, a cannabis extract, on upper limb tremor in MS patients through a sophisticated crossover design. Although the study did not demonstrate significant improvements in tremor via objective assessments like accelerometry or the tremor rating scale, there was a suggestive trend towards subjective relief as reported by patients. This discrepancy highlights the challenges in capturing the full scope of potential benefits using conventional objective measures alone and underscores the importance of patient-reported outcomes in clinical trials assessing symptom management in MS (Fox et al., 2004). In another critical study, Corey-Bloom et al. (2012) investigated the effects of smoked cannabis on spasticity and pain in MS. This randomized, double-blind, placebo-controlled crossover trial found significant reductions in spasticity and pain scores following cannabis use compared to placebo.

Notably, while there were some cognitive side effects observed, these did not outweigh the potential benefits related to symptom relief. This study not only supports the efficacy of smoked cannabis in reducing MS-related spasticity and pain but also highlights the need to carefully consider side effects in the broader context of therapeutic gains (Corey-Bloom et al., 2012).

In a prospective study published in *Neurodegenerative Disease Management*, Haupts et al. (2024) evaluated the effectiveness of nabiximols oromucosal spray in a real-world setting over 12 weeks. The study involved 51 MS patients who reported improvements in patient-reported spasticity and associated symptoms, significantly in the Goal Attainment Scale (GAS) and on measures like gait speed, pain, and sleep quality. The treatment was well-tolerated, aligning with previous research suggesting that patient-reported outcomes may be more reflective of the real-world benefits of such treatments (Haupts et al., 2024). Killestein et al. (2002) provided insights into the use of THC and Cannabis sativa extracts in MS patients experiencing severe spasticity. While the study reported no significant reduction in spasticity as measured by the Ashworth scale, it highlighted the treatment's general tolerability and raised important questions about its clinical efficacy and the occurrence of adverse effects such as psychosis (Killestein et al., 2002). Wade et al. (2003) explored the potential of cannabis medicinal extracts in a controlled cross-over trial involving MS and other patients with neurogenic symptoms. Significant improvements were reported in pain, muscle spasms, and bladder control with mild to moderate adverse effects, suggesting the feasibility of using cannabis extracts for intractable symptoms (Wade et al., 2003). Rainka et al. (2023) conducted a retrospective medical record review to assess changes in symptoms and medication use among 141 MS patients using medical cannabis. The study found significant alleviation of pain, spasticity, and improvements

in sleep, with a notable reduction in opioid use, emphasizing the role of medical cannabis in comprehensive symptom management strategies (Rainka et al., 2023).

This multicentre, randomized, double-blind, placebo-controlled trial by Hansen et al. (2023) explored the impact of different compositions of CBM on MS and SCI symptoms. Interestingly, the study concluded that there was no significant difference in the primary outcomes of pain or spasticity intensity between the treatment and placebo groups. This finding suggests that while CBM can be beneficial for some patients, its effectiveness may vary significantly among individuals, and not all patients may experience noticeable symptom relief (Hansen et al., 2023). Koehler et al. (2014) conducted an observational study to assess the effectiveness of THC:CBD spray in patients with resistant MS spasticity. The study found that a significant proportion of the 166 participants reported improved spasticity management, with a mean reduction in the Numerical Rating Scale (NRS) for spasticity from 7.0 to 3.0. Despite the presence of side effects such as dizziness and fatigue, which led to discontinuation for some, the spray was generally well-tolerated, underlining its potential as a viable add-on or monotherapy in routine clinical settings (Koehler et al., 2014). Ferrè et al. (2015) observational study in a monocentric real-world setting involved 144 MS patients and highlighted the efficacy of nabiximols (Sativex®) in reducing spasticity and pain. Notably, approximately 71.7% of participants responded positively by the end of an initial titration phase, experiencing an average 32% reduction in spasticity as measured by sNRS. The study reported sustained benefits and good tolerability up to 48 weeks, supporting the long-term use of nabiximols in managing MS spasticity (Ferrè et al., 2015). Gustavsen et al. (2021) conducted an observational safety study to assess the effectiveness of various formulations of medical cannabis oils in treating MS-related neuropathic pain and spasticity. The study concluded that both THC-rich

and balanced THC/CBD oils significantly reduced pain and spasticity scores, advocating for a careful titration approach to optimize patient outcomes without substantial adverse effects (Gustavsen et al., 2021). In a large-scale retrospective study, Patti et al. (2020) evaluated the improvement in spasticity-related symptoms using THC/CBD spray in a real-world setting. With over 1,432 MS patients completing the trial, significant reductions in the spasticity numerical rating scale were observed, alongside improvements in symptoms such as pain and bladder issues. This study underscores the spray's broad applicability and potential to significantly enhance patient well-being (Patti et al., 2020). Torri Clerici et al. (2023) focused on the effects of nabiximols on urinary symptoms in MS patients. Their prospective observational study involving 31 patients revealed significant improvements in urinary control as measured by the International Prostate Symptom Score and other urodynamic parameters. The use of nabiximols resulted in enhanced quality of life metrics, indicating its utility beyond spasticity management to address comprehensive symptomatology in MS (Torri Clerici et al., 2023).

The precise dosage of THC/CBD crucially impacts the efficacy and safety profile of the treatment. Underdosing may lead to suboptimal management of symptoms, whereas overdosing could increase the risk of adverse effects, such as cognitive disturbances and mood alterations. Thus, clinical guidelines strongly recommend a personalized approach to dosing, often starting at the lowest possible dose and carefully monitoring the patient's response to adjust the dose incrementally. As the therapeutic window for cannabis-based medications can be narrow, detailed knowledge of dosage strategies from current clinical trials and observational studies is essential for healthcare providers. This ensures that the use of medicinal cannabis

in treating MS symptoms and spasticity is based on sound evidence, optimizing patient outcomes and minimizing potential risks.

3.4.2.3.2. Research and clinical practice

Modern treatment paradigms for MS emphasize early use of disease-modifying therapies to delay the progression of disability and mitigate acute relapses. However, managing chronic symptoms of MS requires a broad array of strategies including pharmacological treatments, physical therapy, and neuromodulation. Despite these efforts, many patients experience persistent symptoms that significantly impair their quality of life. Medicinal cannabis has emerged as a potential adjunct therapy for managing various MS symptoms, particularly spasticity and pain, which are poorly controlled by conventional medications. Studies have shown that cannabinoids interact with the endocannabinoid system of the body, which is involved in modulating pain, inflammation, and immune response, all of which are key aspects of MS. For instance, the MUSEC trial indicated that cannabis extracts could significantly reduce muscle stiffness and pain in MS patients compared to placebo (Rainka et al., 2023). Clinical trials and patient reports have suggested that cannabis may also help manage other MS-related symptoms including urinary disorders, spasticity, and sleep disturbances, thus improving patient-reported quality of life (Furguele et al., 2021; Hansen et al., 2021).

Recent research has focused on optimizing the therapeutic regimes of medicinal cannabis, studying the effects of different THC:CBD ratios, and exploring the safest and most effective routes of administration for MS symptoms (Maayah et al., 2020; Guger et al., 2023; de Fátima Dos Santos Sampaio et al., 2024). For example, studies

like those conducted by Torri Clerici et al. (2023) and others have investigated the use of cannabis for urinary disturbances in MS, showing promising results (Hansen et al., 2023; Torri Clerici et al., 2023). The efficacy of cannabis in reducing reliance on traditional pain medications, including opioids, has also been documented, potentially reducing the opioid-related side effects and dependency risks (Filippini et al., 2022). Furthermore, ongoing clinical trials continue to explore the broad therapeutic potential of cannabis, not only in MS but also in other neurological disorders. The integration of medicinal cannabis into clinical practice for MS treatment represents a significant advance in the multidisciplinary approach to managing this complex disease. However, continued research is crucial to address the remaining questions about efficacy, safety, and the regulatory landscape. As clinical practice evolves with these developments, it is essential to maintain rigorous standards of evidence to ensure that the use of cannabis is both safe and effective for patients with MS.

3.4.2.4. Amyotrophic lateral sclerosis

Amyotrophic lateral sclerosis (ALS) is a severe and progressive neuromuscular disorder that ultimately results in the degeneration of motor neurons in the cortex, brainstem, and spinal cord, as outlined by Meyer et al. (2019). This disease commonly manifests between the ages of 50 and 65, leading to progressive muscle weakness, spasticity, and difficulties in speaking and swallowing (Lacroix et al., 2023). While most cases of ALS are sporadic, approximately 10-15% of cases are familial, associated with mutations in genes such as C9ORF72 and SOD1 (Urbi et al., 2019; Lacroix et al., 2023).

Current treatment options for ALS are limited and focus on slowing disease progression. Riluzole and Edaravone are the primary drugs available, which have been shown to only modestly slow disease progression without halting it or significantly extending survival (Meyer et al., 2019). Masitinib is being investigated for its potential to modulate immune cell activity to combat neuroinflammation, a key component in ALS pathology (Aymerich et al., 2018). The potential of medicinal cannabis in ALS treatment has been increasingly recognized due to its interaction with the endocannabinoid system (ECS). The ECS is involved in key physiological processes such as neuroprotection and inflammation, which are crucial in ALS pathology (Aymerich et al., 2018). Cannabinoids such as Δ 9-THC and CBD may modulate pathways implicated in ALS, potentially providing neuroprotective effects (Aymerich et al., 2018). Preclinical studies, such as those cited by Urbi et al. (2019), have shown that cannabinoids can improve motor behaviour and survival in animal models of ALS. These studies suggest that activation of CB2 receptors could significantly slow disease progression and extend survival in these models (Urbi et al., 2019).

Clinical trials and patient reports indicate that cannabinoids may help manage symptoms such as spasticity and pain, which are common in ALS patients. THC:CBD sprays, for example, have been used to manage spasticity with some noted benefits (Meyer et al., 2019). Lacroix et al. (2023) also discuss the potential broader applications of cannabinoids in managing symptoms of neurodegenerative diseases, including ALS. Integrating medicinal cannabis into treatment strategies for ALS could offer a new avenue for improving patient care through symptom management and potentially modifying disease progression. The interaction of cannabinoids with the ECS and their impact on key pathological processes in ALS present a promising area

for future research and clinical application. However, rigorous clinical trials and comprehensive studies are required to further explore these potentials and validate the efficacy of cannabinoids in ALS treatment practices (Meyer et al., 2019; Urbi et al., 2019).

3.4.2.4.1. Recommended dosages in current literature

Lacroix et al. (2023) conducted an observational study using a nationwide online survey to assess the use of cannabis among ALS patients in France (Table 3.13). The study, which collected responses from 129 participants, aimed to evaluate the real-life application of cannabis for managing both motor and non-motor symptoms associated with ALS. The study highlighted the diverse forms of cannabis used, such as CBD oil and cannabis herb, and the variety of administration methods employed by patients, ranging from oral/sublingual use to smoking and vaporization. The primary outcomes reported improvements in symptoms such as rigidity, cramps, and fasciculations, as well as enhancements in sleep quality, emotional state, and overall quality of life. These findings are particularly significant as they suggest that cannabis may offer symptomatic relief in a condition where traditional treatments often fall short. However, the study also noted minor adverse effects like drowsiness and euphoria, which underscores the need for careful monitoring of cannabis use in clinical settings. This study serves as a crucial reminder of the challenges associated with the unregulated use of cannabis, highlighting an urgent need for regulated and safe access to medicinal cannabis for symptom management in ALS. The adherence to General Data Protection Regulation (GDPR) standards in the study also emphasizes the importance of ethical considerations in conducting research involving vulnerable populations.

Authors	Study	Pts	Age	Dose	Delivery	Follow-up	Outcomes
Weber et al. (2010)	RCT	27	34-78	5mg BD	Oral (dronabinol)	2 weeks / phase; 2-week wash-out	No significant improvement in cramp intensity, frequency, or secondary outcomes such as fasciculation intensity, quality of life, sleep quality, appetite, depression, between THC and placebo. THC was generally well tolerated, with only mild dizziness reported as an adverse effect.
Meyer et al. (2019)	Retrospective cohort	32	27-87	5.5 sprays / day (2.7mgTHC + 2.5mgCBD)	Oromucosal spray (nabiximols)	-	Significant patient satisfaction with the treatment for spasticity (TSQM-9 scores showed high satisfaction across effectiveness, convenience, and global satisfaction domains). The Net Promoter Score (NPS) indicated a high recommendation rate, especially among those with moderate to severe spasticity. Mild side effects like dizziness and fatigue were observed in some patients.
Lou et al. (2022)	Case report	1	60	2.43mgTHC + 2.75mgCBD / capsule	Oral (capsule)	-	Improvement in pruritus from a score of 7/10 to 3/10. Initial sedation as a side effect, which subsided with continued use. This case highlights cannabinoids as potentially safe and effective for neuropathic pruritus.
Lacroix et al. (2023)	Cross-sectional	124	48.2 x̄	Varied	Varied	-	Reported improvements in symptoms such as sleep quality, pain, rigidity, cramps, and fasciculations; 53.6% reported an overall positive impression of change. Adverse effects included drowsiness (10.7%) and euphoria (10.7%).
Austin et al. (2024)	Retrospective cohort	344	67 x̄	5-10mg BD	Oral (THC)	-	Medicinal cannabis use correlated with short-term alleviation of pain, poor appetite, and anxiety but did not impact spasticity or insomnia. It was also associated with faster ALS progression, showing a greater decline in ALS Functional Rating Scale-Revised scores than in controls, though patients on THC had higher initial symptom burdens. No significant difference in BMI maintenance was observed between groups.

Table 3.13. *Studies evaluating use of medicinal cannabis in amyotrophic lateral sclerosis.*

Lou et al. (2022) detailed a case report of a 60-year-old male ALS patient treated with a cannabinoid formulation for refractory neuropathic pruritus—a challenging symptom poorly addressed by existing medications. The patient was administered an oral capsule containing balanced doses of THC and CBD, which significantly reduced his pruritus scores from 7/10 to 3/10 on a numeric rating scale. The improvement in pruritus not only enhanced the patient's quality of life but also his sleep quality and overall well-being. The initial side effects such as increased sedation were managed by adjusting the dosage, demonstrating the need for personalized treatment approaches in the use of cannabinoids. This case report is pivotal as it extends the potential applications of cannabinoids beyond pain management to include other neuropathic symptoms such as pruritus, which are common in ALS but often underreported and undertreated. The findings advocate for more extensive clinical trials to verify the efficacy and safety of cannabinoids in this new context. Both studies contribute significantly to the burgeoning field of cannabinoid research in neurodegenerative diseases, particularly ALS. While Lacroix et al. (2023) provide a broad overview of cannabis use across a significant cohort, highlighting widespread symptomatic relief, Lou et al. (2022) offer a focused insight into the potential specific benefits of cannabinoids for neuropathic pruritus in ALS patients.

The Weber et al. (2010) randomized, double-blind, placebo-controlled crossover trial specifically targeted moderate-to-severe muscle cramps, a prevalent and often undertreated symptom in ALS. It involved 27 patients who received 5 mg of oral THC twice daily for two weeks. The results demonstrated that this dosage was well-tolerated but failed to show a significant treatment effect compared to placebo for the primary outcome of cramp intensity. Furthermore, no significant benefits were observed for secondary measures, including cramp frequency, fasciculation intensity,

sleep, appetite, or depression. The authors hypothesized that the lack of efficacy might be attributed to the relatively low dosage (10 mg daily) and the short treatment duration, suggesting that future trials might require dose titration or parallel-group designs to better assess therapeutic potential without the confounding factors of a crossover design. Additionally, the study identified a potential pharmacological carryover effect, where benefits persisted into the washout period, further complicating the interpretation of data within a crossover framework. The authors ultimately concluded that while the 10 mg daily dose was safe, evidenced by only a single report of mild dizziness, it was likely insufficient to achieve the systemic levels necessary for significant symptom control.

Meyer et al. (2019) conducted a retrospective cohort study to evaluate the effectiveness of THC:CBD oromucosal spray in managing spasticity, a common and debilitating symptom in ALS patients. The study involved 32 participants diagnosed with ALS and experiencing varying degrees of spasticity. Patients used an oromucosal spray containing 2.7 mg of THC and 2.5 mg of CBD per actuation, with the mean dosage being 5.5 daily actuations. This dosage variability allows for a personalized approach, reflecting real-world usage where patient sensitivity to cannabinoids can vary significantly. The primary measure of effectiveness was the improvement in spasticity, assessed using the Numeric Rating Scale (NRS). Results showed that THC:CBD spray helped reduce spasticity symptoms in patients, correlating with improved patient satisfaction and quality of life as reported through the Net Promoter Score (NPS) and Treatment Satisfaction Questionnaire for Medication (TSQM-9). This study underscores the potential of cannabinoids in symptom management for ALS, particularly for spasticity. It also highlights the necessity of patient-centric dosages and

personalized treatment plans. The ethical approval and informed consent procedures followed ensure the study's adherence to clinical governance, enhancing its validity.

The EMERALD trial, a rigorous randomized, double-blind, placebo-controlled study led by Urbi et al. (2019), investigated the efficacy of a high-CBD, low-THC cannabis-based medicine extract (CBME) in slowing ALS progression. This trial involved 30 participants who met strict inclusion criteria based on the El Escorial standards. Participants were administered oral capsules containing 25 mg of CBD and less than 2 mg of THC, reflecting a conservative approach to THC dosage likely aimed at minimizing psychoactive effects while leveraging the neuroprotective properties of CBD. The primary outcome focused on disease progression, measured by changes in the ALS Functional Rating Scale-Revised (ALSFRS-R) and Forced Vital Capacity (FVC) scores. Secondary outcomes included assessments of spasticity, pain, weight loss, and overall quality of life, using validated scales such as the Numeric Rating Scale for pain and spasticity.

This trial's structured methodology and the comprehensive nature of the outcomes measured provide substantial evidence of the potential benefits of CBD-dominant cannabis extracts in managing ALS. The findings could pave the way for more extensive studies and potentially guide future therapeutic strategies. Both Meyer et al. (2019) and Urbi et al. (2019) contribute significantly to the existing literature on the use of medicinal cannabis in ALS. Meyer et al.'s findings are particularly valuable for symptomatic treatment, offering evidence for the effective management of spasticity, a frequent concern in ALS. Conversely, the EMERALD trial by Urbi et al. (2019) explores the broader potential of cannabinoids to slow disease progression, a fundamental challenge in ALS treatment. These studies collectively highlight the dual

potential of cannabinoids not only to enhance patient comfort and daily living quality through symptom management but also to address the underlying disease progression mechanisms in ALS. As the body of evidence grows, these insights reinforce the need for more targeted research to optimize cannabinoid formulations and dosing strategies tailored to the needs of ALS patients, ensuring maximum efficacy and safety. The ongoing exploration of these avenues will be crucial in integrating cannabinoids more fully into ALS therapeutic regimens.

In a recent, large retrospective cohort study involving 344 patients, Austin et al. (2024) evaluated the real world clinical effectiveness of medical cannabis on a broader range of ALS symptoms. Patients were typically prescribed a 3:1 CBD:THC tincture, initiated at bedtime and titrated by 2.5 mg increments up to a maximum of 10 mg twice daily based on symptom control. The analysis revealed that medicinal cannabis use was correlated with the alleviation of pain, poor appetite, and anxiety in the short term, validating patient perceptions of efficacy for these specific issues. However, contrary to some prior literature, the study found no correlation between medicinal cannabis use and improvements in spasticity or insomnia. Notably, the data indicated that medicinal cannabis users exhibited a faster decline in functional rating scores (ALSFRS-R) compared to controls. The authors interpreted this not as a causative negative effect of the drug, but likely a reflection of selection bias, where patients with more aggressive disease trajectories and higher symptom burdens were more inclined to seek palliative relief through medicinal cannabis.

3.4.2.4.2. Research and clinical practice

Recent years have seen growing interest in the potential benefits of medicinal cannabis for managing ALS symptoms and possibly modifying disease progression. Notable among the research are studies like those conducted by Lacroix et al. (2023) and Lou et al. (2022), which have provided insights into the real-world application and benefits of cannabis among ALS patients. Lacroix et al. (2023) conducted an observational study using a nationwide online survey in France to explore cannabis use for symptom management in ALS. The study included 129 respondents, showing that 21.7% reported using cannabis primarily in forms such as cannabidiol (CBD) oil and cannabis herb, administered through various methods including oral/sublingual intake and vaporization. The findings indicated improvements in both motor and non-motor symptoms such as rigidity, cramps, and emotional well-being.

Lou et al. (2022) presented a case report of a 60-year-old male ALS patient who experienced significant relief from neuropathic pruritus using a balanced oral cannabinoid formulation. This case highlighted the potential of cannabinoids in managing symptoms that are often resistant to traditional treatments.

A landmark study in this domain is the EMERALD trial by Urbi et al. (2019), detailed in a document reviewed. This randomized, double-blind, placebo-controlled trial aimed to evaluate the efficacy of a cannabis-based medicine extract (CBME) in slowing ALS progression. The trial involved 30 participants who received a high-CBD, low-THC formulation over six months. Primary outcomes were focused on disease progression metrics such as the ALS Functional Rating Scale-Revised and Forced Vital Capacity scores. The study underscored the importance of further clinical trials to confirm the potential disease-modifying properties of cannabinoids in ALS. Meyer et al. (2019)

offered a retrospective insight into the real-world use of THC:CBD sprays for managing ALS-related spasticity. Spanning 32 patients, the study found that cannabinoid treatment could significantly improve spasticity symptoms, enhancing patient quality of life as assessed by treatment satisfaction questionnaires and net promoter scores.

These studies collectively suggest that cannabinoids might play a beneficial role in managing various ALS symptoms and potentially modulating disease progression. However, the evidence also highlights the need for standardized dosages and administration methods to maximize patient safety and treatment efficacy. The integration of cannabinoids into clinical practice for ALS requires rigorous clinical trials to better understand their efficacy and safety profiles. Research should also focus on elucidating the mechanisms by which cannabinoids might affect ALS pathophysiology, which could pave the way for targeted therapies that not only manage symptoms but also potentially slow disease progression. Medicinal cannabis holds promise as a complementary treatment option in ALS, particularly for symptoms inadequately controlled by current medications. Ongoing research and clinical trials will be crucial in determining the precise role of cannabis in ALS treatment protocols, aiming to improve patient outcomes and quality of life in this challenging neurodegenerative disorder.

3.4.2.5. Huntington's Disease

Huntington's Disease (HD) is an inherited neurodegenerative disorder characterized by a combination of motor, cognitive, and psychiatric symptoms. It is caused by a mutation in the huntingtin gene involving an abnormal elongation of the CAG trinucleotide repeat. This genetic alteration leads to the production of an abnormal

protein that gradually damages certain brain cells, prominently in the striatum and cortex (Aymerich et al., 2018; Antonazzo et al. 2019). Clinically, HD manifests as chorea (involuntary jerking movements), rigidity, behavioural disturbances, and dementia. The progressive nature of HD results in complete physical and mental decline, typically culminating in death within 15-20 years of symptom onset (Voicu et al., 2023). Current pharmacological interventions for HD are primarily aimed at symptom management rather than disease modification. The mainstay of treatment includes the use of tetrabenazine, a vesicular monoamine transporter 2 inhibitor, which is approved for the treatment of chorea associated with HD (Aymerich et al., 2018). Other therapeutic agents like antipsychotics and antidepressants are employed to manage the psychiatric symptoms of the disease (Akinyemi et al., 2020). Despite these treatments, options are limited and often come with significant side effects that can exacerbate other HD symptoms or decrease overall quality of life. Recent research has increasingly focused on the potential neuroprotective properties of cannabinoids in HD. Studies have identified changes in the endocannabinoid system in HD, particularly involving CB1 and CB2 receptors, which are implicated in neuroprotective pathways. For instance, cannabinoids have been shown to alleviate motor symptoms and improve neurologic functions in preclinical models of HD by modulating excitotoxicity and inflammation. THC and CBD have been tested in various experimental settings, demonstrating potential benefits in reducing neurodegeneration and alleviating motor symptoms such as dystonia and chorea. Notably, studies using animal models of HD have reported that treatments targeting CB1 receptors could potentially slow disease progression by protecting striatal neurons from excitotoxic damage (Murillo-Rodriguez et al., 2020). On the clinical front, trials have explored the efficacy of cannabinoid-based therapies like Sativex® in managing symptoms and

modifying disease progression in HD patients. While results from some early studies suggested improvements in motor symptoms and patient well-being, a significant impact on disease progression has yet to be conclusively demonstrated. For example, a trial involving Sativex® reported some symptomatic relief but did not conclusively affect disease progression over the short duration of the study (Antonazzo et al. 2019; Murillo-Rodriguez et al., 2020).

3.4.2.5.1. Recommended dosages in current literature

As research into the therapeutic potential of cannabinoids in HD progresses, a critical aspect is the determination of effective dosages that can provide symptom relief and potentially modify disease progression without significant side effects. This section delves into the current recommendations and findings from recent studies regarding the dosage of cannabinoid-based therapies specifically for HD (Table 3.14). The landscape of cannabinoid research in HD is marked by variability in dosage and administration strategies, reflecting the complex interaction between cannabinoid compounds and the pathophysiological features of HD. Various studies have suggested differing dosages based on the type of cannabinoid used, the method of administration, and the specific symptoms targeted. For synthetic cannabinoids like nabilone and dronabinol, used primarily to manage chorea and other motor symptoms, dosages have varied significantly across studies. For instance, one pilot clinical study using nabilone reported improvements in chorea and behavioural disturbances at dosages ranging from 1 to 2 mg twice daily. In contrast, studies using Sativex®, which contains a 1:1 ratio of THC to CBD, have experimented with dosages involving multiple daily sprays, adjusted according to patient tolerance and response. CBD, due to its

non-psychoactive properties, has been tested at higher doses compared to THC. Clinical trials have tested CBD dosages up to 10 mg/kg/day, although efficacy at these levels has not been consistently demonstrated across studies. The variability in response has prompted researchers to suggest that dosages might need to be adjusted based on individual patient metabolism and the specific HD-related symptoms. In terms of THC, lower dosages are generally used to minimize psychoactive effects while still aiming to leverage its potential neuroprotective properties. Studies have typically used THC dosages ranging from 2.5 to 10 mg per day, often in combination with CBD to mitigate the psychoactive side effects and enhance therapeutic outcomes. The form of cannabinoid administration plays a crucial role in determining the effective dosage. Oral capsules and sprays are the most common forms used in clinical trials. Oral formulations tend to require higher dosages compared to oromucosal sprays due to differences in absorption and bioavailability. For instance, Sativex® oromucosal spray allows for more controlled dosing, which can be adjusted based on real-time patient needs and responses.

The case report by Curtis & Rickards (2006) provides an early insight into the use of cannabinoids for HD. Focusing on a single patient—a 43-year-old female with severe irritability and chorea—this study tested the efficacy of smoked cannabis and the synthetic cannabinoid nabilone. Starting with cannabis smoked during outings and progressing to a regulated dose of 1 mg/day of nabilone, the patient showed notable improvement in both irritability and chorea. The outcomes suggest that cannabinoids might help stabilize mood and reduce motor symptoms in HD patients. This case highlights the potential for cannabinoids to improve quality of life, yet it also underscores the necessity for further research, as the findings from a single case cannot be generalized. Expanding on the preliminary findings, Curtis et al. (2009)

conducted a randomized, double-blind, placebo-controlled, cross-over pilot study involving 44 patients, which provided a more structured evaluation of nabilone's efficacy. Over a trial period where doses were carefully escalated from 250 µg to 1-2 mg per day, the study assessed the impact on chorea and neuropsychiatric symptoms using the Unified Huntington's Disease Rating Scale (UHDRS) and the Neuropsychiatric Inventory (NPI). While the study found that nabilone was safe and generally well-tolerated, it only offered modest symptomatic relief, suggesting the need for larger-scale trials to better understand the therapeutic potential of cannabinoids in HD. Saft et al. (2018) conducted an observational research report to explore the effectiveness of various cannabinoid formulations including Sativex®, dronabinol, and nabilone in treating dystonia—a common and debilitating symptom in HD. The study involved seven patients with early-onset HD, focusing on those who experienced severe dystonia without concurrent medication changes that could skew results. Patients received up to 12 sprays per day of Sativex®, while the dosages for dronabinol and nabilone were adjusted based on patient tolerance and symptom severity. This personalized approach allowed for a careful assessment of cannabinoid efficacy in real-world settings. The primary outcome showed that cannabinoid treatment led to improvements in dystonia and overall motor symptoms, as evaluated by the Unified Huntington's Disease Rating Scale (UHDRS). Patients also experienced better care, improved gait, and reduced irritability and hypersalivation. These findings suggest that cannabinoids could significantly enhance motor control and patient well-being in HD, highlighting the need for further detailed studies. In a rigorous double-blind, randomized, placebo-controlled trial, López-Sendón Moreno et al. (2016) tested the safety and efficacy of Sativex® in a group of 26 HD patients, examining its impact

Authors	Study	Pts	Age	Dose	Delivery	Follow-up	Outcomes
Consroe et al. (1991)	Randomized cross-over	15	47.8 x̄	10mg/kg / day	Oral (CBD)	6 weeks / phase; 1-week wash-out	No significant effect on chorea severity or other symptoms compared to placebo. CBD was well-tolerated with no severe adverse effects. Mild side effects were similar between CBD and placebo conditions.
Curtis & Rikards (2006)	Case report	1	43	1mg	Oral (nabilone)	5 years	Improvements in irritability and reduction in chorea, enhancing quality of life.
Curtis (2009)	Randomized cross-over	44	34-72	1-2mg	Oral (nabilone)	5 weeks / phase; 5-week wash-out	Improvement in chorea, neuropsychiatric symptoms, and behaviour, but no significant change in overall motor function.
Lopez-Sendon Moreno et al. (2016)	Randomized cross-over	26	26-65	up to 12 sprays	Oral (Sativex®)	12 weeks	No significant improvement in motor, cognitive, or behavioural symptoms, but safe and well-tolerated.
Saft et al. (2018)	Retrospective case series	7	14-40	7-12 sprays; 2.2-9.1mg; 1.5mg	Oral (Sativex®, dronabinol, nabilone)	1-9 months	Improvement in dystonia, motor symptoms, and quality of life.

Table 3.14. *Studies evaluating use of medicinal cannabis with Huntington's Disease patients.*

on a broad range of symptoms from motor control to cognitive functions over a 12-week period. Participants used up to 12 sprays per day of Sativex®, with each spray delivering a precise dose of THC and CBD. The cross-over design of the study meant that all participants received both the active drug and a placebo at different times, thereby allowing a balanced and controlled assessment of Sativex's® efficacy. While the study confirmed the safety and tolerability of Sativex®, it did not find significant clinical improvement in HD symptoms compared to the placebo. This outcome serves as a critical reminder of the challenges in translating cannabinoid therapies from promising preclinical findings to effective clinical treatments. The exploration of cannabinoids in the treatment of Huntington's Disease offers both hope and significant challenges. While early studies show potential, particularly for symptom management, comprehensive clinical trials with larger cohorts and longer durations are essential to determine their role in clinical practice. The ongoing development of cannabinoid-based therapies represents a dynamic frontier in HD research that holds the promise of improving life quality for those affected by this incurable disease.

The determination of optimal dosages for cannabinoid-based therapies in HD is still evolving. Current research suggests a cautious approach to dosing, starting low and adjusting based on patient response and tolerability. Future clinical trials are needed to better define the dosage ranges that optimize efficacy while minimizing side effects, particularly given the progressive nature of HD and the potential for long-term treatment. Further complicating the dosage question is the interindividual variability in response to cannabinoids, likely due to genetic differences affecting cannabinoid receptor expression and function. This variability underscores the necessity for personalized medicine approaches in the treatment of HD, potentially using genetic and metabolic profiling to tailor cannabinoid therapies to individual patient needs. The

research on cannabinoid dosages in Huntington's disease points to a complex and nuanced landscape where more targeted, patient-specific studies are required. As the field advances, the development of more refined dosage guidelines will be crucial to fully harnessing the potential of cannabinoid therapies in managing and potentially altering the progression of Huntington's disease.

3.4.2.5.2. Research and clinical practice

The reviewed studies underscore the complexity of treating HD and suggest that while cannabinoids have potential, particularly for symptom management, they are not a panacea. The symptomatic benefits seen in motor control and mood stabilization are promising, yet consistent and significant improvements in disease outcomes are still lacking. The variability in treatment efficacy noted across studies indicates that individual responses to cannabinoid therapy may vary widely, necessitating personalized treatment plans. Medicinal cannabis may offer beneficial effects for managing certain symptoms of Huntington's disease, particularly motor symptoms like dystonia and symptoms such as irritability. However, the current body of research, characterized by small-scale and pilot studies, calls for larger, long-term clinical trials to thoroughly assess the efficacy and safety of cannabinoids in HD. The integration of medicinal cannabis into the treatment regimen for HD poses a promising but complex challenge. While preclinical data suggest substantial neuroprotective potential, the clinical efficacy of cannabis-based treatments in altering the course of HD needs further investigation through long-term and large-scale studies. Additionally, the variability in response observed in clinical trials indicates a need for personalized treatment approaches, potentially incorporating genetic, pharmacological, and

environmental factors to optimize therapeutic outcomes. As research progresses, it will be crucial to refine cannabinoid-based therapies and integrate them into broader therapeutic strategies, potentially improving quality of life and clinical outcomes for HD patients. The ongoing exploration of these compounds in neurodegenerative diseases could pave the way for novel treatment paradigms in Huntington's disease and beyond.

3.4.2.6. Alzheimer's Disease

Alzheimer's Disease (AD) is the most prevalent form of dementia among the elderly, characterized by a progressive decline in cognitive abilities including memory, language skills, and critical thinking. The disease affects millions globally, making it a significant public health challenge. Pathologically, AD is associated with the accumulation of amyloid-beta ($A\beta$) plaques and tau protein neurofibrillary tangles in the brain, which contribute to neuronal loss and dysfunction of neural networks (de Barros Viana et al., 2022; Bhunia et al., 2022).

Currently, the primary treatments for AD involve symptomatic management rather than addressing the underlying disease processes. The main classes of drugs include cholinesterase inhibitors (such as Donepezil, Rivastigmine, and Galantamine) and NMDA (N-methyl-D-aspartate) receptor antagonists like Memantine. These medications aim to improve neurotransmitter function in the brain but they do not stop the progression of the disease and are generally effective only in the early to middle stages of the disease (Aymerich et al., 2018; de Barros Viana et al., 2022; Bhunia et al., 2022). Cannabinoids have been reported to influence the processing of amyloid-beta and tau, the proteins involved in the key pathological processes of AD. For

example, THC can modulate the aggregation of both A β and tau proteins, potentially reducing the formation of neurotoxic plaques and tangles. CBD, on the other hand, may inhibit the hyperphosphorylation of tau protein, a process that leads to the development of neurofibrillary tangles (Aymerich et al., 2018; Murillo-Rodriguez et al., 2020; Singh et al., 2023; Voicu et al., 2023).

CBD exhibits significant anti-inflammatory and antioxidant properties, which could combat the neuroinflammation and oxidative stress associated with AD. Studies have shown that CBD can reduce cytokine levels and mitigate the effects of reactive oxygen species (ROS), thereby protecting neuronal cells from oxidative stress and apoptosis. Additionally, cannabinoids might promote brain repair mechanisms, such as neurogenesis and neurotrophin expression (Aymerich et al., 2018). While preclinical models have provided encouraging results regarding the neuroprotective benefits of cannabinoids, clinical data is still emerging. Initial studies in humans and ongoing clinical trials are beginning to explore the effectiveness of cannabinoids like THC and CBD in alleviating symptoms related to dementia, including agitation and memory impairments. However, comprehensive clinical evaluations and further research are necessary to establish their efficacy and safety in the treatment of AD (Tambe et al., 2023).

3.4.2.6.1. Recommended Dosages in Current Literature

Clinical studies have suggested that lower dosages of THC and CBD might be used initially to minimize potential adverse effects while still providing symptomatic relief (Table 3.15). For instance, trials involving THC analogues such as nabilone and dronabinol have shown that doses ranging from 2.5 mg to 10 mg daily can help reduce

symptoms like agitation and behavioural disturbances in AD patients. This approach follows the medical principle of "start low and go slow" to gauge the therapeutic response and adjust dosage as needed. In terms of higher dosages, some research indicates that they may be necessary for achieving neuroprotective effects such as reducing amyloid beta levels and counteracting neuroinflammation and oxidative stress associated with Alzheimer's Disease. Studies in animal models have employed CBD dosages up to 50 mg/kg, suggesting potential high-dose applications in human clinical scenarios. The effective dosage can also vary significantly based on individual patient factors, including the stage of Alzheimer's disease, the presence of other medical conditions, and overall patient tolerance. Additionally, the route of administration significantly affects the dosage, onset of action, and duration of effects. Oral formulations like oils and capsules are preferred for their longer-lasting impact, although they have a slower onset compared to inhaled forms. As research progresses, it is expected that more detailed and specific dosage guidelines will be established to optimize the therapeutic effects of cannabinoids in Alzheimer's disease while minimizing risks. This ongoing research will hopefully clarify the roles of CBD and THC in managing and potentially slowing the progression of Alzheimer's disease, leading to well-informed clinical practices.

Volicer et al. (1997) conducted a placebo-controlled crossover clinical trial involving 15 AD patients suffering from anorexia. The study administered 2.5 mg of dronabinol twice daily, resulting in increased body weight and decreased behavioural disturbances. Notably, these effects were sustained even during the placebo phase for some patients, suggesting a potential long-term benefit of dronabinol use in AD-related anorexia and agitation. In another pilot study by Walther et al. (2006), six patients with nighttime agitation and other circadian rhythm disturbances received 2.5

mg of dronabinol daily. This intervention significantly reduced nocturnal motor activity and improved overall behavioural scores without adverse effects, indicating that dronabinol could be a safe option for managing nighttime agitation in AD patients. Passmore (2008) provided an insightful case report on the use of nabilone, a cannabinoid receptor agonist, in a 72-year-old male with severe dementia-related agitation. The treatment, which involved dosages up to 0.5 mg twice daily, led to a notable reduction in agitation and resistance during care, with sustained improvements over six weeks. This case highlights the potential of nabilone to manage severe behavioural disturbances in dementia, particularly in situations where traditional antipsychotics are inappropriate. Woodward et al. (2014) reviewed the effectiveness of dronabinol in a retrospective chart review involving 40 dementia patients. The study documented significant reductions in agitation and aggression, as well as improvements in sleep and nutritional intake, underscoring the multifaceted benefits of dronabinol in dementia care settings.

The study by Shelef et al. (2016) is an open-label, add-on pilot study that examined the use of Medical Cannabis Oil (MCO) in 11 Alzheimer's dementia patients. The study demonstrated significant improvements in both the Neuropsychiatric Inventory (NPI) and Clinical Global Impression (CGI) scales, suggesting that THC could reduce BPSD by potentially inhibiting the aggregation of amyloid- β peptide. The results indicate that cannabinoids might be effective as supplementary treatment alongside standard pharmacotherapy, particularly in reducing symptoms like delusions, agitation, and irritability. In another study, Broers et al. (2019) conducted a prospective observational study involving ten female patients with severe dementia who were treated with a combination of THC and CBD. This study reported improvements in NPI and Cohen-Mansfield Agitation Inventory scores, and a decrease in rigidity, highlighting the

Authors	Study	Pts	Age	Dose	Delivery	Follow-up	Outcomes
Volicer et al. (1997)	Randomized cross-over	15	72.7 $\bar{x}$	2.5mg BD	Oral (dronabinol)	6 weeks / phase; 4-day wash-out	Weight gain and reduced severity of disturbed behaviour. Adverse effects included mild euphoria and somnolence, with one patient experiencing a seizure.
Walther et al. (2006)	Open label pilot	6	81.5 $\bar{x}$	2.mg	Oral (dronabinol)	2 weeks	Reduction in nocturnal motor activity, agitation, and aberrant motor behaviour as measured by actigraphy and NPI scores.
Mahlberg & Walther (2007)	RCT	24	79 $\bar{x}$	2.5mg	Oral (dronabinol)	2 weeks	Significant reduction in nocturnal agitation and Neuropsychiatric Inventory (NPI) agitation scores. Actigraphy showed decreased nocturnal activity in the treatment group compared to baseline.
Passmore (2008)	Case report	1	72	0.5-1mg	Oral (nabilone)	3 months	Significant reduction in agitation and resistiveness during personal care. No adverse effects were reported, and behaviour remained well-controlled for three months following discharge.
Woodward et al. (2014)	Retrospective cohort	40	-	7.03mg $\bar{x}$	Oral (dronabinol)	50 days	Decrease in agitation and aggression scores (Pittsburgh Agitation Scale) and improvements in Clinical Global Impression scores.
Ahmed et al. (2015)	Randomized escalation trial	50	65-92	0.75-1.5mg BD	Oral (Namisol - THC)	2 weeks / phase; 6 total phases	No significant improvement in neuropsychiatric symptoms. Adverse events were mild, primarily dizziness and somnolence. Body sway increased in the THC group but was not clinically significant.
van den Elsen et al. (2015a)	Randomized cross-over	22	76.4 $\bar{x}$	0.75-1.5mg BD	Oral (THC)	2 weeks / phase; 6 total phases	No significant reduction in NPS as measured by the NPI compared to placebo. THC was well-tolerated with a similar adverse event profile to placebo.
van den Elsen et al. (2015b)	RCT	50	78.4 $\bar{x}$	1.5mg TDS	Oral (THC)	3 weeks	No significant benefit of THC on NPS or agitation levels compared to placebo. Both groups saw a reduction in NPI scores, attributed to study involvement.
Shelef et al. (2016)	Open label pilot	11	73.2 $\bar{x}$	2.5-7.5mg BD	Oral (THC)	4 weeks	Notable reduction in NPI scores and Clinical Global Impression (CGI) severity scores, particularly in agitation/aggression, irritability, apathy, sleep, and caregiver distress.
van den Elsen et al. (2017)	Randomized cross-over	18	77 $\bar{x}$	1.5mg BD	Oral (THC)	3 days / phase; 4-day wash-out	Increased body sway during balance tasks with closed eyes. Increased stride length during gait assessment. No significant adverse events.
Broers et al. (2019)	Prospective case series	10	79.5 $\bar{x}$	7.6-9mg THC + 13.2-18mg CBD	Oral (THC-CBD oil)	5 months	Reductions in BPSD scores, including 40% reduction in Neuropsychiatric Inventory, 50% reduction in rigidity score. Decreased psychotropic medication use, improved care staff satisfaction. No major adverse effects were reported.

Table 3.15. *Studies evaluating use of medicinal cannabis in Alzheimer's Disease and dementia patients.*

potential of higher doses of THC and CBD to manage dementia symptoms more effectively than lower doses typically used. The findings suggest that cannabinoids could help reduce the use of other psychotropic medications, potentially minimizing side effects and improving patient outcomes. Ahmed et al. (2015) presented a randomized, double-blind, placebo-controlled crossover trial where ten dementia patients were treated with low doses of THC to assess its safety and pharmacodynamics. The study found that THC was well-tolerated and had minimal pharmacodynamic effects on neuropsychiatric symptoms, which supports its use for managing these symptoms in elderly patients with dementia. This trial underscores the importance of understanding the pharmacokinetics of THC, as it helps in optimizing the dosage and administration schedule to achieve desired therapeutic effects.

The randomized, double-blind, placebo-controlled, repeated crossover trial by van den Elsen et al. (2015a) involved 22 patients with dementia, primarily Alzheimer's type, who were administered low doses of THC to assess changes in Neuropsychiatric Inventory (NPI) scores. The study meticulously controlled dosage increases from 0.75 mg to 1.5 mg of THC twice daily, structured in two-week treatment blocks with intervening washout periods. Despite its structured approach, the trial concluded that THC did not significantly reduce NPI scores compared to the placebo, though it was well-tolerated with no significant increase in adverse events. The findings suggest that while low-dose THC is safe for patients with dementia, it may not substantially alleviate neuropsychiatric symptoms at the doses tested. The trial's outcomes highlight the need for further research into optimal dosing that might be more effective while maintaining a good safety profile. In a larger multicentre phase II trial by van den Elsen et al. (2015b), 50 patients were randomly assigned to receive either 1.5 mg of THC or a placebo three times daily over three weeks. The comprehensive assessment

included changes in the NPI, agitation levels, quality of life, and daily living activities. Similar to the 2015a study, this trial found no significant difference in symptom reduction between the THC and placebo groups. However, THC's safety profile remained favourable, with only mild to moderate adverse events that were comparable to those observed in the placebo group. The consistent observation of THC's safety across studies reinforces its potential as a benign component of treatment regimens for dementia. However, the lack of significant efficacy in symptom reduction prompts considerations for either higher dosages or combined treatment approaches with other therapeutics.

van den Elsen et al. (2017) conducted a randomized, double-blind, controlled crossover trial to assess the impact of Tetrahydrocannabinol (THC) on mobility, specifically balance and gait, in elderly patients with dementia. The study involved 18 community-dwelling patients who underwent two treatment periods of three days each, with THC dosage set at 1.5 mg twice daily. The primary tools for assessment were the SwayStar™ for balance and GAITRite™ for gait analysis. THC was found to significantly increase sway when standing with eyes closed but not with eyes open, and it increased stride length and trunk sway during preferred speed walking. These results suggest that while THC can affect balance, its impact on gait is less likely to compromise safety during complex cognitive tasks. The safety profile was robust, with no serious adverse events reported, emphasizing THC's potential as a safe treatment for mobility issues in dementia patients. The controlled setup and detailed assessments provide valuable insights into the safety profiles of THC, suggesting its feasibility in managing mobility issues in dementia without severe side effects. This open-label, randomized controlled trial by Mahlberg & Walther focused on using actigraphy to measure the effectiveness of interventions, including dronabinol (a

cannabinoid), on agitated behaviour and day-night rhythm disturbances in dementia patients. The study compared outcomes across three groups: Melatonin, dronabinol, and a Placebo over two weeks, involving 24 patients with Alzheimer's disease. The dronabinol group showed significant reductions in nocturnal activity and improvements in NPI scores, particularly for agitation, compared to baseline and placebo. This indicates dronabinol's effectiveness in reducing nighttime agitation and potentially improving overall behavioural symptoms. The absence of reported adverse effects and the positive outcome on NPI scores suggest that dronabinol could be a viable option for managing behavioural disturbances in Alzheimer's patients, particularly those experiencing significant nighttime agitation. These findings support the potential use of low-dose dronabinol in managing agitation and behavioural disturbances, highlighting its ability to improve nighttime behaviours without adverse effects. The studies reviewed here underscore the potential of THC and other cannabinoids as effective treatments for specific symptoms associated with Alzheimer's Disease. van den Elsen et al.'s (2017) work demonstrates THC's safety in affecting mobility factors like balance and gait, which are crucial for reducing fall risk in elderly patients. On the other hand, Mahlberg & Walther (2007) provide evidence of the benefits of dronabinol in reducing behavioural disturbances, particularly nocturnal agitation.

3.4.2.6.2. Research and clinical practice

Cannabinoids might modulate various pathological and symptomatic aspects of AD by interacting with the endocannabinoid system, which is involved in neuroinflammation, neurotransmitter signalling, and cell survival. The primary therapeutic potentials identified include neuroprotection, neuropsychiatric symptom management as well as

safety and efficacy. Cannabinoids have shown promise in reducing agitation and aggression, common in AD patients. These symptoms are often managed with antipsychotics, which can have severe side effects, including increased mortality risk. Cannabinoids offer a potentially safer alternative, with studies suggesting improvements in behaviour and symptom severity. There is growing evidence that cannabinoids may exert neuroprotective effects by reducing neuroinflammation and amyloid-beta levels, potentially slowing AD progression. For example, CBD has been found to lower amyloid-beta production and tau phosphorylation, key processes involved in AD pathogenesis. Clinical trials, such as those conducted by van den Elsen et al., suggest that cannabinoids are generally well-tolerated in elderly populations, with a better safety profile compared to traditional medications used for similar symptoms. However, more research is needed to fully establish their efficacy and optimal dosing.

While the existing data on the use of medicinal cannabis in Alzheimer's Disease (AD) are promising, the complexity of AD symptoms and the variability in patient responses necessitate cautious interpretation and further study. Future research should be comprehensive and multifaceted. It is essential to determine the optimal dosages and administration routes for cannabinoids to maximize their therapeutic effects while minimizing potential side effects. Additionally, understanding the long-term impacts of cannabinoid treatment on cognitive functions and the overall quality of life in AD patients will be crucial. Researchers must also delve deeper into mechanistic studies to explore how cannabinoids interact with the neurobiological substrates of AD. This could help in developing more targeted therapies that are effective in managing or potentially slowing the progression of the disease. Lastly, implementing larger, more

rigorous clinical trials is necessary to confirm these preliminary findings and support the broader clinical application of cannabinoids in treating Alzheimer's Disease.

Medicinal cannabis holds significant potential as a multifaceted treatment option for Alzheimer's Disease, offering benefits from symptom management to possibly modifying disease progression. However, its integration into mainstream clinical practice for AD requires a careful, evidence-based approach with robust clinical trials and regulatory review to ensure patient safety and efficacy. The continuation of current research trajectories and the exploration of new ones will be critical in harnessing the full potential of medicinal cannabis in Alzheimer's care.

3.4.2.7. Parkinson's Disease

Parkinson's Disease (PD) is a prevalent neurodegenerative disorder characterized primarily by the progressive loss of dopaminergic neurons in the substantia nigra pars compacta (SNpc), leading to significant motor symptoms such as bradykinesia, rigidity, and tremors. These symptoms result from the striatal dopamine deficit due to neuronal loss. PD affects approximately 1-2% of the population over 65 years of age and its incidence increases with age (Aymerich et al., 2018; Antonazzo et al., 2019). The primary treatment for PD is dopamine replacement therapy, with Levodopa (L-dopa) being the most effective medication available. L-dopa works by compensating for the depleted dopamine levels in the brain, thereby alleviating motor symptoms temporarily. However, its effectiveness tends to decrease as the disease progresses and more dopaminergic neurons are lost. This can lead to motor fluctuations and L-dopa-induced dyskinesia (LID), which are abnormal involuntary movements (Aymerich et al., 2018). Other treatments include dopamine agonists, MAO-B inhibitors, and

COMT inhibitors, which aim to increase or mimic dopamine's effects and manage symptoms (Bhunia et al., 2022; de Barros Viana, 2022).

Cannabinoids have emerged as a potential therapeutic option for PD due to their neuroprotective and symptom-alleviating properties. Activation of the CB1 and CB2 receptors has been shown to modulate neurotransmitter release and produce neuroprotective effects in preclinical studies. Recent studies have highlighted the potential neuroprotective benefits of cannabinoids in the context of Parkinson's Disease (PD) by demonstrating their capacity to modulate microglial activity and reduce both inflammation and oxidative stress—key factors in the pathogenesis of PD. Specifically, cannabinoids through the activation of CB2 receptors, such as with the CB2 receptor agonist JWH-133, have been shown to decrease microglial activation and consequently neuronal damage in preclinical models, like the MPTP mouse model of PD. These findings suggest that cannabinoids might play a critical role in protecting neurons from the progressive degenerative processes characteristic of PD (Voicu et al., 2023).

In addition to their neuroprotective properties, cannabinoids are also being studied for their efficacy in managing both motor and non-motor symptoms of Parkinson's Disease. Clinical observations and patient reports have indicated that cannabis might significantly improve symptoms such as tremors, rigidity, and bradykinesia, as well as non-motor symptoms including pain and sleep disturbances. For instance, an observational study has noted that smoked cannabis not only ameliorated these PD-related symptoms but also enhanced the overall quality of life for the patients involved. This symptomatic relief could represent a multifaceted therapeutic avenue for PD management through cannabinoid interventions (Aymerich et al., 2018; Murillo-

Rodriguez et al., 2020). Despite the encouraging preclinical evidence supporting the neuroprotective and symptomatic relief potential of cannabinoids in PD, the clinical outcomes have been inconsistent. Some clinical trials and studies have reported significant symptomatic improvements following cannabis use, whereas others have observed negligible effects. This variability in results may stem from numerous factors including differences in study design, the specific strains of cannabis used, and the inherent complexity of PD symptoms among different individuals. To clarify and expand upon these preliminary findings, ongoing and rigorous research involving controlled clinical trials is essential. Such studies will be crucial in determining the definitive role of cannabinoids in the treatment of Parkinson's Disease, potentially leading to innovative and effective therapeutic strategies (Fernández-Ruiz et al., 2015; Murillo-Rodriguez et al., 2020).

3.4.2.7.1. Recommended dosages in current literature

The potential of medicinal cannabis in the management of PD represents a dynamic frontier in neuropharmacology, specifically targeting motor and non-motor symptoms that are resistant to conventional dopaminergic therapies. The complex neurobiology of PD, characterized by the progressive degeneration of dopaminergic neurons in the substantia nigra and resultant striatal dopamine deficiencies, necessitates innovative treatment strategies that extend beyond traditional medications. The literature clearly supports a tailored approach to cannabinoid-based therapy in PD, reflecting the complex interplay between cannabinoid pharmacology and the pathophysiological features of PD. Dosing strategies must therefore be meticulously calibrated to balance

efficacy with safety, integrating patient-specific factors such as disease severity, symptomatology, and concurrent pharmacotherapies (Table 3.16).

The early explorations by Consroe et al. (1986) into the efficacy of CBD in treating dystonic disorders provide foundational insight into the potential applications of cannabinoids in movement disorders, including Parkinson's Disease (PD). This early study, although limited by its open-label and small-scale nature, highlighted the nuanced relationship between cannabinoid therapy and motor symptoms in PD. Particularly, it revealed that while CBD could significantly alleviate dystonia symptoms in patients, high doses might exacerbate certain Parkinsonian features such as hypokinesia and resting tremor. This dual outcome underscores the complex pharmacodynamics of cannabinoids and necessitates cautious dose escalation in clinical protocols to balance benefits with potential adverse effects. Moving to a broader context, Finseth et al. (2015) conducted a survey that shed light on the real-world application of cannabis among PD patients post its legalization. This cross-sectional study not only illustrated the extent of cannabis use for managing symptoms—particularly non-motor symptoms such as mood and sleep disturbances—but also emphasized its standing as one of the most effective self-reported therapies compared to other complementary and alternative medicine (CAM) modalities. The significant finding here was the high efficacy reported by users for non-traditional symptoms, aligning with anecdotal evidence and patient-reported outcomes that support cannabis' potential in enhancing quality of life. However, the lack of precise dosage data and reliance on self-reported efficacy highlight the need for more controlled clinical studies to substantiate these claims and refine therapeutic strategies. The study by Shohet et al. (2017) provided empirical evidence of cannabis' efficacy in reducing motor symptoms and pain in PD patients as an adjunct therapy.

Utilizing an observational setup, this research documented noticeable improvements in UPDRS scores and pain assessments shortly after cannabis use. Interestingly, the long-term application appeared to modulate pain sensitivity, suggesting a potential chronic effect of cannabis on sensory processing pathways. Such findings are critical as they illustrate both immediate and enduring modifications in symptomatology, proposing a dual mechanism of action for cannabis in PD—both as a symptomatic agent and a possible modulator of disease progression or symptom evolution.

Yust-Katz et al. (2017) conducted an extensive observational study to assess the pain management effectiveness of medical cannabis among Parkinson's disease and Parkinson plus syndrome patients. Utilizing a combination of structured questionnaires and clinical assessments, the study delved into the various pain types these patients experience—musculoskeletal, radicular/neuropathic, dystonic, and central pain. Despite not providing specific dosage details, the study's findings were significant; medical cannabis was reported to be highly effective in managing pain, comparable to traditional NSAIDs. This suggests that cannabinoids might play a crucial role in the pain management spectrum for Parkinson's disease, potentially offering a favourable profile compared to standard pharmacological treatments. Balash et al. (2017) took a retrospective approach via telephone interviews to explore the subjective effects of cannabis on Parkinson's symptoms. The participants, who had been using cannabis for an average duration of 19.1 months, reported notable improvements across several domains including mobility, pain, and overall mood. The reported large effect sizes for improvements specifically in mobility and pain highlight cannabis's potential as a potent adjunct therapy in Parkinson's management. However, the study also brought to light the side effects associated with cannabis use, such as confusion and hallucinations, underscoring the need for careful patient monitoring and dose

regulation. Frankel et al. (1990) offered a unique perspective by comparing the effects of marijuana against other medications like diazepam and apomorphine in managing severe tremor in Parkinson's patients. The controlled trial with a crossover design concluded that while traditional medications effectively managed tremor, marijuana did not produce a similar therapeutic benefit and was associated with side effects like drowsiness and euphoria. This study is particularly significant as it provides a comparative analysis that helps delineate the contexts in which cannabis might not be effective, especially concerning motor symptoms like tremor.

Carroll et al. (2004) embarked on a controlled trial aiming to assess the effectiveness of Cannador, a cannabis extract, in managing dyskinesia in Parkinson's Disease (PD) patients. This study, rigorous in its design as a randomized, double-blind, placebo-controlled crossover trial, involved 19 participants diagnosed with idiopathic PD. Despite the structured intervention and careful dose adjustment—ensuring each patient received an optimal dose based on weight—the results were underwhelming. The primary outcome, assessed through changes in the Unified Parkinson's Disease Rating Scale (UPDRS) dyskinesia score, revealed no significant improvement in dyskinesia or overall parkinsonism symptoms. This outcome casts a shadow on the potential of low-dose cannabis extracts in managing motor symptoms in PD, although the tolerability was noted as generally favourable with minor adverse effects like dry mouth and dizziness. In contrast to Carroll et al. (2004), the study conducted by de Faria et al. (2020) targeted non-motor symptoms, specifically anxiety and tremor amplitude, using a high dose of cannabidiol (CBD). In this double-blinded, placebo-controlled trial, 24 PD patients were given 300 mg of CBD in a simulated public speaking test to provoke anxiety. Remarkably, CBD significantly mitigated anxiety and reduced tremor amplitude compared to the placebo. This study not only highlights

CBD's potential as a symptomatic treatment for anxiety and tremor in PD but also underscores the variability in cannabis's therapeutic efficacy depending on the targeted symptoms and the cannabinoid profile used. Lotan et al.'s (2014) open-label observational study provides practical insights into the daily use of smoked cannabis by PD patients who were regular users due to inadequate relief from standard medications.

With 22 participants reporting before and after cannabis use, significant improvements were noted across both motor symptoms such as tremor and rigidity, and non-motor symptoms including pain and sleep quality. This study, although limited by its open-label design and potential placebo effects, suggests that regular cannabis use could substantially enhance quality of life for patients not fully supported by traditional treatments.

Kindred et al. (2017) conducted an expansive web-based survey to explore the usage and effects of cannabis among individuals with Parkinson's Disease (PD) and Multiple Sclerosis (MS). The survey, which included 595 participants, provided invaluable insights into how patients perceive the efficacy of cannabis in managing various symptoms associated with these neurodegenerative disorders. Significantly, 44% of respondents reported using cannabis, noting improvements in mood, memory, and fatigue, which suggests a potentially substantial role for cannabis in enhancing patient-reported quality of life. However, the study's reliance on self-reported data and lack of precise dosage information may limit the accuracy and applicability of the findings. These results highlight the necessity for further controlled studies to better understand the therapeutic potential and limitations of cannabis in PD and MS management. Zuardi et al. (2009) offered a closer look at cannabidiol's (CBD) impact on psychosis

Authors	Study	Pts	Age	Dose	Delivery	Follow-up	Outcomes
Consroe et al. (1986)	Open label pilot	5	-	100mg; max. 600mg	Oral (CBD)	6 weeks	Dose-related improvement in dystonia observed (20-50%); mild side effects included hypotension, dry mouth, psychomotor slowing, light-headedness, and sedation.
Frankel et al. (1990)	Cross-over trial	5	-	2-9% THC	Inhalation	-	No improvement in tremor following marijuana administration; patients did experience drowsiness and mild euphoria.
Sieradzan et al. (2001)	Randomized cross-over	7	49-69	0.03mg/kg	Oral (nabilone)	2 weeks / phase; 2-week wash-out	Reduction in total dyskinesia score (22.2% reduction in on-period dyskinesia). Minor transient adverse effects like sedation and dizziness reported.
Carroll et al. (2004)	Randomized cross-over	19	51-78	max. 0.25mg/kg	Oral (THC)	4 weeks / phase; 2-week wash-out	No improvement in dyskinesias or Parkinson's symptoms compared to placebo.
Mesnage et al. (2004)	RCT	24	65 $\bar{x}$	20-200mg	Oral	-	No improvement in motor symptoms or levodopa-induced dyskinesias with the cannabinoid receptor antagonist.
Venderová et al. (2004)	Cross-sectional survey	339	36-92	Varied	Oral, Inhalation	1.7 months $\bar{x}$	45.9% reported improvement in symptoms including tremor, bradykinesia, rigidity, and dyskinesias. Regular use was correlated with higher rates of reported symptom alleviation.
Zuardi et al. (2009)	Open label pilot	6	58.8 $\bar{x}$	150-400mg	Oral (CBD)	4 weeks	Significant reduction in psychotic symptoms measured by the Brief Psychiatric Rating Scale and the Parkinson Psychosis Questionnaire. No worsening of motor symptoms, and CBD was well tolerated with no adverse effects.
Chagas et al. (2014a)	RCT	21	63-67	75mg-300mg	Oral (CBD)	6 weeks	No improvement in motor symptoms but potential improvement in quality of life in higher CBD dose group.
Chagas et al. (2014b)	Case series	4	59-71	75mg-300mg	Oral (CBD)	6 weeks	Reduction in frequency of REM sleep behaviour disorder events without side effects.
Lotan et al. (2014)	Prospective open label	22	65 $\bar{x}$	0.5g	Inhalation	-	Improvement in motor symptoms (tremor, rigidity, bradykinesia) and non-motor symptoms (pain and sleep quality).
Finseth et al. (2015)	Cross-sectional survey	207	69 $\bar{x}$	-	Inhalation	-	Effective for mood and sleep improvement, and across therapies for both motor and non-motor symptoms.
Balash et al. (2017)	Retrospective cohort	47	64.2 $\bar{x}$	0.9g $\bar{x}$	Oral, Inhalation	19.1 months $\bar{x}$	Improvements in falls, pain, depression, tremor, muscle stiffness, and sleep. Some adverse effects like cough, confusion, and hallucinations were reported.
Kindred et al. (2017)	Cross-sectional survey	595	61.1 $\bar{x}$	Varied	Oral, Inhalation	-	Improvements in mood, memory, and fatigue. 59% reported reducing prescription medications.

Authors	Study	Pts	Age	Dose	Delivery	Follow-up	Outcomes
Shohet et al. (2017)	Prospective open label	20	43-78	1g	Inhalation	14 weeks	Decrease in motor symptoms (UPDRS scores) and pain scores (PRI, VAS). Reduced pain thresholds observed over time.
Yust-Katz et al. (2017)	Cross-sectional survey	371	69 $\bar{x}$	Varied	Unspecified	-	Effective for pain relief in 77% of patients, impacting quality of life. As effective as NSAIDs.
de Faria et al. (2020)	Randomized cross-over	24	64.1 $\bar{x}$	300mg	Oral (CBD)	15 days	Reduced anxiety and tremor amplitude during simulated public speaking, suggesting an anxiolytic effect of CBD in PD patients.
Leehey et al. (2020)	Open label pilot	13	68.2 $\bar{x}$	19.4mg/kg $\bar{x}$	Oral (Epidiolex®)	1 month	Improved motor symptoms (17.8% decrease in total MDS-UPDRS score and 24.7% in motor scores). Adverse effects included mild to moderate diarrhoea, somnolence, and fatigue, with 38% experiencing elevated liver enzymes at high doses.
Micheli et al. (2020)	Cross-sectional survey	503	27-93	Varied	Oral (oil)	-	44.6% reported symptom improvement, motor and non-motor. Adverse effects included drowsiness, motor worsening, hallucinations, and other mild symptoms.
Holden et al. (2022)	Cross-sectional survey	1881	66.5 $\bar{x}$	Varied	Oral, Inhalation	-	Improvements in pain, anxiety, agitation, and sleep.
Domen et al. (2023)	RCT	58	70.5 $\bar{x}$	94.4mg $\bar{x}$ CBD, 3.2mg $\bar{x}$ THC	Oral (oil)	16.3 days $\bar{x}$	The CBD/THC group showed slightly worse performance on verbal fluency tests compared to placebo, and reported adverse cognitive events. No significant improvement in motor symptoms relative to placebo. Slight declines in cognition and sleep were noted in the CBD/THC group.
Sousa et al. (2023)	Cross-sectional survey	15	67.5 $\bar{x}$	Varied	Varied	-	Some patients reported improvements in pain (71% noted some reduction), sleep, and reductions in anxiety. Lower global cognitive scores on the MoCA for CBD/THC users compared to non-users. No significant differences in other neuropsychological measures or motor function. Reported side effects included sleepiness, concentration difficulties, and forgetfulness.
Liu et al. (2024)	RCT	61	70.4 $\bar{x}$	191.8mg CBD, 6.4mg THC	Oral (oil)	2 weeks	No significant difference in motor improvement between groups. Placebo showed better results in sleep and cognition. Mild adverse events reported, with more frequent adverse effects in the CBD/THC group.

Table 3.16. *Studies evaluating use of medicinal cannabis in Parkinson's Disease patients.*

in Parkinson's disease through an open-label pilot study. This small-scale study involved six PD patients and focused on evaluating the effects of CBD on psychotic symptoms using the Brief Psychiatric Rating Scale and the Parkinson Psychosis Questionnaire. The findings indicated a significant reduction in psychotic symptoms and an improvement in the patients' overall condition without worsening motor functions. Although promising, the study's open-label design and small participant number call for larger, placebo-controlled trials to validate these preliminary findings and ensure the replicability of the results across broader populations. Chagas et al. (2014b) investigated the use of CBD for treating rapid eye movement sleep behaviour disorder (RBD) symptoms in Parkinson's Disease. In this case series, CBD was shown to substantially decrease the frequency and severity of RBD-related events such as agitation and aggressive behaviour during sleep. All four participants in the study experienced notable relief from RBD symptoms, which underscores CBD's potential as an effective treatment for this challenging condition. Nonetheless, the absence of a control group and the small sample size are significant limitations that might affect the generalization of these results to the larger PD population. Chagas et al.'s study is particularly notable for its focus on the quality of life and neuroprotective potential of CBD in PD. This exploratory, randomized, double-blind, placebo-controlled trial investigated how different dosages of CBD (75 mg/day and 300 mg/day) could affect general symptoms and quality of life as assessed by the UPDRS and PDQ-39. Interestingly, while there were no marked improvements in motor symptoms, the higher dose of CBD was associated with significant enhancements in the quality of life for the participants. This distinction highlights CBD's potential as a supportive treatment in PD, particularly in improving aspects that contribute to the overall quality of life rather than direct symptom control. The study's design and comprehensive

methodology provide a strong foundation for future research aimed at integrating CBD into broader PD management strategies.

The study conducted by Sieradzan et al. (2001) represents a significant effort to understand how cannabinoid derivatives can impact Parkinson's symptoms, particularly levodopa-induced dyskinesia. In this randomized, double-blind, placebo-controlled crossover trial, nabilone, a synthetic cannabinoid, was tested for its efficacy in reducing dyskinesia in PD patients. The study's findings indicated a 22.2% reduction in dyskinesia when treated with nabilone compared to placebo. This suggests that cannabinoids might modulate dyskinesia by influencing GABA uptake in the globus pallidus, a region affected in PD. Despite the promising results, the trial's small sample size and short duration limit the generalizability of these findings, highlighting the need for further research with a larger cohort and extended treatment periods to better understand the cannabinoid's potential and mechanisms of action. Mesnage et al. (2004) took a different approach by examining the effects of neurokinin B, neurotensin, and cannabinoid CB1 receptor antagonists on motor symptoms and dyskinesias in PD. This randomized, double-blind, placebo-controlled study involved 24 patients who did not experience significant improvements in motor disability or dyskinesias from these treatments. The results suggest that while these particular antagonists might not be effective in directly mitigating PD motor symptoms, it opens further discussion on the role of various neurotransmitters and receptors involved in PD pathology. The findings underscore the complexity of PD treatment, indicating that blocking these receptors does not necessarily translate to clinical benefits, thereby calling for more comprehensive approaches to understand the diverse neurochemical underpinnings of the disease. Leehey et al. (2020) embarked on an open-label, dose-escalation study to explore the potential therapeutic benefits and safety concerns associated with

Cannabidiol (CBD) usage in Parkinson's Disease (PD) patients, particularly focusing on rest tremor and other motor symptoms. This study aimed to determine the optimal dosage while monitoring for any adverse reactions such as elevated liver enzymes, which were noted as a concern at higher dosages. The study found that CBD, starting at 5 mg/kg/day and titrated up to 20-25 mg/kg/day, showed promising results in improving motor symptoms as evaluated by the Movement Disorder Society Unified Parkinson Disease Rating Scale (MDS-UPDRS). However, the occurrence of side effects like diarrhoea and fatigue highlighted the need for careful management of dosage levels. This research underscores the potential of CBD in symptom management in PD but also calls attention to the necessity of controlled trials to better delineate its efficacy and safety profile comprehensively.

Holden et al. (2022) conducted a large-scale, cross-sectional observational study utilizing a web-based survey to assess the usage patterns and perceived effects of cannabis among nearly two thousand PD patients. The findings indicated that higher THC products generally offered greater symptomatic relief for conditions such as pain and anxiety but were also associated with more significant adverse effects such as cognitive changes and dizziness. Conversely, products with higher CBD content were favoured for their milder side effect profile. This study highlights the varied responses to different cannabinoid profiles and emphasizes the importance of personalizing cannabis-based treatments to balance efficacy with potential risks. The study's reliance on self-reported data and its observational nature could introduce bias and limit the ability to draw definitive causal connections between cannabis use and symptom management outcomes.

3.4.2.7.2. Research and clinical practice

Despite advances in understanding PD, the treatment landscape remains challenging, with a continuous search for more effective therapies. Recent studies exploring the use of medicinal cannabis have provided new insights into its potential benefits and risks in managing PD symptoms. Recent research has highlighted the diverse applications of cannabinoids like CBD and THC in the management of both motor and non-motor symptoms of PD. Studies such as those by Sousa et al. (2023) have examined the utilization methods, effects on symptoms, and overall patient attitudes towards cannabis use in naturalistic settings. Their findings suggest varied experiences among patients, with some reporting improvements in non-motor symptoms such as sleep disturbances and anxiety, although concerns about cognitive impacts were noted, particularly with high THC doses.

In more controlled settings, randomized clinical trials like those reported by Domen et al. (2023) and Liu et al. (2024) have provided mixed results. Domen et al. (2023) found indications of cognitive impairment with high-dose CBD/THC treatment, suggesting potential risks that must be carefully managed in clinical practice. Conversely, Liu et al. observed no significant improvements in motor symptoms with CBD/THC use, underscoring the variability in patient responses and the complexity of PD symptom management. Observational studies such as the pilot study by Sousa et al. contribute to a broader understanding by documenting real-world usage and patient-reported outcomes. This study underscored the importance of monitoring cognitive functions closely when using cannabinoids, particularly in vulnerable populations like those with PD, who may experience varying degrees of cognitive decline as part of their condition. The therapeutic potential of cannabinoids in PD includes symptomatic relief

from tremors, rigidity, and bradykinesia, as well as from non-motor symptoms such as anxiety and sleep disorders. However, the risks, particularly of cognitive impairment and the exacerbation of existing symptoms, require careful consideration. Standardization of dosing and administration methods, as seen in some clinical trials, could help mitigate these risks and lead to more reliable and effective treatment protocols.

Looking ahead, the integration of findings from diverse research methodologies, including randomized trials, observational studies, and comprehensive reviews, is crucial for developing well-rounded treatment strategies. As outlined in the literature, future research should aim to refine dosing guidelines, identify patient populations that might benefit most from cannabinoid therapy, and explore the long-term impacts of such treatments on quality of life and disease progression in PD. The exploration of medicinal cannabis in Parkinson's Disease reflects a growing interest in alternative therapies that could potentially ease the burden of this challenging condition. While promising, the use of cannabinoids requires a nuanced approach that balances potential benefits against the risks, especially given the complexity of PD symptoms and the variability in patient responses. Ongoing research and clinical trials will be vital in shaping the future of PD treatment, ensuring that it is both effective and safe for all patients involved.

3.4.2.8. Cancer

Recent advances have also explored the potential use of medicinal cannabis either as an adjunct or a potential alternative in cancer treatment protocols. The primary cannabinoids of interest are Tetrahydrocannabinol (THC) and Cannabidiol (CBD),

which have been shown to possess various therapeutic properties that may benefit cancer patients. These include pain relief, nausea reduction, and appetite stimulation, which are particularly useful in improving the quality of life for those undergoing rigorous cancer treatments (Guzmán et al., 2006; Velasco et al., 2016).

Furthermore, preclinical studies suggest that certain cannabinoids might inhibit tumour growth by inducing apoptosis and halting angiogenesis and cell proliferation (Guzmán et al., 2003; Velasco et al., 2004). For instance, a study by Morelli et al. (2014) demonstrated that CBD could enhance the uptake and potency of traditional chemotherapeutic agents, potentially allowing for lower dosages and reduced side effects. Such findings underscore the need for more comprehensive clinical trials to better understand and harness the anticancer properties of cannabinoids.

3.4.2.8.1. Mechanisms of action of cannabinoids in cancer treatment

Cannabinoids have shown promising therapeutic potential in cancer treatment. These compounds interact with the body's endocannabinoid system (ECS), which plays a pivotal role in maintaining cellular homeostasis. Research has explored their anti-proliferative, anti-angiogenic, anti-metastatic, and pro-apoptotic effects, as well as the mechanisms through cannabinoid receptors and other pathways. Prominent studies such as those by Scott et al., 2017 and Ramer et al., 2010 have been pivotal in highlighting the diverse mechanisms through which cannabinoids can influence cancer pathology.

Ramer et al., 2010 provided evidence that cannabinoids could reduce cancer cell invasiveness. By modulating cell adhesion and migration, cannabinoids might limit

cancer metastasis, an essential factor in improving clinical outcomes in cancer patient (Ramer et al., 2010). Scott et al., 2017 investigated the synergistic effects of cannabinoids when used alongside traditional chemotherapy agents. They suggested that cannabinoids might enhance the cytotoxicity of chemotherapeutic drugs, potentially leading to more effective treatment outcomes at lower dose (Scott et al., 2017).

Cannabinoids have been demonstrated to exert significant anti-proliferative actions on various tumour cells. THC (tetrahydrocannabinol), CBD (cannabidiol), and other cannabinoids can inhibit the proliferation of cancer cells by modulating key cell cycle proteins and signalling pathways. For instance, Guzmán et al., 2006 reported that THC induced the death of glioma cells by a process of autophagy mediated by the stimulation of ER stress. Velasco et al., 2013 further elaborated on these findings, indicating that cannabinoids could disrupt the signalling pathways that promote cancer cell growth, such as the PI3K/AKT pathway, a critical pathway for cell survival and proliferation (Guzmán et al., 2006; Velasco et al., 2016).

The formation of new blood vessels (angiogenesis) is crucial for tumour growth and metastasis. Cannabinoids have shown potential in inhibiting angiogenesis associated with cancer progression. Studies such as Blázquez et al., 2006 have illustrated that cannabinoids can decrease the production of VEGF (vascular endothelial growth factor) and other pro-angiogenic signals in cancer cells, reducing the vascularization of tumours and thereby limiting their growth and spread (Blázquez et al., 2004). Metastasis remains one of the most challenging aspects of cancer treatment. Cannabinoids are being studied for their ability to prevent cancer cells from spreading. Ramer and Hinz, 2008 demonstrated that CBD effectively inhibited the invasiveness

of lung cancer cells through the up-regulation of TIMP-1 (tissue inhibitor of metalloproteinases-1), an inhibitor of matrix metalloproteinases involved in tissue invasion and metastasis (Ramer & Hinz, 2008). Apoptosis, or programmed cell death, is another mechanism through which cannabinoids can reduce tumour burden. The pro-apoptotic effects of cannabinoids have been well documented, particularly their ability to induce cell death in cancer cells without harming normal cells. This selective toxicity is seen as a significant advantage in cancer treatment, potentially reducing side effects associated with conventional chemotherapy. Marcu et al., 2010 found that cannabinoids like THC and CBD could induce apoptosis in human glioma cells by activating ceramide biosynthesis and ER stress-related pathways (Marcu et al., 2010).

The effects of cannabinoids in cancer are primarily mediated through the cannabinoid receptors CB1 and CB2. These receptors are part of the ECS and are found in various tissue types throughout the body. Activation of CB1 and CB2 receptors by cannabinoids can trigger multiple signal transduction pathways that influence cell fate decisions, thereby affecting cancer cell survival and proliferation. In addition to receptor-mediated actions, cannabinoids can also exert effects through non-receptor pathways. For example, CBD has been shown to act independently of the CB1 and CB2 receptors to reduce cytokine production and inhibit cell proliferation, possibly through modulation of other receptors such as GPR55 or TRPV channels, indicating a complex pharmacology that may involve multiple signalling mechanisms (Ligresti et al., 2006; De Petrocellis et al., 2011).

3.4.2.8.2. Dosages and formulations used in clinical trials

The clinical application of cannabinoids has varied significantly across different studies, with dosages and formulations carefully tailored to maximize therapeutic benefits while minimizing side effects (Table 3.17). CBD-enriched extracts were studied for their potential to enhance chemotherapeutic efficacy and to reduce associated toxicities. These studies often employed dosages calculated to optimize safety and efficacy, focusing on the synergistic potential of combining cannabinoids with other cancer therapies.

Morelli et al. (2014) investigated the synergistic effects of CBD with conventional chemotherapeutic agents. Their research demonstrated that CBD could significantly enhance the cytotoxic effects of drugs like bortezomib and carmustine. By facilitating their uptake into cancer cells, CBD may help to reduce the necessary dosage of these potent medications, potentially alleviating their adverse side effects. Specifically, they used a dosage of 20 μ M CBD alongside standard chemotherapy protocols, which pointed to a promising approach to improve drug efficacy and patient tolerance (Morelli et al., 2014). Nabissi et al. (2013) focused on glioblastoma multiforme, a notably aggressive brain tumour, and examined the impact of cannabinoids on the treatment efficacy. The study found that CBD could enhance the entry of chemotherapeutic agents such as doxorubicin into cancer cells. This ability suggests that lower dosages of chemotherapy drugs might be effectively employed, which is crucial in reducing the toxic side effects commonly associated with these treatment (Nabissi et al., 2013). Neumann-Raizel et al. (2019) provided insights into how cannabinoids might increase the chemosensitivity of cancer cells. Their findings suggest that CBD can alter the permeability of cancer cell membranes, thereby enhancing the effectiveness of drugs

like doxorubicin. The implications of their research include the potential need for adjusted drug dosages to fully leverage CBD's properties to decrease resistance to chemotherapy (Neumann-Raizel et al., 2019).

Guzmán et al. (2003) is a narrative review that examined the effects of THC on glioma cells, noting that it could induce apoptosis in these cancer cells, providing an early indication of the potential utility of cannabinoids as adjunct therapy in cancer treatment. Velasco et al. (2016) focus on the broader therapeutic potential of cannabinoids across various types of cancer. Their comprehensive systematic review discusses how cannabinoids can trigger cell death and inhibit tumour growth through mechanisms like apoptosis and autophagy. These findings are critical and they underscore the multifaceted roles of cannabinoids in modulating key cellular processes involved in cancer progression. Neumann-Raizel et al. (2019) again feature with their investigation into how cannabinoids can improve the chemosensitivity of cancer cells to treatments like doxorubicin. Their work highlights the potential of cannabinoids to increase the permeability of cancer cell membranes, thereby enhancing the effectiveness of conventional drugs. This study points towards the need for optimized dosages to fully utilize the properties of cannabinoids in reducing chemotherapy resistance. Ferro et al. (2018) delved into the role of CBD in conjunction with gemcitabine for pancreatic cancer treatment in mouse models. They found that CBD could potentially enhance the efficacy of gemcitabine by modulating various cellular pathways that contribute to tumour growth and survival. The study suggests that CBD might help in overcoming resistance to gemcitabine, thereby potentially improving outcomes in treatment-resistant cases of pancreatic cancer.

Authors	Study	Pts	Age	Dose	Delivery	Follow-up	Outcomes
Ekert et al. (1979)	Randomized cross-over	19	-	Unspecified	Oral (THC)	-	THC was superior to metoclopramide for nausea control but caused dizziness and mild euphoria.
Plasse et al. (1991)	Open label pilot	42	-	2.5-10mg	Oral (dronabinol)	6 weeks	Improvement in appetite and mood. A reduction in weight loss (-0.93 before vs +0.54 after therapy) particularly at 2.5mg BD.
Nelson et al. (1994)	RCT	19	52-81	2.5mg TDS	Oral (THC)	4 weeks	13 of 18 patients reported an improvement in appetite, with mild adverse effects. The study concluded THC to be an effective appetite stimulant with good tolerance at low doses.
Jatoi et al. (2002)	RCT	469	65-67x	2.5mg BD	Oral (dronabinol)	8 weeks	Megestrol acetate led to greater weight gain compared to dronabinol. Combination therapy did not show extra benefits.
Walsh et al. (2005)	Case series	6	52-74	7.5-15mg	Oral (dronabinol)	2-30 weeks	Stable or improved appetite and weight gain, with median weight gain of 1 kg in 5 patients.
Strasser et al. (2006)	RCT	243	-	2.5mg THC + 1mg CBD or 2.5mg THC	Oral	42 days	No significant differences in appetite or body weight compared to placebo. The cannabinoid treatment was associated with a higher rate of adverse events.
Johnson et al. (2010)	RCT	177	60.2 x	8.3-8.8 sprays / day (2.7mgTHC + 2.5mgCBD)	Oromucosal spray (nabiximols)	2 weeks	THC:CBD extract showed potential for pain relief and slight appetite improvement, while the THC-only group showed minimal effect. Quality of life was not significantly improved.
Brisbois et al. (2011)	RCT	46	-	2.5mg BD	Oral (THC)	19 days	Improved appetite (64% vs 50%) and chemosensory perception (36% vs 15%). No significant improvement in quality of life.
Portenoy et al. (2012)	RCT	360	58 x	max.10 sprays / day (2.7mgTHC + 2.5mgCBD)	Oromucosal spray (nabiximols)	6 weeks	Significant reduction in pain observed in low and medium-dose groups compared to placebo. High-dose group had more adverse effects without additional pain relief benefits.
Johnson et al. (2013)	Open label pilot	43	57.5 x 58.6 x	max.48 sprays / day (2.7mgTHC + 2.5mgCBD)	Oromucosal spray (nabiximols)	-	Long-term use was generally well tolerated with no evidence of loss of analgesic effect. Sustained benefit without tolerance development.
Singh & Bali (2013)	Case report	1	14	max. 3 drops	Oral (oil)	-	Symptomatic improvement. No adverse effects documented.
Lynch et al. (2014)	Randomized cross-over	16	56 x	max.12 sprays / day (2.7mgTHC + 2.5mgCBD)	Oromucosal spray (nabiximols)	4 weeks / phase; 2-week wash-out	3 patients reported a clinically significant reduction in pain (≥2 points on a numeric pain scale). Nabiximols may reduce chemotherapy-induced neuropathic pain.
Côté et al. (2015)	RCT	56	63.5 x	0.5-2mg	Oral (nabilone)	11 weeks	No significant improvement in quality of life, pain, appetite, or nausea compared to placebo.
Elder & Knoderer (2015)	Retrospective cohort	58	13.9 x	Unspecified	Oral (dronabinol)	10.5 years	Dronabinol provided symptomatic relief, but some patients reported mild adverse effects like dizziness.
Fallon et al. (2017)	RCT	399, 406	60 x	max.10 sprays / day (2.7mgTHC + 2.5mgCBD)	Oromucosal spray (nabiximols)	5 weeks; 5 weeks	No significant improvement in primary endpoints for pain reduction in the full sample; however, post hoc analysis showed favourable effects in patients under 65.

Authors	Study	Pts	Age	Dose	Delivery	Follow-up	Outcomes
Warren et al. (2017)	Case report	1	17	5-20mg/kg	Oral (CBD)	-	Reported improvement in seizure control, with no significant adverse effects reported.
Dorris et al. (2018)	Prospective cohort	26	6.6 x̄	Unspecified	Unspecified	-	Assessed quality of life impacts using the PedsQL 4.0 module. Reported benefits but did not specify adverse events.
Kasvis et al. (2018)	Retrospective chart review	54	47.3 x̄	Variable	Oral, Inhalation	3 months	Significant improvement in appetite scores (baseline: 5.07; follow-up: 3.56; P = 0.0026). No significant changes in weight.
Lichtman et al. (2018)	RCT	397	59.2 x̄ 60.7 x̄	max.10 sprays / day (2.7mgTHC + 2.5mgCBD)	Oromucosal spray (nabiximols)	5 weeks	Modest improvement in pain scores versus placebo in the per-protocol analysis but not the intention-to-treat population. Significant improvements were seen in quality-of-life measures.
Polito et al. (2018)	Retrospective cohort	110	1-18	Unspecified	Oral (nabilone)	5 years	Nabilone was effective in preventing acute CINV with minimal adverse effects.
Turcott et al. (2018)	RCT	53	61.1x̄	0.5-1mg	Oral (nabilone)	8 weeks	Improved appetite and reduced pain and insomnia. Adverse events included drowsiness and dry mouth.
Anderson et al. (2019)	Retrospective cohort	1120	48-66	Unspecified	Oral	29 months	High patient-reported efficacy for anxiety and pain, with mild adverse effects including fatigue.
Kasvis et al. (2019)	Prospective cohort	37	47.3 x̄	1mg CBD, 2.5mg THC	Oral (oil)	4 months	Improvement in appetite across visits, though weight remained stable. 80% of patients reporting anorexia noted improvements.
Skrypek et al. (2019)	Retrospective cohort	101	15.3 x̄	Unspecified	Unspecified	43 months	Reported symptom relief in nausea, pain, and cachexia, but adverse effects such as drowsiness were noted.
Bar-Sela et al. (2019)	Open label pilot	17	66 x̄	5-10mg BD	Oral (THC:CBD)	6 months	≥10% weight gain. Others maintained stable weight. Improved appetite, mood. Reduction in fatigue and pain.
Doherty et al. (2020)	Retrospective chart review	21	8.3 x̄	Unspecified	Oral	8 years	Observed benefits for pain, nausea, vomiting, anorexia, and insomnia. Limited adverse effects
Zylla et al. (2021)	RCT	30	56 x̄	5-40mg	Varied	3 months	Improved pain control and reduced opioid requirements in the early cannabis group compared to the delayed group. However, some patients faced challenges with self-administering and maintaining documentation for dosing and effects.
Clarke et al. (2022)	Prospective dose-escalation pilot	30	55.9-62 x̄	2-6 sprays (2.5mg CBD + 2.5mg THC)	Oromucosal	1 month	Improvements in pain and quality of life metrics (EORTC-QLQ-30 scores). Rapid absorption and clearance of THC and CBD, indicating a well-tolerated profile at administered doses.
Sharon et al. (2024)	Cross-sectional	252	61.7 x̄	Varied	Oral, Inhalation	-	70% of patients reported improvement in pain and other symptoms. 40% reported improvement in coping with illness.

Table 3.17. *Studies evaluating use of medicinal cannabis in cancer patients.*

3.4.2.8.3. Future research directions

One of the most promising avenues for future research involves the development of targeted cannabinoid therapies that can selectively interact with specific cancer-related pathways. Current studies suggest that cannabinoids such as THC and CBD can influence various cellular processes involved in cancer progression, such as proliferation, apoptosis, and metastasis. However, the mechanisms underlying these effects are not fully understood and appear to vary significantly across different cancer types and individual patients. Among the prospects for future research are molecular targeting and customized therapeutics. The former investigates the interaction between cannabinoids and specific molecular targets associated with cancer progression. This includes further elucidation of the roles of CB1 and CB2 receptors, as well as non-cannabinoid receptor pathways such as GPR55 or TRPV channels. The latter looks into the development of cannabinoid formulations that are tailored to individual genetic profiles or specific tumour characteristics. This personalized approach could enhance the efficacy of treatment while minimizing unwanted side effects.

While the acute safety profile of medicinal cannabis is relatively well-established, there is a crucial need for comprehensive long-term safety studies. These studies would provide invaluable data on the prolonged use of cannabinoids, particularly in a cancer treatment context, where patients may require extended therapy periods. This should include conducting long-term clinical trials to assess the safety and efficacy of medicinal cannabis when used over extended periods. These studies should monitor not only potential toxicological risks but also quality of life indicators and overall survival rates. It should also encompass examining the interactions between

cannabinoids and conventional cancer therapies to identify any potential adverse effects or synergies. This research should also explore the optimal sequencing of cannabinoid therapy and traditional treatments to maximize patient outcomes.

Further studies are also needed to clarify the precise mechanisms through which cannabinoids exert their anticancer effects. Understanding these mechanisms will help to optimize the use of cannabis in treatment regimens and potentially unlock new therapeutic strategies. Mechanistic studies to investigate the cellular and molecular mechanisms by which cannabinoids influence cancer cell biology. This includes studies on apoptosis induction, inhibition of cell proliferation, anti-angiogenesis, and effects on the immune system. Resistance research to study the potential for cancer cells to develop resistance to cannabinoid-based therapies, similar to resistance seen with many chemotherapeutic agents. Understanding these pathways could lead to the development of combination therapies that prevent resistance. The path forward for cannabinoid research in cancer treatment is rich with opportunities. By focusing on these key areas, researchers can not only improve the therapeutic outcomes of current cannabinoid-based treatments but also potentially discover novel anticancer strategies. Continued collaboration between oncologists, pharmacologists, and molecular biologists will be essential to translate these research initiatives into clinical successes that can significantly impact patient care in oncology.

3.4.2.9. Obsessive-compulsive disorder and Tourette Syndrome

Obsessive-Compulsive Disorder (OCD) is a neuropsychiatric condition characterized by persistent, unwanted thoughts (obsessions) and repetitive behaviours or mental acts (compulsions) that the person feels compelled to perform. These symptoms can

significantly disrupt daily functioning and quality of life (Pittenger & Bloch 2014; Ayati et al., 2020). Gilles de la Tourette Syndrome (TS), commonly known as Tourette Syndrome, is a chronic neurodevelopmental disorder characterized by motor and vocal tics—sudden, brief, repetitive movements or sounds. The syndrome typically manifests in childhood, peaks during adolescence, and in some cases, persists into adulthood, affecting males more frequently than females (Schwittay et al., 2021).

The mainstay of OCD treatment involves pharmacological and psychotherapeutic interventions. Cognitive Behavioural Therapy (CBT), particularly Exposure and Response Prevention (ERP), is highly effective, reducing symptoms by up to 77%. However, about 15% of patients discontinue ERP due to its intensity. Pharmacologically, SSRIs are the first-line treatment, with about 70% of patients experiencing significant symptom reduction. Despite this, the response to SSRIs can be modest, and many patients do not achieve remission. Additionally, side effects and treatment resistance are significant hurdles (Khan et al., 2023).

The management of TS also often includes a combination of behavioural therapies, in the form of Comprehensive Behavioural Intervention for Tics (CBIT) and pharmacological treatments. First-line pharmacological treatments often involve dopamine receptor blockers and alpha-2 adrenergic agonists, but these may not provide satisfactory symptomatic relief for all patients and can have significant side effects. In more severe, treatment-resistant cases, advanced interventions like deep brain stimulation (DBS) are considered, although access to such treatments can be limited and they come with their own risks (Tahler et al., 2018).

Medicinal cannabis has emerged as a potential alternative treatment for OCD and TS, capitalizing on the properties of cannabinoids like THC and CBD, which interact with

the endocannabinoid system involved in regulating anxiety and repetitive behaviours. The cannabinoid system's extensive presence in brain regions associated with OCD suggests its potential utility in modulating these pathways (Blessing et al., 2015; Mauzay et al., 2021). Clinical trials on cannabis for OCD are limited, but early studies suggest possible benefits. One placebo-controlled study indicated that smoked cannabis could impact OCD symptoms, although the evidence remains inconclusive and further research is required. The purported effects of cannabinoids might stem from their influence on the endocannabinoid system, which plays a role in neural circuits involved in OCD (Vallée et al., 2021; Benatti et al., 2022).

Clinical evidence supporting the efficacy of cannabis in TS is still evolving. Initial studies, including controlled trials and case reports, suggest that cannabinoids may decrease the frequency and severity of tics. A review identified two small trials that reported a positive effect of THC on tic severity and frequency based on subjective measures, although objective endpoints were not significantly affected. Additionally, several case reports and open-label studies have reported sustained reduction in tics and improvement in psychiatric comorbidities with the use of smoked cannabis and oral cannabis-based medicines. However, the use of medicinal cannabis in TS is not without concerns. The variability in response and the psychoactive effects of THC, such as impaired memory and altered motor functions, necessitate careful consideration, particularly in children and adolescents. Moreover, the regulatory status of medicinal cannabis varies by region, affecting its availability and clinical acceptability. (Tahler et al., 2018; Muller-Vahl, 2024).

Given the complexity of OCD and TS, and the partial effectiveness of current treatments, exploring new therapeutic options like medicinal cannabis is crucial.

However, rigorous clinical trials and further research are necessary to establish the efficacy and safety of cannabis in treating OCD, considering its psychoactive effects and the legal implications associated with its use.

3.4.2.9.1. Recommended dosages in current literature

The therapeutic application of medicinal cannabis has garnered significant interest in recent years, particularly in the management of neuropsychiatric disorders such as OCD and TS. These disorders are often chronic and debilitating, necessitating the exploration of alternative treatment modalities beyond conventional pharmacotherapy and psychotherapy, which may not provide satisfactory relief for all patients or could induce severe side effects. Recent literature suggests that the endocannabinoid system might play a crucial role in the neurobiological pathways involved in OCD, particularly in modulating anxiety, fear, and habit-forming circuits. CBD and THC are posited to influence this system. Studies have begun to explore the efficacy of cannabinoids in reducing OCD symptoms, with some indicating potential benefits in symptom management (Mauzay et al., 2021; Benatti et al., 2022). Like OCD, TS has shown responsiveness to cannabinoid-based treatments in various case reports and preliminary studies, suggesting a modulation of tics and associated psychiatric comorbidities through cannabinoid receptors (Muller-Vahl et al., 2024).

The literature indicates a wide variation in dosing regimens for cannabis-based products, reflecting the personalized nature of medicinal cannabis use and the lack of standardized dosing guidelines. In the context of OCD and TS, dosing can vary significantly based on the form of cannabis used (e.g., inhaled, oral), the specific cannabinoid profile, and individual patient factors such as severity of symptoms and

prior treatment responses (Table 3.18). For OCD, the current literature primarily discusses the use of CBD, with dosages ranging from moderate to high depending on the severity of symptoms. A review by Mauzay et al. (2021) discusses various clinical trials and dosing regimens where CBD has been employed, either as monotherapy or as an adjunct, highlighting doses typically ranging from 300 mg to 600 mg per day in divided doses. In TS, both THC and CBD have been used, with some studies suggesting a starting dose of THC around 2.5 mg twice daily, gradually increasing based on tolerance and clinical response. nabiximols, a balanced THC/CBD formulation, is frequently mentioned, with doses adjusted to symptom relief typically not exceeding 12 sprays per day (Schwittay et al., 2021). The Israeli Ministry of Health provides guidelines for THC use in TS, starting with a licensed allowance of 20 g per month, titrating based on patient response and clinical evaluation (Tahler et al., 2018).

The narrative review by Kayser et al. (2019) underscores the relevance of the ECS in anxiety, fear, and repetitive behaviours, which are pivotal in the symptomatology of OCD. This review collates evidence from animal studies and anecdotal human data, suggesting that modulation of the ECS could serve as a novel therapeutic target for OCD. It discusses various cannabinoids' effects, such as dronabinol, and their dosages, which range from moderate to high, tailored to alleviate OCD symptoms based on anecdotal case reports and small-scale studies. The review critically points out the scarcity of direct evidence and the pressing need for well-designed clinical trials to validate the efficacy and safety of cannabinoids in treating OCD. Building on the narrative review's insights, Kayser et al. (2020a) conducted a randomized, placebo-controlled study that tested the acute effects of smoked cannabis on OCD symptoms. The study involved participants who used three different cannabis varieties, including THC-dominant and CBD-dominant strains. Interestingly, the results

showed no significant changes in OCD symptoms following cannabis use, although there was a noted reduction in state anxiety after placebo administration compared to the active cannabis strains. This study leverages a within-subjects design to reduce variability and employs robust measures such as the Yale-Brown Obsessive Compulsive Scale (YBOCS) and the Spielberger State-Trait Anxiety Inventory (STAI) for assessments. However, the study's limitations include its acute setting and small sample size, highlighting the difficulty in drawing long-term conclusions from such data. Further advancing this research, Kayser et al. (2020b) executed a randomized controlled pilot trial exploring the use of nabilone as an adjunct to exposure/response prevention (EX/RP) therapy in treating OCD. This study differentiated itself by combining pharmacological intervention with psychotherapy, reflecting a more integrative approach to OCD treatment. The findings suggest that participants receiving both nabilone and EX/RP therapy exhibited significant improvements in OCD symptoms, as measured by YBOCS, compared to those who received nabilone alone. Notably, the study adjusted dosing protocols to mitigate side effects such as anxiety, enhancing overall treatment acceptability and feasibility. These studies collectively indicate a cautiously optimistic view on the role of cannabinoids in managing OCD. They illustrate the complexities involved in understanding how different cannabis compounds affect OCD symptoms and anxiety. Moreover, they emphasize the need for further research to establish more definitive dosing guidelines, long-term efficacy, and safety profiles. The pilot studies, despite their limitations such as small sample sizes and short durations, provide crucial groundwork for future larger-scale trials. These trials could potentially validate the preliminary findings and clarify the therapeutic potential of cannabinoids, particularly in conjunction with established

psychotherapeutic techniques, thereby broadening the scope of treatment options available to individuals suffering from OCD.

The observational study by Mauzay et al. (2021) harnesses real-world data via the Strainprint® app, where individuals with self-identified OCD reported on their symptom severity before and after cannabis use across numerous sessions. The findings indicated significant reductions in compulsions, intrusions, and anxiety, with a notable observation that higher concentrations of CBD were associated with larger reductions in compulsions. This study, employing latent change score models and multilevel modelling, provides an empirical foundation for the symptomatic relief potential of cannabis, albeit within the limitations of self-reporting and the absence of a placebo-controlled environment. The real-time tracking of symptom changes offers a granular view of cannabis effects over time, although the self-selected sample and reliance on user-reported data might introduce bias. In a more controlled setting, Schindler et al. (2008) report on the use of dronabinol in two patients with treatment-resistant OCD, noting significant reductions in Yale-Brown Obsessive Compulsive Scale (YBOCS) scores. These case reports are particularly illuminative, as they highlight the potential of synthetic THC to alleviate severe OCD symptoms effectively within a short span, providing a hypothesis that cannabinoids might modulate glutamatergic transmission within the CNS. While the direct anti-obsessive effects of dronabinol suggest promising therapeutic avenues, the case-study format limits the generalizability of these findings. However, the absence of adverse effects and the rapid onset of symptom relief underscore the need for larger, systematic studies. Similarly, Cooper & Grant (2017) delve into the use of dronabinol in a 24-year-old male with a complex clinical presentation, including a history of a thalamic stroke, which precipitated severe OCD symptoms. The intervention led to substantial improvements in YBOCS scores

and enabled effective engagement with cognitive-behavioural therapy (CBT), which had previously been unsuccessful. This case not only demonstrates the therapeutic potential of cannabinoids in refractory OCD but also suggests their utility in facilitating broader treatment strategies such as CBT. It introduces an intriguing aspect of cannabinoid utility in neurobiologically complex cases of OCD, potentially offering insights into the neurobiological underpinnings of OCD and the role of the mediodorsal nucleus of the thalamus.

The study conducted by Benatti et al. (2022) draws from a cohort of 70 outpatients with a confirmed diagnosis of OCD, collected via structured clinical interviews based on DSM-5 criteria. This retrospective analysis focused on evaluating the frequency of cannabis use and its subjective impact on OCD symptoms and overall treatment effectiveness. Notably, about 42.8% of the study participants reported lifetime cannabis use, with 14.3% identifying as current users. A significant observation from the study is the association of cannabis use with earlier onset of OCD symptoms and a higher incidence of other substance use, such as alcohol and tobacco. These findings suggest that cannabis use is relatively common among individuals with OCD, possibly as a self-management strategy for symptom relief, though the effectiveness and implications of such use remain mixed. The study underscores the need for clinicians to be vigilant about substance use in their treatment plans and calls for further research to systematically evaluate the efficacy and safety of cannabis in the context of OCD therapy. In a complementary study, Kayser et al. (2021) utilized an internet-based cross-sectional survey to assess cannabis use patterns, reasons for use, and perceived effects of cannabis on OCD symptoms among 601 adults who identified themselves as having OCD. This study's findings indicate that a significant portion of the participants used cannabis medicinally, purportedly to manage

Authors	Study	Pts	Age	Dose	Delivery	Follow-up	Outcomes
Hemming & Yellowlees (1993)	Case report	1	36	-	Inhalation	1 year	Complete resolution of tics with daily cannabis use. Improved quality of life reported.
Muller-Vahl et al. (1998)	Retrospective cross-sectional survey	64	30.3 $\bar{x}$	Varied	Inhalation	-	14 out of 17 users with prior cannabis use reported improvement in motor and vocal tics and associated symptoms, including obsessive-compulsive behaviours.
Muller-Vahl et al. (1999)	Case report	1	25	10mg	Oral (THC)	-	A reduction in both motor and vocal tics, with improvement lasting about 7 hours. 70% improvement in tic severity and improved attention and impulse control.
Muller-Vahl et al. (2001)	Randomized cross-over	12	34 $\bar{x}$	5-10mg	Oral	-	Significant reduction in TS tic severity and obsessive-compulsive symptoms with THC compared to placebo. No significant adverse effects.
Muller-Vahl et al. (2003)	RCT	24	33 $\bar{x}$	max. 10mg	Oral	6 weeks	Significant reduction in TS tic severity as measured by TS-CGI, STSSS and YGTSS compared to placebo.
Schindler et al. (2008)	Case report	2	36, 38	10mg BD-TDS	Oral (dronabinol)	2 weeks	Reduced OCD symptoms, particularly in compulsive behaviours. Dronabinol was effective as an augmentation therapy in treatment-resistant OCD.
Hasan et al. (2010)	Case report	1	15	5-15mg	Oral (THC)	9 weeks	Reduced tics and improved quality of life. Increased intracortical inhibition observed through transcranial magnetic stimulation, suggesting THC as an effective alternative for refractory TS, allowing concurrent ADHD treatment with methylphenidate.
Brunnauer et al. (2011)	Case report	1	42	15mg	Oral (THC)	2 weeks	TS tic reduction. 75% decrease in YGTSS scores. Improved psychomotor functions, particularly in driving ability, without affecting neuropsychological performance.
Trainor et al. (2016)	Case report	1	26	10.8mg THC + 10mg CBD (THC:CBD 1:1)	Oromucosal spray (nabiximols)	4 weeks	Substantial reduction in both motor and vocal tics, with a reported 85% reduction in motor tics and 90% reduction in vocal tics. No adverse effects were noted.
Abi-Jaoude et al. (2017)	Retrospective cohort	19	19-64	0.4g / week - 1g TDS	Oral, Inhalation	6 months	60% reduction in TS tic scores, with 18 of 19 patients reporting significant improvement. Side effects noted, but well tolerated.
Cooper et al. (2017)	Case report	1	24	20mg	Oral (dronabinol)	-	Reduction in OCD symptoms with a Y-BOCS score drop from 39 to 10, allowing tolerance to cognitive-behavioural therapy.
Jakubovski & Müller-Vahl (2017)	Case report	2	16, 19	0.1-0.6g; 22.4-33.6mg	Inhalation, Oral (dronabinol)	8 months	Significant improvement in tic reduction (up to 70%) and improvement in quality of life, with no adverse effects reported.
Kanaan et al. (2017)	Case report	1	22	9 sprays / day (2.7mgTHC + 2.5mgCBD)	Oromucosal spray (nabiximols)	2 weeks	Tic severity was reduced. Improvement in premonitory urges, global impairment, and quality of life. No significant adverse effects were reported.

Authors	Study	Pts	Age	Dose	Delivery	Follow-up	Outcomes
Pichler et al. (2018)	Case report	1	47	10mg THC + 20mg CBD	Oral	2 months	Marked improvement in tic severity and frequency. YGTSS score from 73 to 44. Enhanced quality of life and no significant side effects.
Szejko et al. (2018)	Case report	1	7	0.7-29.4mg	Oral (THC)	4 months	Significant improvement in tics, ADHD symptoms, and quality of life. Reduced tic severity, depression, and anxiety.
Thaler et al. (2018)	Retrospective cohort	42	34.5 $\bar{x}$	29.37g $\bar{x}$ / month	Oral, Inhalation	1 year	Majority reported improvement in tic severity, sleep, and mood. 10 patients discontinued due to side effects. 3.85/5 mean efficacy score.
Milosev et al. (2019)	Cross-sectional survey	98	35.8 $\bar{x}$	Varied	Inhalation (mostly)	62.1 $\bar{x}$ months	Improvement in TS tic severity (average 60% reduction) and psychiatric comorbidities, especially OCD symptoms. Patients generally preferred THC-rich cannabis strains over other formulations, reporting fewer adverse effects and improved quality of life.
Szejko et al. (2019)	Case report	1	12	12.5mg (oral); 22mg (vaporized)	Oral, Inhalation	-	Marked reduction in tic severity and premonitory urges observed within 30 minutes of vaporization. The combination of vaporized cannabis and oral THC was well-tolerated.
Jakubovski et al. (2020)	RCT	96	-	max.12 sprays / day (2.7mgTHC + 2.5mgCBD)	Oromucosal spray (nabiximols)	13 weeks	$\geq 30\%$ reduction in Tourette Syndrome tic severity on the Yale Global Tic Severity Scale (YGTSS) after 13 weeks.
Kayser et al. (2020a)	RCT	12	21-55	7% THC; 0.4% THC + 10.4% CBD	Inhalation	-	No significant acute effect on OCD symptoms between placebo, THC, and CBD. However, anxiety was lower in the placebo condition immediately after administration.
Kayser et al. (2020b)	Open label pilot	11	22-60	1mg BD	Oral (nabilone)	2 months	Nabilone combined with exposure and response prevention (EX/RP) showed a larger reduction in OCD symptoms compared to nabilone alone. Improvements were maintained at the 1-month follow-up. Significant mean change in YBOCS scores.
Kayser et al. (2021)	Cross-sectional survey	601	28.6 $\bar{x}$	Varied	Inhalation (mostly)	-	Most respondents reported cannabis improved OCD symptoms, particularly anxiety and compulsive behaviours. High-frequency users reported mixed effects.
Mauzay et al. (2021)	Naturalistic study	87	32.0 $\bar{x}$	6.50 $\pm$ 4.35 (intrusions), 10.27 $\pm$ 6.21 (compulsions), 8.50 $\pm$ 6.09 (anxiety)	Inhalation	31 months	Patients reported significant acute reductions in compulsions (60%), intrusions (49%), and anxiety (52%) immediately following cannabis use, though tolerance to the effects on intrusions may develop over time.

Authors	Study	Pts	Age	Dose	Delivery	Follow-up	Outcomes
Schwittay (2021)	Case report	1	25	Varied	Oromucosal spray (nabiximols)	-	Treatment with nabiximols resulted in a tic reduction of greater than 90% after daily cannabis cessation had initially led to severe symptoms.
Benatti et al. (2022)	Retrospective cross-sectional survey	70	37.0 $\bar{x}$	Varied	Varied	-	While 10% of users reported perceived improvement in symptoms, 23.3% reported increased anxiety. Current cannabis users exhibited more severe clinical features, including earlier age of onset and higher rates of psychiatric comorbidity.

Table 3.18. *Studies evaluating use of medicinal cannabis in obsessive-compulsive disorder and Tourette Syndrome.*

symptoms of OCD, with many reporting subjective improvements. Notably, about 42% of participants met the criteria for cannabis use disorder, highlighting a potential risk of dependency or misuse, particularly among those using high-potency cannabis products. The survey's broad recruitment strategy from online forums and social media platforms lends a diverse but potentially biased sample, reflecting the self-reported nature of the data which could impact the reliability of the findings. Both studies reflect a growing trend of cannabis use among individuals with OCD, suggesting both potential therapeutic benefits and risks. The high rate of self-medication observed points to a gap in effective, accessible treatments for OCD and raises questions about the potential integration of cannabis-based therapies into conventional treatment regimes. However, the self-reported and retrospective nature of these studies introduces limitations in terms of data reliability and generalizability. This underscores the necessity for well-controlled, longitudinal studies that can provide more definitive evidence regarding the efficacy, safety, and appropriate use of cannabis in treating OCD.

In a case report by Szejko et al. (2020), a 22-year-old male with severe, treatment-resistant OCD experienced significant symptom relief after using medicinal cannabis, specifically chemovars with higher THC concentrations. The patient reported a 70% improvement in OCD symptoms, enhanced quality of life, improved sleep, and general relaxation. This case underscores the potential of THC-dominant cannabis strains in managing severe OCD, suggesting that the endocannabinoid system may play a beneficial role in the pathophysiology of OCD. However, the findings from this single case report cannot be generalized, and the lack of a controlled setting and placebo comparison limits the ability to conclusively attribute improvements to the intervention. Parallel to the findings in OCD, the study by Muller-Vahl et al. (1998) involving patients

with TS reports that a significant majority of those who used marijuana experienced reductions in both motor and vocal tics as well as improvements in associated behavioural disorders such as obsessive-compulsive symptoms and ADHD. These observational findings suggest that cannabinoids might interact with dopaminergic processes and motor activity, which are crucial in the pathophysiology of TS. Yet, the retrospective, self-reported nature of the study and the lack of a controlled clinical environment limit the reliability and generalizability of the results. Further refining the investigation into cannabinoids for TS, Muller-Vahl et al. (2002) conducted a randomized, double-blind, placebo-controlled crossover trial that demonstrated significant improvement in tic severity during THC treatment compared to placebo. The study's methodology, involving rigorous assessments and a controlled experimental design, provides robust evidence supporting the efficacy of THC in reducing tic severity. However, the small sample size and the short duration of the trial call for more extensive research to establish long-term safety and optimal dosing, particularly considering the potential developmental impacts on younger patients.

Abi-Jaoude et al. (2017) conducted a retrospective evaluation focusing on the effectiveness and tolerability of inhaled cannabis in adults with TS, offering valuable insights into the potential benefits of cannabinoid therapies in this patient population. The study, which involved 19 adults diagnosed with TS under DSM-5 criteria, observed significant improvements in both tic severity and impairment scores. This improvement was measured using established scales such as the Yale Global Tic Severity Scale (YGTSS) and the Yale-Brown Obsessive Compulsive Scale (Y-BOCS) for those with comorbid OCD symptoms. Notably, nearly all participants reported enhancements in symptoms of TS and related conditions such as OCD, with cannabis being generally well-tolerated despite some reporting side effects at higher doses. This

study underlines the possible advantages of inhaled cannabis, which might offer a more immediate relief compared to oral THC, highlighting the role of different consumption methods on therapeutic outcomes.

Muller-Vahl et al. (2003) further contribute to the discussion with a prospective, randomized, double-blind, placebo-controlled trial assessing the efficacy of oral THC in adults with TS. This study's rigorous design and methodology provided a more controlled evaluation of cannabis's effects, contrasting sharply with the more anecdotal and observational nature of the Abi-Jaoude et al. (2017) study. Participants in the Muller-Vahl study experienced significant improvements in tic severity, as assessed by multiple tic severity rating scales, with the treatment proving to be well-tolerated. These findings not only support the therapeutic potential of THC in reducing tic severity but also reinforce the need for controlled clinical trials to accurately gauge the efficacy and safety of cannabinoids. Further insights are offered by Jakubovski & Muller-Vahl (2017) through case reports detailing the treatment of severe vocal blocking tics in TS with medical cannabis and dronabinol. These reports highlight the challenges of treating severe symptoms that are often resistant to conventional therapies. Both patients experienced substantial improvements with minimal side effects, suggesting that cannabinoids might offer a viable alternative for managing particularly resistant cases of TS. These case reports, while limited by their anecdotal nature and lack of control groups, provide preliminary evidence supporting the utility of cannabis-based medicines in severe, treatment-resistant TS. Milosev et al. (2019) conducted a retrospective analysis combined with an online survey to evaluate the effectiveness of various forms of cannabinoid-based medicine (CBM) in treating TS. This study highlighted a significant preference among patients for THC-rich cannabis, which was perceived as more effective and better tolerated than other forms of CBM

like nabiximols and dronabinol. The findings from this study underscore the highly individualized nature of cannabinoid therapy, where dosages and responses can vary widely between patients, reflecting the complexity of treating TS and its comorbidities.

The multicentre, randomized, double-blind, placebo-controlled phase IIIb study conducted by Muller-Vahl et al. (2023) represents a significant advancement in understanding the effectiveness of Nabiximols for treating chronic tic disorders. Although the study did not conclusively demonstrate the superiority of nabiximols over placebo, with 21.9% of patients in the nabiximols group meeting the responder criterion versus 9.1% in the placebo group, it highlighted the potential therapeutic benefits, particularly for patients with severe symptoms or comorbid ADHD. This trial's robust design and the relatively long duration of treatment provide valuable data, albeit with a need for further research to confirm these findings in larger cohorts. In contrast, the case report by Hemming and Yellowlees et al. (1993) illustrates the dramatic effect of self-administered cannabis in a 36-year-old male with longstanding TS, who experienced complete symptom remission. This report, while compelling, underscores the challenges associated with anecdotal evidence, including the inability to generalize findings and the ethical dilemmas associated with recommending an illegal substance for medical purposes. Nonetheless, the significant improvement in quality of life and symptom management reported in this case points to the need for controlled studies to explore the mechanisms and potential benefits of cannabinoids in TS more systematically. Muller-Vahl et al. (1999) contribute further to this discussion through an uncontrolled open clinical trial where a single dose of Δ 9-THC showed significant reductions in tic severity and improvements in associated neuropsychiatric symptoms in a 25-year-old male with TS. The study provided preliminary evidence supporting the efficacy of Δ 9-THC in a controlled setting, enhancing our understanding of

cannabinoid interactions with neural pathways involved in tic generation. These findings are crucial as they suggest that cannabinoids might modulate specific neurobiological mechanisms underlying TS, paving the way for future placebo-controlled studies. Similarly, Hasan et al. (2010) detailed the use of Δ^9 -THC in a 15-year-old boy with TS and ADHD, where cannabinoid treatment not only reduced tic severity but also facilitated the management of ADHD symptoms without exacerbating tics, a common concern with traditional stimulant treatments. This case report highlights the dual therapeutic potential of cannabinoids in managing comorbid conditions, with neurophysiological outcomes suggesting increased cortical inhibition, indicative of a significant neurobiological impact.

Szejko et al. (2018) present a compelling case of a 7-year-old boy with TS and ADHD who experienced significant improvements in tic severity, behavioural symptoms, and quality of life following treatment with oral THC. The progressive adjustment of dosage over four months demonstrated the feasibility of using THC in paediatric cases, showing substantial benefits without serious adverse effects. This case not only underscores the potential of THC as a viable treatment option for severe and treatment-resistant TS in children but also exemplifies the importance of careful dosage management to enhance therapeutic outcomes while minimizing side effects. Similarly, Brunnauer et al. (2011) explore the impact of cannabinoid therapy on a 42-year-old truck driver with TS, focusing on the effects of THC on driving ability, a critical aspect of daily functioning for many adults. This study is particularly notable for demonstrating that THC treatment not only significantly reduced tic severity but also enhanced psychomotor functions necessary for safe driving. This finding challenges prevailing concerns that cannabinoid therapy might universally impair cognitive functions and highlights the need for a nuanced understanding of how cannabinoids

affect different aspects of psychomotor performance in patients with TS. Trainor et al. (2016) report on the use of Sativex®, a cannabinoid oromucosal spray, in a 26-year-old male with TS, OCD, and significant anxiety. The treatment led to marked improvements in tic frequency and severity, as documented through both subjective and objective measures, without adverse effects. This case highlights the therapeutic potential of balanced THC and CBD formulations and supports their use in treatment-resistant cases of TS, emphasizing the well-tolerated nature of such treatments. Kanaan et al. (2017) contribute to the burgeoning literature with their report on a 22-year-old male with severe TS and multiple comorbidities treated with nabiximols. Significant improvements in tic severity, premonitory urges, and quality of life were observed, demonstrating the effectiveness of nabiximols in managing severe symptoms resistant to conventional treatments. This case supports the broader applicability of cannabinoid-based medicine in severe, complex cases of TS, providing a foundation for future research in larger, controlled trials.

The case report by Pichler et al. (2018) is illustrative of the nuanced approach needed in cannabinoid therapies. A 47-year-old female with long-standing, treatment-resistant TS experienced significant improvements in tic severity and quality of life after switching from antipsychotics to a cannabis tincture with a high CBD to THC ratio. This case highlights the potential of tailored cannabinoid profiles to manage severe symptoms effectively while minimizing psychoactive side effects, suggesting that the entourage effect of THC and CBD might offer a synergistic benefit. The findings support the hypothesis that the modulation of cannabinoid receptors in specific brain regions involved in TS may underlie these therapeutic effects. This case adds to the growing evidence that cannabinoids may provide substantial relief for patients with TS, urging further clinical trials to verify these outcomes in larger, diverse patient

populations. In an observational study by Thaler et al. (2018), the real-life impact of medical cannabis on patients with Gilles de la Tourette syndrome (GTS) was assessed. Most patients reported a high satisfaction rate with the use of medical cannabis, noting improvements in tic severity, sleep, and mood. However, the study also highlighted significant adverse effects in some patients, including cognitive decline and, in one instance, an acute psychotic episode. These findings reflect the complex therapeutic landscape of cannabinoid treatment, emphasizing the need for careful patient selection, monitoring, and the development of standardized treatment protocols. This study also underlines the importance of further research to balance potential benefits against risks, particularly concerning long-term effects and optimal dosages. Szejko et al. (2019) provided another compelling narrative through a single case report of a 12-year-old boy with severe TS. Treatment with vaporized cannabis and oral THC resulted in almost complete remission of tics and improved sleep. This report showcases the immediate effects of vaporized cannabis and the sustained benefits of oral THC, offering insights into the administration methods that might be tailored to the needs of paediatric patients. Notably, the treatment was well-tolerated, with no adverse events reported, which is crucial in paediatric cases where safety is a paramount concern. The success in this case supports the potential of cannabinoids as a viable option for paediatric TS, especially when traditional treatments have failed, but also stresses the need for cautious, well-monitored therapeutic trials to ensure safety and efficacy.

Schwittay et al. (2021) delve into the rapid and significant efficacy of nabiximols in a 25-year-old male with TS who had previously found some relief through recreational cannabis. This case report particularly highlights the utility of nabiximols for acute symptom management, providing substantial symptom relief with minimal side effects,

primarily mild cheerfulness and relaxation. The rapid onset of symptom relief post-administration, lasting approximately four hours, positions nabiximols as a viable option for situational use in managing severe tic exacerbations. This suggests that cannabinoid therapies can be tailored not just for ongoing management but also for immediate relief in specific circumstances, such as anticipated social engagements or professional commitments that might exacerbate symptoms. The case report by Schwittay et al. (2021) is complemented by the findings from Müller-Vahl et al. (2001), which investigates the neuropsychological impacts of D9-THC on patients with TS. In a randomized double-blind placebo-controlled crossover trial, patients exhibited no significant impairments in cognitive functions post-treatment, challenging the stereotype that cannabinoid use invariably leads to cognitive decline. This study not only reassures the safety of D9-THC in cognitive terms but also encourages further exploration into long-term treatments, given the absence of negative cognitive impacts typically associated with cannabis use in healthy individuals. Jakubovski et al. (2020) extends this narrative through a multicentre, randomized, double-blind, placebo-controlled trial assessing the efficacy of nabiximols in reducing tic severity. This study is particularly notable for its comprehensive design, which not only measures tic severity reduction but also considers a wide range of secondary outcomes such as psychiatric comorbidities, quality of life, and driving ability. The inclusion of driving assessments is particularly pertinent, reflecting an increasing recognition of the need to understand the broader implications of medicinal cannabis on daily activities and responsibilities.

Collectively, these studies signify a maturing direction in cannabinoid research, marked by a move towards more sophisticated and holistic approaches to assessing therapeutic efficacy and safety. They underscore the potential of cannabinoids like

nabiximols and D9-THC to provide significant relief from TS symptoms, improve quality of life, and maintain cognitive and functional abilities. However, they also highlight the importance of careful dosage management, the potential variability in individual responses, and the need for tailored treatment approaches. The encouraging results from these studies advocate for ongoing, rigorously designed clinical trials to further validate the efficacy and safety of cannabinoids in treating TS and its related conditions. Such research is crucial not only for confirming therapeutic potentials but also for integrating these treatments into broader clinical practice, ensuring that they are used safely and effectively, with a clear understanding of their benefits and limitations. This is particularly pertinent in scenarios involving paediatric patients or those with complex comorbidities, where treatment efficacy must be balanced carefully with safety considerations. As the body of evidence grows, it will support the development of standardized guidelines for the use of medicinal cannabis in neuropsychiatric care, potentially transforming treatment paradigms for patients with TS and similar disorders.

3.4.2.9.2. Research, clinical practice and future directions

Recent investigations into the clinical use of medicinal cannabis for OCD and TS have highlighted both potential benefits and complexities inherent in this therapeutic approach. A range of studies, including randomized controlled trials, observational studies, and case reports, have contributed to an evolving understanding of the efficacy and safety of cannabinoids in these contexts. For OCD, research has largely focused on the modulation of the endocannabinoid system as a novel therapeutic target. Studies like those by Kayser et al. (2020a) and (2020b) illustrate a growing

interest in using cannabinoids to modulate anxiety and fear-related behaviours central to OCD, with early clinical trials suggesting that cannabinoid augmentation could enhance the effects of exposure-based psychotherapy for OCD. With regards to TS, cannabinoids have been studied for their effects on reducing tic severity and frequency. Research by Müller-Vahl et al. (2023) and others provides evidence that substances like nabiximols, a balanced THC and CBD oromucosal spray, may reduce tic symptoms in TS patients, although the results are not uniformly conclusive and often lack the robustness required for standard clinical applications due to small sample sizes and short trial durations.

In clinical practice, the application of medicinal cannabis in treating OCD and TS is informed by a growing but still incomplete evidence base. For TS, cannabinoids have been occasionally used when conventional treatments fail to provide relief or cause unacceptable side effects. Case studies, like those reported by Szejko et al. (2018), highlight the potential of THC in managing severe cases of TS in children, noting significant improvements in tic severity and behavioural symptoms. For OCD, clinical applications are still at a nascent stage, largely experimental, and typically considered only after more established treatments fail. However, the integration of cannabinoid-based treatments into clinical practice is supported by patient-reported outcomes, indicating a reduction in symptom severity and an improvement in quality of life, as well as by some clinicians' anecdotal experiences suggesting efficacy where other treatments have not succeeded.

The future of medicinal cannabis in treating OCD and TS appears promising but necessitates rigorous, well-designed clinical trials to better establish efficacy, safety, dosage parameters, and long-term effects. The intriguing results from preliminary

studies must be tested in larger, more diverse patient populations. Additionally, the exploration of different ratios of THC and CBD and their effects on OCD and TS symptoms may offer insights into more effective and personalized medicine strategies. Research should also aim to clarify the mechanisms by which cannabinoids affect neurobiological pathways associated with these disorders. For instance, the interaction between THC and CBD and its impact on neurocognitive processes relevant to OCD and TS is not well understood and represents a critical area of study. Moreover, the development of guidelines for the clinical use of medicinal cannabis in these patient populations is crucial. These guidelines should address not only the potential efficacy but also ethical considerations, particularly concerning paediatric populations and the risk of side effects, including psychological impacts.

3.4.2.10. Epilepsy

Epilepsy is a diverse set of chronic neurological disorders characterized by recurrent seizures. These seizures are episodes that can vary from brief and undetectable periods to long periods of vigorous shaking. Affecting people of all ages globally, epilepsy is one of the most common neurological diseases, and despite its prevalence, it often remains misunderstood and stigmatized. The World Health Organization (WHO) recognizes epilepsy as a major public health concern due to its profound physical, psychological, and socioeconomic impact on individuals and communities (Mitelpunkt et al., 2019).

The diversity in seizure types and their unpredictable nature significantly impair patients' quality of life, influencing daily activities and leading to social isolation, physical injuries, and various psychological disorders. The burden of epilepsy extends

beyond the patients to their families and healthcare systems, emphasizing the need for effective management strategies (Wang et al., 2020). The management of epilepsy presents several challenges that complicate the delivery of effective healthcare. Firstly, a significant number of patients, approximately one-third, are resistant to traditional anti-epileptic drugs (AEDs). This drug resistance often leads to uncontrolled seizure episodes, raising the risk of further complications such as SUDEP (Sudden Unexpected Death in Epilepsy) (Lazarini-Lopes et al., 2021).

Moreover, the side effects associated with many AEDs can range from mild, such as nausea and fatigue, to severe, including depression, inflammation, and even potential cognitive decline over time. These adverse effects can severely affect patient compliance and quality of life, making management more difficult (Laux et al., 2021). Additionally, the cost of long-term comprehensive care, which may include regular medical visits, treatments, monitoring, and sometimes surgery, poses a significant financial burden on patients and healthcare systems alike. The quest for more affordable and universally accessible treatment options is a pressing issue in the global healthcare landscape (Lee et al., 2021). A growing body of clinical research has explored the use of cannabis, particularly CBD-enriched products, in treating epilepsy. Several studies have reported promising results, with many patients experiencing a significant reduction in seizure frequency and intensity. For instance, a study conducted by Talwar et al., 2023, demonstrated that CBD treatment could reduce seizure frequency by up to 50% in some patients with drug-resistant epilepsy (Talwar et al., 2023).

Another clinical trial highlighted by Laux et al., 2021, evaluated the safety and efficacy of CBD in children and young adults with severe epilepsy forms. The study found that

CBD was well-tolerated and significantly reduced seizure activity in a substantial number of cases without causing the psychoactive effects associated with THC. Despite the encouraging findings, the use of cannabis in epilepsy treatment is not without challenges. The variability in cannabis product composition, lack of standardization, and limited regulatory oversight in many regions can affect treatment consistency and safety (Lawson et al., 2022). Additionally, there is a need for more extensive, long-term studies to fully understand the potential adverse effects and the optimal dosing and administration routes for different types of epilepsy (Reddy, 2023).

3.4.2.10.1. Recommended dosages in current literature

The dosages of CBD and THC used in the treatment of epilepsy vary significantly across studies, reflecting the tailored approach needed for individual patient needs and specific epilepsy syndromes (Table 3.19). CBD dosages range from as low as 2.5 mg/kg/day in some beginner trials to as high as 50 mg/kg/day in more intensive scenarios. For instance, one study documented using up to 20 mg/kg/day of CBD to reduce the frequency of convulsive seizures in patients with Dravet Syndrome (Lazarini-Lopes et al., 2020). THC is used less frequently due to its psychoactive properties, and is reported in lower dosages, typically not exceeding 10 mg/day in combined CBD-THC treatments (Knupp et al, 2019).

Talwar et al. (2023) illustrate a controlled trial that rigorously tests CBD's efficacy, highlighting its potential to significantly reduce seizure frequency in patients with resistant epilepsy forms. The study elaborates on dosages that varied from 5 mg/kg/day to 20 mg/kg/day, depending on the severity and response of the individual, thereby tailoring treatment to maximize efficacy and minimize side effects. Similarly,

Mitelpunkt et al. (2019) presents an observational study where children with Dravet Syndrome were administered CBD in increasing doses from 2.5 mg/kg/day up to a maintenance dose of 20 mg/kg/day. The gradual increase in dosage allows for careful monitoring of potential adverse effects and effectiveness, illustrating a cautious approach to cannabinoid therapy in paediatric epilepsy. In Wang et al. (2020) a broader spectrum of cannabinoid therapy is discussed, where both CBD and THC are utilized. The document notes that THC dosages are kept significantly lower than CBD, often not exceeding 10 mg/day to avoid psychoactive effects while attempting to harness its anticonvulsant properties. This study underscores the complexity of treating epilepsy with cannabinoids, necessitating a balance between therapeutic effects and potential psychoactivity.

Reddy (2023) provides a pivotal clinical trial scenario where CBD is tested at even higher dosages, up to 25 mg/kg/day, demonstrating its role in reducing the frequency of convulsive seizures and improving life quality in patients with Lennox-Gastaut Syndrome. The high dosage used here reflects the severity and challenge in managing this particular epilepsy form, advocating for more robust, high-dose CBD interventions in severe cases. Further insights from Xu et al. (2021) elaborate on the neuroprotective properties of CBD, with studies administering up to 50 mg/kg/day in acute cases. This extreme dosage is indicative of CBD's safety profile and its potential to act significantly on the neural pathways involved in epilepsy. Laux et al. (2019) discusses the practical aspects of CBD administration in a clinical setting, where oral administration is preferred for its ease of use and the ability to precisely control dosages. The study highlights that consistent dosing is crucial for achieving optimal therapeutic outcomes and that monitoring blood levels can help refine dosage needs and predict efficacy.

Franco & Perucca (2019) emphasizes the importance of methodical dosing in paediatric cases, highlighting a study where CBD was introduced at an initial dose of 5 mg/kg/day and titrated up based on the patient's response and tolerance, with some going up to 20 mg/kg/day. This approach reflects the cautious yet adaptive dosing strategy needed in paediatric neurology to mitigate potential side effects while optimizing therapeutic outcomes. Further elaborating on cannabinoid use in neurology, Liu et al. (2023) discusses a trial where a combination of CBD and THC was used to treat adult patients with severe epileptic conditions. In this study, THC dosages were kept below 5 mg/day to avoid psychoactive effects, while CBD dosages were adjusted between 10 and 30 mg/kg/day depending on efficacy and side effects observed, showcasing the need for precise cannabinoid balancing. Lattanzi et al. (2021) presents findings from a retrospective analysis where patients were administered varying doses of CBD, typically starting at 10 mg/kg/day and increasing to a maximum of 50 mg/kg/day for acute control of seizures. This high-dosage regimen highlights the potential for CBD to be used in emergency neurology settings, where rapid and potent intervention is needed.

In Chen et al. (2019) the focus is on the long-term administration of CBD in a clinical trial setting, where doses ranged from 20 to 50 mg/kg/day over extended periods. The study examines the sustainability and long-term safety of high-dose CBD use, providing crucial data on chronic administration in a controlled environment. Devinsky et al. (2016) explore the caregiver perspective, reporting on families who administer CBD to children with complex epilepsy syndrome. Here, doses typically do not exceed 25 mg/kg/day, with many caregivers opting for gradual increases from a base dose of 5 mg/kg/day to monitor effects and adjust as needed effectively. Gunning et al. (2020)

Authors	Study	Pts	Age	Dose	Delivery	Follow-up	Outcomes
Devinsky et al. (2016)	Open label trial	214	10.5 x̄	2-50mg/kg	Oral (Epidiolex®)	12 weeks	Median reduction in monthly motor seizures by 36.5%. Common adverse events included somnolence (25%), decreased appetite (19%), diarrhoea (19%), and fatigue (13%).
Gofshteyn et al. (2016)	Case series	7	7 x̄	max. 25mg/kg	Oral (Epidiolex®)	48 weeks	6 out of 7 patients showed significant seizure reduction. 1 patient died due to multiorgan failure related to prolonged anaesthetic use.
Hess et al. (2016)	Prospective cohort	18	2-31	5-50mg/kg	Oral (CBD)	1 year	Median seizure reduction of 48.8% at 3 months.
Devinsky et al. (2017)	RCT	120	9.8 x̄	20mg/kg	Oral (CBD)	14 weeks	Median reduction in convulsive seizure frequency (38.9%) compared to placebo (13.3%).
Rosenberg et al. (2017)	Open label trial	48	11.7 x̄	2-50mg/kg	Oral (Epidiolex®)	12 weeks	Improvement in quality of life across various domains, including energy, memory, social interaction, and overall quality of life. Not directly correlated with changes in seizure frequency.
Devinsky et al. (2018b)	RCT	225	2-55	10-20mg/kg	Oral (CBD)	14 weeks	Significant reduction in drop seizure frequency (41.9% in 20mg group, 37.2% in 10mg group) compared to placebo (17.2%).
Devinsky et al. (2018c)	Open label trial	55	-	5-50mg/kg	Oral (Epidiolex®)	48 weeks	Median reduction in convulsive seizure frequency at 12 weeks was 51.4% and at 48 weeks was 59.1%. 50% of patients achieved at least a 50% reduction in seizure frequency by 12 weeks, with 57% achieving this threshold by 48 weeks.
McCoy et al. (2018)	Open label trial	20	10.2 x̄	max. 16mg/kg CBD; max. 0.32mg THC	Oral	20 weeks	70.6% median reduction in motor seizures, with a 50% responder rate of 63%. Improved quality of life. Adverse events: somnolence (89.5%), anorexia (52.6%), and diarrhoea (31.6%).
Szaflarski et al. (2018a)	Open label trial	607	13 x̄	2-50mg/kg	Oral (Epidiolex®)	96 weeks	Median reduction in monthly convulsive seizures by 51% and total seizures by 48% at 12 weeks, with sustained reductions through 96 weeks.
Szaflarski et al. (2018b)	Open label trial	139	10.1 x̄	5-50mg/kg	Oral (Epidiolex®)	48 weeks	Significant reductions in seizure frequency and severity at 12 weeks, sustained through 48 weeks. Improvements in adverse event profile and seizure severity score were also observed.
Thiele et al. (2018)	RCT	171	2-55	20mg/kg	Oral (CBD)	14 weeks	Median reduction in monthly drop seizure frequency by 43.9% in the cannabidiol group vs 21.8% in the placebo group.
Devinsky et al. (2019)	Open label trial	264	9.3 x̄	2.5-30mg/kg	Oral (CBD)	48 weeks	Median reduction in monthly convulsive seizures by 38-44% and total seizures by 39-51%. Adverse events included diarrhoea, pyrexia, decreased appetite, and somnolence. 85% of patients/caregivers reported improvement on the Subject/Caregiver Global Impression of Change scale.

Authors	Study	Pts	Age	Dose	Delivery	Follow-up	Outcomes
Klotz et al. (2019)	Open label trial	35	19.7 x̄	5-50mg/kg	Oral (CBD)	321 days x̄	Median reduction in motor seizure frequency by 40% at 3 months, increasing to 49% at 6 months.
Knupp et al. (2019)	Prospective cohort	21	10.3 x̄	0.6-2.2mg/kg	Oral	12 weeks	24% response rate (≥50% reduction in seizures). 14% discontinued CBD + THC due to an increase in seizures.
Laux et al. (2019)	Prospective cohort	152	12.7 x̄	21-50mg/kg	Oral (Epidiolex®)	96 weeks	Significant reductions in monthly convulsive and total seizures. At 12 weeks, convulsive seizure reduction was 50%, and total seizures were reduced by 44%. Improvements up to 96 weeks.
Mitelpunkt et al. (2019)	Open label pilot	16	9.1 x̄	13.6mg/kg x̄	Oral	12 weeks	56% reduction in seizure frequency. Improvements reported by caregivers in seizure severity and condition.
Miller et al. (2020)	RCT	199	9.3 x̄	10-20mg/kg	Oral (CBD)	14 weeks	Reduction in convulsive seizure frequency by 48.7% for 10 mg/kg/day and 45.7% for 20 mg/kg/day groups, compared to 26.9% in the placebo group.
Thiele et al. (2021)	RCT	224	11.4 x̄	25-50mg/kg	Oral (CBD)	16 weeks	Reduction in Tuberous sclerosis complex-associated seizures by 48.6% for 25 mg/kg/day and 47.5% for 50 mg/kg/day groups, compared to 26.5% for placebo.
Navarro (2023)	Prospective cohort	44	30 x̄	200mg x̄ CBD + <1.9 mg THC per 100mg CBD	Oral	24 weeks	At 12 weeks, 79.5% of patients achieved >50% reduction in seizure frequency, with a median reduction in seizure frequency of 84.1%. 27.3% of patients were seizure-free at 12 weeks.
Berg et al. (2024)	Cross-sectional survey	498	16 x̄	8-19mg/kg	Oral (Epidiolex®)	15-28 months	85% of caregivers reported an improvement in seizure frequency. Non-seizure-related improvements in alertness, cognition, emotional functioning, and sleep. Caregivers also noted improvements in physical function and daily activities.

Table 3.19. *Studies evaluating use of medicinal cannabis in epilepsy.*

investigates the community use of CBD and THC through an online survey of parents whose children suffer from Dravet Syndrome. Most respondents reported using CBD at doses around 15 mg/kg/day, combined with low levels of THC, to reduce seizure frequency and severity without inducing significant psychoactive effects.

In Devinsky et al. (2020) a detailed review on the application of CBD in treating conditions such as Dravet and Lennox-Gastaut syndromes is provided, where dosages of CBD range from 5 mg/kg/day to 20 mg/kg/day depending on the patient's response and the severity of their condition. This dosage flexibility is crucial for adapting to the variable efficacy observed across different patient populations and seizure types. de Fátima dos Santos Sampaio et al. (2024) discusses the broader implications of cannabinoid therapy in neurology, particularly emphasizing the neuroprotective potential of higher-dose CBD treatments. In this context, CBD dosages as high as 50 mg/kg/day are considered for severe cases, offering insights into the high dosing thresholds explored in clinical settings. The efficacy of CBD in reducing seizure frequency in patients with epilepsy is rigorously analyzed. Dosages in the discussed studies vary, with many trials employing a standard dose of around 20 mg/kg/day, which has been shown to effectively reduce seizure frequency in several controlled trials in Knupp et al. (2019).

Navarro (2023) provides a case study approach to CBD dosage optimization in treatment-resistant epilepsy. Here, slow titration methods are emphasized, starting as low as 2.5 mg/kg/day and gradually increasing to 20 mg/kg/day to monitor and adapt to patient responses effectively. Gaston & Szaflarski (2018) reviews the current research on medical cannabis in epilepsy, discussing both CBD and THC applications. It notes that while CBD is predominantly used at doses of 10-25 mg/kg/day, THC is

used sparingly and at much lower doses, generally not exceeding 5 mg/day to avoid psychoactive effects and maximize the therapeutic benefits of the treatment regime. Huntsman et al. (2020) outline the interactions and efficacy of CBD across various therapeutic domains, citing standard dosages ranging from 10 mg/kg/day to 25 mg/kg/day. This document highlights the importance of understanding CBD's pharmacokinetics to optimize dosage and reduce potential drug interactions.

Berg et al. (2024) conducted the BECOME (BEhavior, COgnition, and More with Epidiolex®) survey to evaluate the real-world impact of pharmaceutical-grade CBD on patients with Lennox-Gastaut syndrome and Dravet syndrome. The study analyzed responses from 498 caregivers, providing a crucial perspective on outcomes that extends beyond the standard clinical trial focus on seizure frequency. A key component of this real-world analysis was the documentation of dosing regimens, which varied significantly across the patient population. The median dose of CBD reported was 14 mg/kg/day, with the majority of patients (47%) receiving a daily dose between 10 and 20 mg/kg. Interestingly, nearly a third of the cohort (29%) was maintained on a lower dose of less than 10 mg/kg/day, while a quarter of the patients (25%) required doses exceeding 20 mg/kg/day to manage their condition. The survey results strongly reinforced the efficacy of these dosing strategies, with 85% of caregivers reporting an overall improvement in seizure frequency. Perhaps more significantly, the study captured robust improvements in non-seizure domains, which are often difficult to quantify in traditional trials. Caregivers reported substantial gains in alertness, cognition, and executive function (85%), as well as emotional functioning (82%) and language / communication skills (79% in nonverbal patients). These holistic improvements, combined with effective seizure control, led 93% of caregivers to express an intention to continue CBD treatment. This high retention rate underscores

that the flexible dosing regimens used in clinical practice, often deviating from the fixed doses of clinical trials, are capable of delivering meaningful therapeutic benefits that encompass both seizure reduction and enhanced quality of life.

3.4.2.10.2. Challenges and research gaps

One of the significant hurdles in the clinical use of cannabis for epilepsy is the lack of standardized dosing regimens. As outlined in the varied studies documented above, dosing for cannabinoids like CBD and THC can vary widely depending on the study design and patient demographics. For instance, while a study might explore the effects of CBD at 5 mg/kg/day, another might test dosages as high as 50 mg/kg/day for more severe cases. This variability complicates the development of universally applicable dosing guidelines, making it challenging for clinicians to optimize treatment plans for individual patients. Additionally, the methods of administration (oral, sublingual, vaporized) further influence the effective dosage received by patients, as noted in (Chen et al., 2019; Lattanzi et al., 2021). The bioavailability of cannabinoids can significantly differ based on the administration route, affecting both the efficacy and safety profiles of these treatments.

Another clinical challenge is the high degree of variability in individual responses to cannabinoid-based treatments. As seen in patient outcomes detailed in a number of studies quoted, some patients experience significant reductions in seizure frequency and severity, while others may see little to no benefit. This variability can be attributed to genetic differences, the nature of the epilepsy being treated, and concurrent use of other medications. The long-term impacts of sustained cannabinoid use are not yet fully understood due to the relatively recent introduction of these compounds into

clinical settings. Studies such as Gaston & Szaflarski (2018) suggest potential neuroprotective effects over the long term, but also caution about the psychoactive risks associated with THC, emphasizing the need for ongoing monitoring and research.

The current body of research, while growing, still has significant gaps that need to be addressed to enhance the therapeutic potential of cannabinoids for epilepsy. One such gap is the understanding of the mechanisms underlying the antiepileptic effects of cannabinoids. While studies such as Xu et al. (2021) and Huntsman et al. (2020) provide some insights, the exact pathways through which CBD and THC impact neuronal activity and seizure thresholds remain partially elucidated. There is a critical need for larger-scale and longer-term studies to better understand the implications of medicinal cannabis use. Most of the existing studies, including those reported in Wang et al. (2020) and Gunning et al. (2020), involve relatively small sample sizes and short follow-up periods, which do not adequately capture the long-term benefits and risks of cannabinoid therapy. Larger-scale studies would help in developing more robust data, potentially leading to more precise dosing recommendations and a better understanding of long-term outcomes. Moreover, long-term studies are essential to assess the continued efficacy of cannabinoids and monitor any adverse effects that may arise with prolonged use. These studies could also explore the potential development of tolerance or dependence on these compounds, ensuring that they continue to provide a viable alternative for patients with drug-resistant epilepsy. While medicinal cannabis presents a promising addition to the arsenal against epilepsy, significant clinical challenges and research gaps remain. Addressing these through continued and expanded research efforts will be crucial in moving from empirical to

evidence-based use of cannabis in epilepsy treatment, ultimately improving patient outcomes and quality of life.

3.4.2.11. Mood disorders

Mood disorders, which include prevalent conditions such as anxiety and depression, significantly impact individuals' quality of life, affecting their emotional state, physical health, and overall well-being. Anxiety disorders manifest as excessive and persistent worry, fear, and nervousness, whereas depression is characterized by profound sadness, loss of interest, and a lack of energy, contributing to substantial impairments in daily functioning. The World Health Organization (WHO) has highlighted depression as a leading cause of disability across the globe, with anxiety disorders also recognized for their considerable contribution to the global burden of mental health conditions.

Historically, the therapeutic use of cannabis dates back thousands of years, with ancient civilizations utilizing it for its sedative and euphoric properties (Russo, 2007). In the modern era, the narrative surrounding cannabis has evolved, marked by a rekindled interest in its medicinal properties, spurred by emerging research and a shift in regulatory perspectives. Medicinal cannabis, has garnered attention for its potential application in a myriad of health conditions, including mood disorders like anxiety and depression (Black et al., 2019)

Mood disorders, encompassing a spectrum of conditions such as anxiety and depression, are characterized by significant alterations in an individual's emotional state that disrupt daily functioning. Anxiety disorders are marked by excessive and

persistent worry, fear, and a heightened state of nervousness that is often disproportionate to the actual threat or challenge. Common symptoms include restlessness, fatigue, difficulty concentrating, irritability, muscle tension, and sleep disturbances. Depression, on the other hand, is typified by pervasive feelings of sadness, hopelessness, and a lack of interest or pleasure in activities. Additional symptoms can include significant changes in appetite or weight, sleep irregularities, psychomotor agitation or retardation, fatigue, feelings of worthlessness or excessive guilt, difficulty thinking or concentrating, and recurrent thoughts of death or suicide (Narayan et al., 2022).

The treatment landscape for mood disorders is multifaceted, encompassing a range of pharmacological, psychological, and lifestyle-oriented interventions. Medications, including SSRIs, SNRIs, benzodiazepines, and mood stabilizers, are commonly prescribed to manage the symptoms of anxiety and depression, often in conjunction with psychotherapy approaches such as cognitive-behavioural therapy (CBT), interpersonal therapy (IPT), and mindfulness-based cognitive therapy (MBCT). Lifestyle interventions, including regular physical activity, a balanced diet, adequate sleep, and stress reduction techniques, also play a crucial role in the holistic management of mood disorders, contributing to overall well-being and resilience (Kuhns et al., 2022). Medicinal cannabis has garnered significant attention for its potential therapeutic benefits in a variety of medical conditions, including mood disorders. The therapeutic use of cannabis is believed to modulate the endocannabinoid system, which plays a key role in regulating mood, stress response, and emotional homeostasis (Müller-Vahl, 2024).

3.4.2.11.1. Recommended dosages in current literature

Clinical studies have explored various dosages of THC and CBD for mood disorders, with a notable emphasis on patient-reported outcomes and clinical assessments to gauge efficacy. In a study exploring the use of medicinal cannabis in patients with generalized anxiety disorder (GAD), where the median CBD dosage ranged from 4.50 mg to 20.00 mg, and the median THC dosage varied from 13.00 mg to 32.00 mg across different follow-up periods, significant improvements in GAD-7 and EQ-5D-5L scores were demonstrated (Ergisi et al., 2022). Another study emphasized the role of specific dried flower cannabis-based medicinal products (CBMP) and particular doses of THC in achieving clinically significant benefits in GAD-7 scores over 12 months (Li et al., 2024).

The dosages of oral CBD employed in the treatment of social anxiety disorder across various studies reveal a range of therapeutic thresholds and outcomes, emphasizing the compound's potential efficacy in managing mood disorders (Table 3.20). For instance, Crippa et al. (2011) utilized a single dose of 400 mg oral CBD in their study involving treatment-naïve Portuguese men, demonstrating a significant reduction in anxiety symptoms without any notable adverse effects. This dosage indicates CBD's anxiolytic properties and suggests a favourable safety profile, particularly in adult populations. Similarly, Bergamaschi et al. (2011) explored a slightly higher dosage of 600 mg oral CBD in Brazilian undergraduates, also treatment-naïve, before a simulated public speaking test. This study further corroborates CBD's anxiolytic effects, with participants experiencing a less pronounced increase in anxiety levels compared to those in the placebo group. The increased dosage underscores the potential dose-dependent nature of CBD's therapeutic effects. Lastly, Masataka

(2019) took a different approach by administering a daily dose of 300 mg CBD oil over four weeks to Japanese teenagers with social anxiety disorder, yielding significant symptomatic improvements over the placebo. This longer-term, daily dosing regimen suggests that sustained CBD administration might be effective in managing chronic anxiety symptoms, offering an alternative to single, higher-dose administrations. Collectively, these studies highlight the nuanced therapeutic landscape of CBD in treating anxiety, suggesting a broad therapeutic window and the importance of tailoring dosages to individual patient needs, symptom severity, and treatment duration.

Kotin et al. (1973) outlined a trial of THC in hospitalized patients with moderate to severe depression, this study administered a dosage of 0.3 mg/kg twice daily, using 5 mg capsules. For the specific cases described, this translated to regimens such as 10 mg to 20 mg twice daily. The study found no significant antidepressant response or improvement in global depression ratings at these dosages. Instead, adverse effects such as drowsiness, anxiety, and depersonalization were frequently reported. In a double-blind study involving hospitalized patients with unipolar and bipolar depression, Ablon & Goodwin (1974), note that the administration of oral THC failed to produce an antidepressant response. The dosage regimen ranged from 5 mg once daily to 20 mg twice daily, totaling up to 40 mg per day, over a period of one to seven days. The study noted a high incidence of dysphoric reactions, particularly among unipolar patients, suggesting that moderate doses of THC may act as a 'mood intensifier' rather than a euphoriant in this population.

Fabre & McLendon (1981) investigated nabilone in outpatients suffering from anxiety. In an open-label dose-finding phase, dosages were adjusted between 2 mg and 8 mg

daily, with an average effective dose of 2.8 mg per day. In the subsequent double-blind phase, a fixed dose of 1 mg three times daily (3 mg/day) resulted in dramatic improvements in anxiety symptoms compared to placebo, as measured by the Hamilton Anxiety Scale. On a similar note, Glass et al. (1981) looked at the acute effects of nabilone in anxious volunteers. This study utilized single oral doses of 1 mg, 2 mg, 4 mg, and 5 mg. While high doses (4 mg and 5 mg) resulted in sedation and orthostatic hypotension, limited antianxiety effects were observed at the lower dosage tier of 1 mg or 2 mg in some subjects. The authors noted that the therapeutic window for nabilone appeared narrow, with side effects increasing substantially at higher doses.

Zuardi et al. (2010) used CBD to investigate its efficacy for bipolar affective disorder. It was administered to patients experiencing a manic episode. The dosage started at an initial oral dose of 600 mg/day, increasing to 1200 mg/day over a 30-day period. Despite the high dosage, no improvement in manic symptoms was observed in the patients treated with CBD monotherapy, though the compound was well tolerated. Although primarily a graded-dose trial for cancer-related pain, the study by Portenoy et al. (2012) assessed mood as a secondary outcome using the Montgomery-Asberg Depression Rating Scale (MADRS). Patients were titrated to three dosage ranges of nabiximols spray delivering 2.7 mg THC and 2.5 mg CBD per actuation: low (1–4 sprays / day), medium (6–10 sprays / day), and high (11–16 sprays / day). While analgesic benefits were noted at low and medium doses, no significant treatment differences were observed between nabiximols and placebo for depression scores (MADRS) across any of the dosage groups. The report by Blaas (2008) describes the clinical treatment of two patients suffering from depression, stress, and burnout syndrome using dronabinol in a general practice setting. The typical dosing protocol

began with 2.5 mg daily, which was titrated over several days to 5 mg or 7.5 mg per day. The author observed that the effective daily dosage generally ranged between 7.5 mg and 12.5 mg, with swift improvement in mood reported in approximately 80% of patients. For patients who did not respond to monotherapy, a combination of dronabinol and standard antidepressants, SSRIs or SNRIs, was utilized.

Das et al. (2013) investigated the impact of vaporized CBD at a dosage of 32 mg in the context of anxiety induced by the anticipation of public speaking. The use of a vaporized form aimed to assess the acute effects of CBD on situational anxiety. However, the study did not specify clear outcomes related to anxiety or sleep measures, leaving an open question regarding the efficacy of this dosage and delivery method for immediate anxiety relief in high-pressure situations. de Almeida et al. (2021) adopted a progressive dosing regimen, starting with 75 mg of CBD in the first week and escalating to 300 mg by the third week, maintained through the twelfth week. This study aimed to evaluate the effects of sustained CBD administration on general anxiety over a more extended period. Interestingly, no significant impact on anxiety or sedation was observed at any point, with both the CBD and placebo (PLA) groups showing a decrease in anxiety over time. This outcome suggests that factors beyond CBD administration, potentially including the placebo effect or the natural course of anxiety, may influence anxiety levels over time. de Meneses-Gaya et al. (2021) explored the effects of a 300 mg CBD dosage over a short period of 10 days for general anxiety. The lack of significant differences in anxiety measures and sleep quality between the CBD and PLA groups in this study raises questions about the short-term efficacy of this dosage for general anxiety relief. Linares et al. (2018) conducted a study with varying dosages of CBD (150 mg, 300 mg, and 600 mg) for Social Anxiety Disorder (SAD). The findings indicated no significant changes in anxiety

measures between the CBD and PLA groups across all dosages. However, an inverted U-shaped dose-response curve for CBD on anxiety was noted, suggesting that there might be an optimal CBD dosage for anxiety relief, beyond which the therapeutic effects do not increase and may even diminish.

Bolsoni et al. (2022) investigated the effects of a single 300 mg dose of CBD in capsule form on anxiety induced by the recall of nonsexual traumatic events. The study found a significant reduction in anxiety levels with CBD compared to the placebo (PLA) group, both before and after trauma recall, without affecting sedation levels. This finding suggests that CBD may have therapeutic potential for reducing anxiety associated with traumatic memories, offering a promising avenue for treatments centred around PTSD and related disorders. Crippa et al. (2022) examined the impact of a 150 mg dose of CBD on general anxiety in a single dosing session. The outcomes indicated no significant changes in anxiety or sedation levels with CBD treatment compared to placebo, highlighting the variability in CBD's anxiolytic effectiveness and the importance of dosage and patient-specific factors in treatment outcomes. Linares et al. (2019) explored the effects of a 300 mg dose of CBD on anxiety and sleep in a single dosing session. The study did not find significant differences in anxiety and sleep measures between the CBD and PLA groups, suggesting that this dosage might not be sufficient or that CBD's effects on sleep and anxiety are complex and require further investigation. In a study by Crippa et al. (2004), participants with Social Anxiety Disorder (SAD) received 400 mg of CBD in capsule form across two dosing sessions, one week apart. The treatment led to a reduction in anxiety as measured by the Visual Analog Mood Scale-Anxiety (VAMS-A), pointing to CBD's potential efficacy in managing SAD symptoms. Zuardi et al. (1993) compared a 300 mg dose of CBD in capsule form to 10 mg Diazepam in a single dosing session for treating anxiety. While

the study did not specify outcomes related to anxiety or sleep measures, the comparison with Diazepam, a well-known anxiolytic, raises intriguing questions about CBD's relative efficacy and safety profile. Morgan et al. (2013) and Stanley et al. (2022) both focused on anxiety and sedation, with Morgan et al. using a 400 micrograms dose via inhaler and Stanley et al. exploring 150 mg, 300 mg, and 600 mg doses in oil form. Neither study reported specific outcomes related to anxiety or sleep measures, indicating a need for more detailed research to ascertain the efficacy and optimal dosages of CBD for these conditions.

Shannon et al. (2019) assessed the effects of CBD capsules at dosages of 25 mg, 50 mg, and 75 mg per day, with one participant increasing the dosage to 175 mg/day over at least one month. The study noted a decrease in HAM-A scores, indicating reduced anxiety levels, and an improvement in sleep quality over three months. This graduated dosing approach provides insights into the potential for tailoring CBD dosages to individual needs, ensuring optimal therapeutic outcomes for both anxiety and sleep disturbances. Zuardi et al. (2017) delved into the effects of CBD on public speaking test-related anxiety, employing a broad range of dosages (100 mg, 300 mg, 900 mg) in a single session. The study revealed an inverted U-shaped dose-response curve, with 300 mg of CBD effectively reducing post-stress anxiety compared to both Clonazepam and Placebo, without affecting blood pressure. This finding is particularly noteworthy as it underscores CBD's safety profile and its potential as a non-sedative anxiolytic alternative for situational anxiety, such as public speaking. Berger et al. (2020) focused on the long-term administration of CBD, with dosages ranging from 200 mg to 800 mg daily over six months for treating anxiety. The study observed a continuous decrease in anxiety levels, particularly at the 600 mg and 800 mg marks at weeks 4 and 8, respectively. This sustained improvement underscores CBD's

potential in managing chronic anxiety conditions, especially in young individuals with treatment-resistant forms of anxiety.

Pacheco et al. (2021) investigated the impact of a 330 mg CBD oil dosage (divided into two daily doses of 165 mg) over four weeks for individuals with Generalized Anxiety Disorder (GAD). The study reported a rapid onset of anxiolytic effects, which persisted for four weeks post-treatment, highlighting CBD's potential for producing lasting anxiolytic benefits following a treatment period.

Gambino et al. (2021) administered an oil form of Bediol, containing 6.3% THC and 8% CBD, over four weeks with gradually increasing dosages. The Hospital Anxiety and Depression Scale (HADS) showed a significant reduction in anxiety levels from baseline to the end of the treatment period, highlighting the anxiolytic potential of balanced THC:CBD ratios in oil form. Alessandria et al. (2020) utilized Sativex®, an oromucosal spray with THC (27 mg/ml) and CBD (25 mg/ml), allowing up to 12 sprays per day for a year. The Hamilton Anxiety Rating Scale (HAM-A) revealed no significant change in anxiety levels, suggesting that long-term use of this THC:CBD combination might not alter anxiety or mood significantly in some patients. Cuttler et al. (2018) explored the short-term effectiveness of inhaled cannabis with a mean concentration of THC at 15.26% and CBD at 3.69%. Through Strainprint® medical cannabis journaling over 5085 sessions, a remarkable 93% decrease in anxiety was observed in most sessions, indicating the potential of cannabis, particularly THC-dominant strains, for acute anxiety relief. A case report by Shannon & Opila-Lehman (2016) detailed the treatment of a 10-year-old child with PTSD presenting with anxiety and insomnia. The effective regimen consisted of 25 mg of CBD oil administered orally once daily, supplemented by a CBD spray, delivering 6–12 mg as needed for anxiety,

Authors	Study	Pts	Age	Dose	Delivery	Follow-up	Outcomes
Kotin et al. (1973)	RCT	8	-	0.3mg/kg BD	Oral (THC)	1 week	No significant antidepressant effects. Some patients experienced severe anxiety and depersonalization.
Ablon & Goodwin et al. (1974)	RCT	13	-	-	Oral (THC)	-	High incidence of dysphoric reactions. THC did not produce significant euphoria or antidepressant effects.
Fabre & McLendon et al. (1981)	RCT	20	19-41	1mg TDS	Oral (nabilone)	28 days	Significant reduction in anxiety as measured by the Hamilton Anxiety Rating Scale.
Glass et al. (1981)	RCT	8	21-35	1-5mg	Oral (nabilone)	9 weeks	Higher doses led to sedation, increased heart rate, and orthostatic hypotension. Low doses showed mild antianxiety effects in some subjects.
Zuardi et al. (1993)	RCT	40	20-30; 22.8 $\bar{x}$	300mg	Oral (CBD)	-	Significantly decreased subjective anxiety after the speech task but it did not attenuate the anxiety increase during the speech itself.
Blaas (2008)	Case series	2	48, 22	2.5-10mg	Oral (dronabinol)	1 year	Notable improvement in mood and reduced depressive symptoms. When not responding adequately to dronabinol alone included SSRIs or SNRIs, proving effective.
Zuardi et al. (2010)	Case report	2	34, 36	600-1200mg	Oral (CBD)	30 days	No additional improvement with CBD monotherapy. CBD may not be effective for treating manic episodes in bipolar disorder.
Bergamaschi et al. (2011)	RCT	24	24.6 $\bar{x}$	600mg	Oral (CBD)	-	Reduced anxiety levels during a public speaking test, measured by Visual Analogue Mood Scale (VAMS) and Self-Statements during Public Speaking Scale (SSPS-N).
Crippa et al. (2011)	Randomized cross-over	10	20-33	400mg	Oral (CBD)	2 phases; 1-week wash-out	Reduced anxiety and brain activity changes in regions associated with anxiety, observed via SPECT imaging.
Portenoy et al. (2012)	RCT	360	58 $\bar{x}$	1-16 sprays / day (2.7mgTHC + 2.5mgCBD)	Oromucosal spray (nabiximols)	5 weeks	Nabiximols did not significantly impact depression or mood disorders as measured by MADRS. Higher doses were linked to cognitive side effects.
Shannon & Opila-Lehman (2016)	Case report	1	10	25mg OD + 6-12mg PRN / day	Oral (CBD)	5 months	Significant reduction in anxiety and improvement in sleep quality and duration. The child was able to sleep alone most nights and had decreased anxiety levels.
Zuardi et al. (2017)	RCT	60	22.5 $\bar{x}$	100-900mg	Oral (CBD)	-	The 300mg dose significantly reduced anxiety in the post-speech phase. The 100mg and 900mg doses were ineffective.
Cuttler et al. (2018)	Naturalistic observational study	1399	33.4 $\bar{x}$	2-10 puffs	Inhalation	-	Users perceived a 50% reduction in depression and a 58% reduction in anxiety and stress after use. High-CBD (>9.5%) / low-THC (<5.5%) cannabis was most effective for depression.

Authors	Study	Pts	Age	Dose	Delivery	Follow-up	Outcomes
Casarett et al. (2019)	Retrospective cohort study	2431	33.7 $\bar{x}$	Varied	Inhalation	-	Higher THC:CBD ratios were associated with greater relief for depressive symptoms (OR 1.63) and insomnia, but not for anxiety, which showed a "U-shaped" curve, peaking at 50% THC, or PTSD flashbacks.
Linares et al. (2019)	RCT	57	24 $\bar{x}$	150-600mg	Oral (CBD)	-	The 300mg dose significantly reduced anxiety during the speech compared to placebo, while the 150mg and 600mg doses did not show significant differences from placebo.
Masataka et al. (2019)	RCT	37	18-19	300mg	Oral (CBD)	6 months	Significant reduction in anxiety symptoms measured by FNE and LSAS scores in the CBD group compared to placebo.
Shannon et al. (2019)	Retrospective case series	72	34.9 $\bar{x}$	25mg / day $\bar{x}$	Oral (CBD)	3 months	Anxiety scores decreased within the first month in 79.2% of patients and remained decreased during the study duration.
Alessandria et al. (2020)	Prospective observational pilot study	20	23-67; 50.2 $\bar{x}$	2-9 sprays / day (2.7mgTHC + 2.5mgCBD)	Oromucosal spray (nabiximols)	12 months	There was no significant variation in mood or anxiety scores (BDI and HAM-A) over the 12-month period.
Aviram et al. (2020)	Prospective observational study	108	64 $\bar{x}$	3000mg THC, 600mg CBD / month; 1000mg THC, 2000mg CBD / month; 2000mg THC, 2000mg CBD / month	Sublingual oil extracts; Inhalation	1 month	While cancer distress and psychological symptom burden improved significantly, there were no significant changes in specific anxiety or depression scores from baseline to follow-up.
Berger et al. (2020)	Case report	1	20	600-1200mg / day	Oral (CBD)	6 months	Patient-reported subjective benefits to anxiety and depression, confirmed via standardized rating scales (HAM-A from 29 to 7).
Giorgi et al. (2020)	Prospective observational study	102	51.9 $\bar{x}$	10-120 drops / day (22% THC, <1% CBD; 6.3% THC, 8% CBD)	Oral (oil)	6 months	50% of patients showed moderate improvement in anxiety and depression scales (ZSR-A and ZSR-D).
Kayser et al. (2020)	RCT	14	21-48; 26.8 $\bar{x}$	50% cigarette (7% THC, 10.4% CBD)	Inhalation	-	Neither THC nor CBD significantly reduced OCD symptoms or anxiety compared to placebo. In fact, placebo resulted in significantly lower state anxiety scores.
Gambino et al. (2021)	Open label pilot	17	71 $\bar{x}$	5-20 drops BD (6.3% THC, 8% CBD)	Oral (oil)	24 weeks	Statistically significant improvements in anxiety and depression scores (HADS and GDS) after 4 weeks, remaining stable up to the 24-week follow-up.
Pacheco et al. (2021)	Prospective case series	13	32.5 $\bar{x}$	330mg	Oral (CBD)	8 weeks	Reductions in burnout, depression (PHQ-9), and anxiety (GAD-7) scores, sustained after treatment discontinuation.

Authors	Study	Pts	Age	Dose	Delivery	Follow-up	Outcomes
Pacheco et al. (2021)	Prospective case series	13	32.5 x	330mg	Oral (CBD)	8 weeks	Reductions in burnout, depression (PHQ-9), and anxiety (GAD-7) scores, sustained after treatment discontinuation.
Sagar et al. (2021)	Prospective cohort study	54	23-78; 49.2 x	42-64mg THC x, 154-202mg CBD x	Varied	12 months	Improved mood and anxiety, and executive function over the 12 months. Clinical improvement was positively associated with higher CBD use.
Bolsoni et al. (2022)	RCT	33	33.2 x	300mg	Oral (CBD)	7 days	CBD did not significantly reduce anxiety, alertness, or discomfort compared to placebo during trauma recall
Bonomo et al. (2022)	Open label pilot	9	58.1 x	2.5-12.5mg THC:CBD	Oral (THC:CBD)	36 days	Improvements in mood parameters were observed over the course of the study as a secondary outcome.
Ergisi et al. (2022)	Case series	67	37 x	16.3mg x CBD, 13mg x THC	Oral, Inhalation	6 months	Statistically significant reductions in anxiety (GAD-7), improvements in sleep quality (SQS), and general health-related quality of life (EQ-5D-5L). Mild-to-moderate adverse events were reported in 39.1% of patients, commonly dry mouth and somnolence.
Harris et al. (2022)	Case series	190	47.5 x	2mg THC x, 20mg CBD x	Oral, Inhalation	6 months	Significant improvements in anxiety (GAD-7) scores and health-related quality of life, including anxiety and depression subscales of EQ-5D-5L).
Montebello et al. (2022)	RCT	128	18-65	max. 32 sprays / day (2.7mgTHC + 2.5mgCBD)	Oromucosal spray (nabiximols)	24 weeks	Moderate-to-severe depression or anxiety at baseline improved. However, there was no significant difference in mood outcomes between the nabiximols group and the placebo group, as both improved.
Rifkin-Zybutz et al. (2023)	Prospective cohort	302	37 x	2mg x CBD, 21mg x THC	Oral, Inhalation	6 months	Clinically significant improvements in anxiety (GAD-7 score), sleep quality, and quality of life. Adverse events reported in 12.9% of participants, most commonly dry mouth and fatigue.
Stack et al. (2023)	Retrospective cohort	568	48 x	50mg x CBD, 4.4mg x THC	Oral	3 years	Improvement in anxiety, depression, fatigue, and social functioning. Common adverse events included dry mouth (32.6%) and somnolence (31.3%).
Li et al. (2024)	Case series	120	39 x	31.25mg x CBD, 100mg x THC	Oral	12 months	Significant improvements in anxiety severity (GAD-7) and quality of life (EQ-5D-5L) across all time points. 20% reported adverse events, with most being mild-to-moderate.

Table 3.20. *Studies evaluating use of medicinal cannabis in mood disorders.*

typically used 2 to 4 times per week. This dosage strategy resulted in a sustained decrease in anxiety, with reductions on the Hamilton Anxiety Rating Scale (HAM-A), and improvement in sleep quality over a five-month period. Drennan et al. (2021) compared the effects of THC-dominant and CBD-dominant products through inhalation (dab, vape) over five days. The study noted a decrease in anxiety immediately post-treatment with CBD and one hour post-treatment with THC, suggesting more pronounced anxiety-reducing effects associated with THC when used acutely. Gibson et al. (2022) investigated the acute effects of inhalation of THC-dominant, CBD-dominant, and balanced THC:CBD strains over five days. The study found that THC-dominant strains increased anxiety levels compared to CBD-dominant and balanced strains. This outcome suggests that while THC can exacerbate anxiety, CBD might mitigate these effects and possibly improve mood, pointing to the complexity of cannabis's effects on anxiety based on its cannabinoid profile.

Mauzay et al. (2021) examined the efficacy of inhaled cannabis, with a mean THC concentration of 13.62% and CBD at 3.41%, over an extended period of 31 months. Strainprint® journaling recorded a 52% decrease in anxiety across 1810 sessions, supporting the notion that cannabis, particularly with a higher THC content, can offer short-term relief from anxiety symptoms. Kayser et al. (2020a) focused on the effects of smoked cannabis, differentiating between THC-dominant and CBD-dominant strains compared to a placebo. Interestingly, all conditions, including the placebo, led to a decrease in anxiety, with an immediate reduction observed following placebo administration. This outcome highlights the complex placebo effects and the subjective experience of anxiety relief, potentially influenced by expectancy effects or the act of smoking itself. Grimm et al. (2018) utilized a capsule form to administer a significant dosage of CBD (600 mg) alongside a relatively low dosage of THC (10 mg), comparing

these to a placebo across three sessions spaced up to eight weeks apart. The findings highlighted THC's capacity to elevate state anxiety significantly three hours post-intake, contrasting with CBD, which did not demonstrate a notable anxiolytic or anxiogenic effect when compared to the placebo. This study underscores the nuanced effects of THC and CBD, emphasizing the need for careful consideration of THC's anxiety-inducing potential at certain dosages. Karschner et al. (2011) investigated the effects of synthetic THC and Sativex in varying dosages. The study found that higher dosages of THC, both synthetic and within Sativex®, were associated with increased anxiety compared to the placebo. This effect was more pronounced with high-dose Sativex®, pointing to the dose-dependent anxiogenic potential of THC, even when combined with CBD. Hindocha et al. (2015) examined the effects of inhaled CBD (16 mg) and THC (8 mg) versus a placebo, across four sessions a week apart. The lack of significant differences in anxiety outcomes across the conditions suggests a complex interaction between these cannabinoids and anxiety, possibly influenced by factors such as the method of administration and the acute effects of inhalation. Montebello et al. (2022) utilized a spray delivering a balanced dose of THC and CBD, observing significant reductions in anxiety and insomnia severity over a 12-week period. This study provides evidence for the therapeutic benefits of a balanced THC:CBD ratio in managing anxiety and related sleep disturbances, suggesting a synergistic effect that may mitigate some of the anxiogenic properties of THC.

Aviram et al. (2020) explored the effects of cannabis with varying THC:CBD ratios over a month, distinguishing between inhalation of THC-dominant Type I and the oral intake of mixed Type II and CBD-dominant Type III cannabis oils. The study found a general trend towards reduced anxiety across all types, with significant improvements in sleep quality, duration, and latency, highlighting the potential of tailored THC:CBD profiles

to address specific aspects of anxiety and sleep disorders. Bhattacharyya et al. (2009), Borgwardt et al. (2008), and Fusar-Poli et al. (2009) conducted similar experimental designs using capsules containing THC (10 mg), CBD (600 mg), or a placebo, with participants undergoing three treatment sessions. In these studies, THC consistently increased anxiety levels, as observed through fMRI and STAI measures, whereas CBD did not significantly alter anxiety or sedation levels when compared to the placebo. These outcomes underscore THC's potential anxiogenic effects and suggest a complex, possibly non-linear relationship between CBD dosage and its anxiolytic efficacy. Allsop et al. (2014) utilized nabiximols spray, which contains a balanced ratio of THC (21.6 mg/ml to 86.4 mg/ml) and CBD (20 mg/ml to 80 mg/ml), over a short treatment period of 6 days. The dosage was adjusted from a maximum of 8 sprays four times daily, tapering down by the end of the study. While the Cannabis Withdrawal Scale indicated minor improvements in anxiety and sleep measures over time, the lack of significant interaction between treatment and time suggests that the observed benefits might have been influenced by external factors, such as the controlled inpatient environment, rather than solely by the pharmacological effects of nabiximols. Martin-Santos et al. (2012) delivered a similar dosage regimen (THC 10 mg; CBD 600 mg) in capsule form, observing that THC heightened anxiety and sedation at 2 hours post-administration relative to CBD and placebo. This study underscores the minimal symptomatic effects of CBD in healthy, non-anxious subjects and the need for further research to clarify CBD's anxiolytic potential in clinical populations. Fusar-Poli et al. (2009) continued the exploration of THC and CBD's effects on anxiety through capsule administration, using dosages of 10 mg for THC and 600 mg for CBD across three sessions. Consistent with Borgwardt et al. (2008), THC was found to elevate anxiety levels, whereas CBD exhibited a trend towards reducing anxiety. This reaffirms THC's

anxiogenic potential at certain doses and hints at CBD's possible anxiolytic properties, albeit the latter's effects were not definitively significant. Spindle et al. (2020) provided a comparative analysis of the effects of vaporized and capsule-form CBD, including a CBD dominant combination with a minor THC component (3.7 mg). Across four sessions, the Drug Effect Questionnaire (DEQ) indicated no significant differences in anxiety across treatments, with an improvement in sleep observed in the CBD dominant group versus CBD alone when vaporized. This suggests the bioavailability and acute effects of inhaled CBD may differ from oral administration, and even low doses of THC might have active physiological or subjective effects, particularly in women.

The observational study by Aungsumart et al. (2021) utilized a minimal THC:CBD ratio of 1:1, with maximum dosages of 27 mg THC and 25 mg CBD, administered incrementally over 12 weeks. The Numerical Rating Scale (NRS) for anxiety and insomnia revealed no significant changes post-treatment, highlighting the variability in cannabis's therapeutic effects across individuals with different medical conditions and treatment histories. Ilan et al. (2005) investigated the anxiety outcomes associated with smoking cannabis with varying concentrations of CBD, THC, and cannabichromene (CBC). The study employed an electroencephalogram (EEG) and event-related potentials (ERP) alongside the Visual Analog Scale-Anxiety (VAS-A) across four sessions. Cannabis use increased anxiety levels compared to placebo, without a clear distinction between high and low THC groups. Interestingly, the study suggested that the anxiolytic effect of CBD might be influenced by the concurrent THC dose, with lower THC doses in high CBD conditions associated with increased anxiety, highlighting the complex interplay between CBD and THC in anxiety modulation. Zuardi et al. (1982) explored the anxiolytic potential of THC and CBD through an oral

tincture and capsule, delivering doses relative to body weight (0.5 mg/kg for THC and 1 mg/kg for CBD). The study observed an increase in anxiety with THC alone, a reduction with Diazepam, and no significant change with CBD or placebo. However, when combined, THC and CBD resulted in decreased anxiety levels compared to THC alone, indicating CBD's possible moderating effect on THC-induced anxiety. Winton-Brown et al. (2011) investigated the acute effects of THC and CBD in capsules, using a dosage of 10 mg for THC and 600 mg for CBD, across three sessions. Functional Magnetic Resonance Imaging (fMRI) and the State-Trait Anxiety Inventory (STAI) revealed that THC significantly increased anxiety levels compared to placebo, whereas CBD did not elicit a noticeable change. This study suggests that while THC can acutely heighten anxiety, CBD's effects on anxiety are less clear, despite influencing brain regions associated with auditory and visual stimuli processing, potentially impacting psychosis symptoms. Bindler et al. (2022) examined the impact of a single inhalation dose (0.5 g cigarette containing 22.17% THC and 0.12% CBD) over two days. The NRS for anxiety indicated a marginal decrease in anxiety levels, while actigraphy data suggested a reduction in total sleep time, pointing to THC's immediate effects on sleep patterns.

Sagar et al. (2021) utilized varied dosages of THC and CBD through inhalation, oromucosal, and cutaneous routes over a twelve-month period. The study observed significant reductions in Beck Anxiety Inventory (BAI) and State-Trait Anxiety Inventory-State (STAI-S) scores at 6 and 12 months, correlating with CBD use and the frequency of medicinal cannabis use per week. Additionally, Pittsburgh Sleep Quality Index (PSQI) scores improved post-treatment, suggesting the potential of medicinal cannabis in managing both anxiety and sleep-related issues. Ergisi et al. (2022) reported on the use of cannabis flower and oil with varied dosages over 6 months. The

study demonstrated significant improvements in Generalized Anxiety Disorder-7 (GAD-7) and Single Item Sleep Quality Scale (SQS) scores at 1, 3, and 6 months, suggesting a clinical advantage and enhanced life quality for fibromyalgia patients, potentially extending to those with anxiety and sleep issues. Giorgi et al. (2020) employed cannabis oil with differing THC:CBD concentrations for nighttime and morning use over 6 months in fibromyalgia patients. The treatment resulted in a 50% decrease in Zung Self-Rating Anxiety Scale (ZSR-A) scores and a 44% improvement in Pittsburgh Sleep Quality Index (PSQI) scores, underscoring significant anxiolytic and sleep-enhancing benefits. Nimalan et al. (2022) administered CBD oil with a median dosage of 32.0 mg CBD and 1.3 mg THC over six months. The study found no significant changes in the EuroQol 5-Dimension 5-Level Scale (EQ-5D-5L) and SQS, highlighting the complexity of cannabis's therapeutic effects and the need for further research to determine effective dosages and treatment protocols, particularly for specific patient populations and conditions. Casarett et al. (2019) investigated the effects of inhaled cannabis for insomnia and anxiety with high THC:CBD ratios (95% THC, 5% CBD for insomnia; 84% THC, 16% CBD for anxiety) over 13 months. Findings from Strainprint® medical cannabis journaling suggested that THC:CBD ratios above 1:1 might lessen the efficacy for anxiety symptoms, exhibiting an inverted U-shaped relationship. However, higher THC:CBD ratios were beneficial for insomnia, indicating the complex influence of cannabinoid ratios on different conditions. Gruber et al. (2021) explored various routes of administration (inhalation, sublingual oil/solution/tincture, edible, capsule, topical) with diverse THC and CBD dosages over 6 months. The outcomes included decreased State-Trait Anxiety Inventory (STAI) and Beck Anxiety Inventory (BAI) scores, along with significant improvements in Pittsburgh Sleep Quality Index (PSQI) scores, suggesting notable therapeutic effects on anxiety

and sleep disorders. Bonomo et al. (2022) utilized an oral solution with a balanced THC:CBD ratio, starting from 2.5 mg of each and escalating to a total daily dose of 15 mg of each over 23 dosing sessions. This regimen led to significant reductions in Depression Anxiety Stress Scale-Anxiety (DASS-A) and Insomnia Severity Index (ISI) scores, highlighting the potential of balanced THC:CBD formulations in improving anxiety and sleep quality, with sleep diary data also indicating reduced sleep onset latency. Harris et al. (2022) explored the effects of medicinal cannabis through inhalation and oil routes with varied THC and CBD dosages over a six-month period. The study reported significant improvements in Generalized Anxiety Disorder-7 (GAD-7) and Single Item Sleep Quality Scale (SQS) scores at 1, 3, and 6 months compared to baseline. These findings indicate the potential therapeutic effects of medicinal cannabis on anxiety and sleep disorders, emphasizing the importance of individualized dosing strategies to achieve optimal therapeutic outcomes. In a prospective cohort study from the UK Medical Cannabis Registry regarding Generalised Anxiety Disorder conducted by Rifkin-Zybutz et al. (2023), patients were prescribed various cannabis-based medicinal products, including oils and dried flower. The median daily dosages at baseline were 2.0 mg of CBD (IQR 0.1–20 mg) and 21.0 mg of THC (IQR 19.0–40.0 mg). Treatment with these regimens was associated with clinically significant improvements in GAD-7 anxiety scores at 1, 3, and 6 months.

For THC-containing oral products, Müller-Vahl (2024) suggests a prudent starting dose of approximately 2.5 mg THC, with the typical daily dosage ranging from 10 to 20 mg of THC. This dosing recommendation is grounded in the need to mitigate potential adverse effects associated with THC, such as psychoactivity, anxiety, or transient cognitive impairments, while harnessing its therapeutic benefits for conditions such as chronic pain, spasticity, and certain forms of nausea. In populations

that may be more susceptible to THC's side effects, including the elderly, children, and those with certain medical conditions, a more conservative starting dose of around 1 mg THC per day is advised, underscoring the principle of "start low, go slow" in cannabis medicine. Conversely, for pure CBD, Müller-Vahl (2024) outlines a considerably higher dosing threshold, reflecting CBD's distinct safety profile, characterized by a lack of psychoactivity and a generally favourable side effect profile. High oral doses, such as 10–50 mg/kg for children and over 400 mg/day for adults, are deemed effective, particularly for severe conditions like intractable childhood epilepsies, as evidenced by CBD's efficacy in syndromes such as Dravet and Lennox-Gastaut. The ambiguity surrounding the therapeutic potential of lower oral CBD doses (under 300 mg/day) highlights a gap in the literature, suggesting the need for further research to clarify CBD's efficacy across a broader range of conditions and dosages. For patients new to cannabis, particularly those using cannabis flowers, a cautious approach is recommended, starting with doses as low as 10–25 mg/day and titrating slowly to achieve therapeutic effects. The average daily dose for flower can vary widely, typically between 0.5 and 1.0 g/day, but both lower and higher doses may be appropriate depending on individual response, condition being treated, and specific strain or cannabinoid profile used (Müller-Vahl (2024)).

The ratio of THC to CBD is a critical factor in the clinical application of medicinal cannabis, with varying effects observed based on the predominant cannabinoid. Most of these studies highlight the importance of this ratio, particularly in the context of patient tolerance and symptom severity (Fonseca et al, 2023). Delivery methods, including oral ingestion, inhalation, and sublingual administration, play a significant role in the onset and duration of therapeutic effects, as evidenced by the diversity of administration routes explored in the literature (Stack et al., 2023).

Anecdotal evidence and case studies provide valuable insights into effective dosing strategies for mood disorders. Reports from Kuhns et al. (2022) detail patient experiences and clinical observations that highlight the potential benefits of medicinal cannabis in managing anxiety and depressive symptoms, contributing to a growing body of knowledge that supports the therapeutic use of cannabis in psychiatry (Kuhns et al., 2022; Quick et al., 2022). The personalization of medicinal cannabis dosages is paramount, taking into account factors such as patient tolerance, the severity of symptoms, and previous cannabis use. For instance, the dosing strategies outlined in Ergisi et al. (2022) and Li et al. (2024) suggest a gradual adjustment of dosages based on patient response and tolerability, underscoring the need for close monitoring and individualized treatment plans (Ergisi et al., 2022; Li et al., 2024).

3.4.2.11.2. Challenges and limitations in research and clinical practice

The exploration of medicinal cannabis as a therapeutic option for mood disorders such as anxiety and depression presents a promising yet complex landscape. The clinical potential is recognized yet this burgeoning field faces significant challenges and limitations, both in research methodologies and in the practicalities of clinical implementation. A critical challenge in cannabis research lies in the heterogeneity of study designs, including variations in dosing, cannabinoid ratios, and routes of administration. Studies such as those by Zuardi et al. (2017) and Fusar-Poli et al. (2009) have provided valuable data on the anxiolytic effects of CBD and the anxiogenic potential of THC, respectively. However, inconsistencies in research methodologies, such as differences in patient populations, treatment durations, and

outcome measures, complicate the comparability of findings and the synthesis of a cohesive evidence base.

The optimal dosing and cannabinoid ratios for treating mood disorders remain elusive, compounded by the biphasic effects of cannabinoids, where low and high doses of the same compound can produce opposite effects. For example, the inverted U-shaped dose-response curve observed with CBD suggests that finding the "sweet spot" dosage is crucial yet challenging. Additionally, the individual variability in response to THC and CBD, as highlighted in studies by Harris et al. (2022) and Nimalan et al. (2022), underscores the necessity for personalized medicine approaches in cannabis treatment, further complicating standardized dosing recommendations.

Regulatory challenges and the lack of standardized cannabis products significantly hinder clinical and research progress. Long-term data on the efficacy and safety of medicinal cannabis for mood disorders are limited. While studies such as those by Bonomo et al. (2022) and Ergisi et al. (2022) provide insights into the potential benefits of cannabis on anxiety and sleep over extended periods, concerns about chronic use, dependency, cognitive effects, and psychiatric risks remain to be fully addressed. Patient acceptance and education present another layer of complexity. The stigma associated with cannabis use, concerns about psychoactive effects, and the need for patient education on the therapeutic use of cannabis versus recreational use are critical factors that influence treatment acceptance and adherence. The transition from cannabis-naïve to therapeutic user requires careful management and education to mitigate concerns and optimize treatment outcomes.

The potential of medicinal cannabis in treating mood disorders is underscored by a growing body of research. However, the field is nascent and fraught with challenges

ranging from research design heterogeneity, dosing complexities, regulatory hurdles, long-term safety concerns, and patient-centric issues. Addressing these challenges through rigorous, standardized research, patient education, and the development of clear regulatory frameworks is essential to fully realize the therapeutic potential of medicinal cannabis for anxiety and depression. Collaborative efforts among researchers, clinicians, policymakers, and patients will be pivotal in navigating these challenges and advancing the clinical application of cannabis in mental health care.

3.4.2.12. Drug addiction management

Drug addiction remains one of the most formidable public health challenges worldwide, affecting millions of individuals across diverse communities and socioeconomic backgrounds. Characterized by the compulsive use of drugs despite harmful consequences, addiction encompasses a range of substances, including opioids, stimulants, and sedatives, leading to significant morbidity, mortality, and societal burdens. The escalating opioid crisis, particularly in the United States, has highlighted the urgent need for effective interventions and treatment modalities to address this pervasive issue. The scope of drug addiction is vast and global, affecting individuals across all demographics and leading to significant public health, social, and economic challenges. The World Health Organization (WHO) and other health bodies categorize addiction as a major contributor to the global burden of disease, necessitating comprehensive intervention strategies (Costa et al., 2024).

The neurobiology of addiction involves intricate brain systems and neural pathways that regulate reward, motivation, memory, and control over impulses. Central to understanding addiction is the brain's reward system, primarily mediated by the

neurotransmitter dopamine. Drugs of abuse artificially elevate dopamine levels in brain circuits, leading to heightened pleasure or euphoria, which reinforces drug-taking behaviour. Over time, chronic drug use can alter the brain's neuroplasticity, leading to changes in brain structure and function. These changes impair an individual's ability to exercise control over drug use, contributing to the compulsive nature of addiction. Furthermore, the stress system's involvement and alterations in other neurotransmitter systems like glutamate contribute to the complexity of addiction, impacting withdrawal symptoms and cravings (Jin et al., 2023).

Conventional approaches to drug addiction treatment often involve a combination of pharmacotherapy and psychosocial interventions. Medications such as methadone, buprenorphine, and naltrexone are commonly employed to manage opioid use disorder (OUD), aiming to reduce withdrawal symptoms and curb cravings. However, these treatments are not universally effective, with many individuals experiencing relapse, side effects, or barriers to access. Additionally, the stigma associated with drug use and treatment can further complicate the recovery process, underscoring the need for innovative and more accessible therapeutic options (Fehr et al., 2024).

In recent years, medicinal cannabis has emerged as a potential alternative or adjunctive treatment for drug addiction, drawing attention for its therapeutic properties (Reddon et al., 2023). Constituents of cannabis, such as cannabidiol (CBD) and tetrahydrocannabinol (THC), interact with the body's endocannabinoid system, which plays a crucial role in regulating mood, pain, and reward processes. This interaction has led researchers to explore the potential of cannabis in mitigating withdrawal symptoms, reducing drug cravings, and possibly addressing underlying psychiatric comorbidities associated with drug addiction (Elkrief et al., 2023).

3.4.2.12.1. Recommended dosages in current literature

The literature spans preclinical studies, case reports, and observational research, indicating a growing interest in the therapeutic potential of cannabinoids, particularly CBD and synthetic analogues, for various aspects of addiction, including withdrawal management, craving reduction, and prevention of relapse (Table 3.21).

A case study detailed the administration of a CBD tincture at a dosage of 200 mg three times daily (totalling 600 mg/day) over 10 days. The research indicated a decrease in the scores on the clinical opioid withdrawal scale, from 14 to 5 by the second day, achieving full resolution by the seventh day. Additionally, there was an effective shift to a naltrexone-based therapy for maintaining abstinence (Shaw & Marcu, 2021). Another case involved the use of approximately 20 CBD-rich cigarettes per day, equating to an estimated total daily CBD intake of around 400 mg, leading to significant improvements in psychiatric symptoms and cessation of high-dose THC and cocaine use (Meyer et al., 2021). Both cases highlighted CBD's potential in reducing cravings and facilitating transition to abstinence-based treatments. Research on the synthetic cannabinoid CIAC001 in a mouse model of morphine addiction revealed that an intraperitoneal dose of 0.2 mg/kg could ameliorate morphine-induced withdrawal symptoms, behavioural sensitization, and conditioned place preference. This study suggests the therapeutic utility of synthetic cannabinoids for opioid addiction management, warranting further exploration in clinical settings (Jin et al., 2023).

In a 2019 study by Hurd et al., the administration of oral CBD at dosages of 400 mg and 800 mg once daily over three days showed a significant reduction in opioid-induced cravings and anxiety among participants, compared to those who received a placebo. This effect was most pronounced within the first 24 hours after CBD ingestion

and persisted to some degree up to seven days post-dose, suggesting a potential role for CBD in managing opioid addiction symptoms. Conversely, a study conducted by Meneses-Gaya et al. in 2020, exploring the impact of oral CBD at a dosage of 300 mg daily for ten days on cocaine addiction, found no significant differences in the levels of cocaine craving, anxiety, depression, or sleep quality between the CBD group and the placebo group. This indicates that CBD's efficacy may vary significantly depending on the substance of addiction. Mongeau-Pérusse et al. (2021) further investigated CBD's effects on cocaine addiction, administering 800 mg of oral CBD daily for 13 weeks. Their findings echoed those of Meneses-Gaya et al., as no notable differences were observed between CBD and placebo groups across various measures, including drug-cue-induced craving, stress, daily craving, withdrawal symptoms, sustained abstinence, and time-to-relapse.

An earlier study by Hurd et al. (2015) also examined the effects of oral CBD on opioid addiction, using dosages of 400 mg and 800 mg once daily for three days. Results showed a decrease in subjective cue-induced drug craving post-dose when compared to placebo, alongside a reduction in general drug craving from baseline up to seven days post-dose, supporting CBD's potential in addiction treatment. Suzuki et al. (2022) studied the effects of a 600 mg oral CBD dosage administered once daily for three days on opioid addiction, noting a significant reduction in drug-cue-induced craving after CBD dosing compared to baseline. However, no significant changes were observed in secondary measures such as depression, anxiety, pain, or opioid withdrawal symptoms.

Authors	Study	Pts	Age	Dose	Delivery	Follow-up	Outcomes
Saxon et al. (1993)	Retrospective cohort	98	43.9 $\bar{x}$	Unspecified	Unspecified	16 months	No difference in other-drug positive urines for THC+ vs THC- ($z=-0.48$, ns); retention/employment/cognition similar. Routine THC screening not supported.
Nirenberg et al. (1996)	Retrospective cohort	70	39.0 $\bar{x}$	Unspecified	Unspecified	-	Cannabis-positive urines were not associated with opiate-positive urines; combined cocaine + benzodiazepine positivity was associated with opiate positivity (harm-reduction context).
Saxon et al. (1996)	RCT	353	38.2 $\bar{x}$	Unspecified	Unspecified	18 months	Higher cocaine-positive urines predicted by less pre-treatment marijuana use and lower methadone dose; retention improved with older age and higher methadone dose.
Budney et al. (1998)	Prospective cohort	107	34 $\bar{x}$	Variable	Inhalation	26-32 weeks	No significant adverse effect of concurrent marijuana use on opioid treatment outcome. No improvement in treatment retention or opioid abstinence.
Wasserman et al. (1998)	Prospective cohort	74	42.8 $\bar{x}$	Unspecified	Unspecified	6 months	Cannabis use predicted higher risk of heroin lapse; goal of absolute abstinence predicted lower risk; stress variables not predictive (Cox models/logistic regression).
Best et al. (1999)	Cross-sectional survey	200	17-54	Variable	Inhalation	-	Daily users younger ($F(2,197)=4.51$, $p<.05$); non-users reported more heroin days; daily users had higher diazepam dose (35.5 mg vs 23.6–19.7 mg; $F=4.53$, $p<.05$).
Labigalini et al. (1999)	Case series	25	16-28	Unspecified	Unspecified	9 months	68% (17/25) ceased crack; many reported reduced craving and behavioural improvements with cannabis use.
Church et al. (2001)	Prospective cohort	47	20-54	Unspecified	Inhalation	6 months	Intermittent cannabis use during naltrexone therapy was associated with better opiate outcomes than abstinence or heavy cannabis use; no linear correlation overall.
Dreher (2002)	Prospective cohort	33	-	Variable	Inhalation	9 months	13/14 women who quit crack attributed success to cannabis; used to blunt paranoia, appetite loss; seasoned spliffs culturally distinct from pipe use. Qualitative, no inferential stats.
Epstein & Preston (2003)	Retrospective cohort	408	21-57	Unspecified	Inhalation	29 weeks	Cannabis use did not predict retention or cocaine/heroin use ($r^2 < 0.03$, ns); no increased lapse risk in abstinent patients (HRs $\approx 0.90-1.54$, ns). Cannabis-use disorders weakly linked to later psychosocial problems.
Weizman et al. (2004)	Prospective cohort	196	37.4 $\bar{x}$	Unspecified	Unspecified	1 year	Cannabis abuse did not significantly affect treatment outcomes, retention rates, or health risks in the methadone maintenance treatment setting.
Aharonovich et al. (2005)	Prospective cohort	250	36.9 $\bar{x}$	Unspecified	Unspecified	18 months	Post-discharge cannabis use $\uparrow$ hazard of first use of any substance and $\downarrow$ stable remission; effects for alcohol and cocaine, not heroin (Cox models).

Authors	Study	Pts	Age	Dose	Delivery	Follow-up	Outcomes
Hermann et al. (2005)	Cross-sectional survey	89	34 $\bar{x}$	Unspecified	Unspecified	-	Cannabis rated low efficacy for opioid withdrawal (3.6 $\pm$ 1.0 on 1–5 scale); 37.5% reported worsening. Benzodiazepines best (3.2 $\pm$ 1.1).
Li et al. (2005)	Cross-sectional study	26	36.8 $\bar{x}$	Variable	Unspecified	-	Recent cannabis abuse was associated with altered stress-related BOLD responses in cortico-limbic regions vs non-abusers; behavioural/physiological differences during imagery also noted; study does not test cannabis as a treatment.
Nava et al. (2007)	Prospective cohort	121	28.9 $\bar{x}$	~7.15 g/week	Inhalation	12 months	Methadone normalized ACTH/cortisol and reduced heroin withdrawal/craving regardless of cannabis use; no adverse impact of chronic cannabis on treatment outcomes reported.
Reiman (2007)	Cross-sectional survey	130	39.9 $\bar{x}$	Variable	Unspecified	-	Many participants reported substituting cannabis for alcohol/illicit drugs; descriptive data support perceived reductions in other substance use.
Oliveira & Nappo (2008)	Qualitative study	62	15-45	Unspecified	Inhalation	-	Identified controlled (non-daily) crack-use strategies alongside prevalent compulsive use; suggests user-devised harm-reduction tactics worth further study.
Lindsay et al. (2009)	Cross-sectional study	1183	39.0 $\bar{x}$	Unspecified	Unspecified	-	Frequent marijuana users were younger and showed worse baseline severity: more cocaine days (F=13.5, p<.0001) and alcohol days (F=18.26, p<.0001) vs others—suggesting no benefit of concurrent cannabis.
Raby et al. (2009)	RCT	63	35.5 $\bar{x}$	Variable	Inhalation	6 months	Intermittent cannabis users showed improved retention in naltrexone treatment compared to abstinent or consistent cannabis users (days: 133 $\bar{x}$ vs 35 $\bar{x}$).
Reiman (2009)	Cross-sectional survey	350	39.4 $\bar{x}$	Variable	Unspecified	-	40% substituted cannabis for alcohol, 26% for illicit drugs, 65.8% for prescription drugs; main reasons included fewer side effects (65%), better symptom management (57%), less withdrawal (34%).
Ribeiro et al. (2010)	Qualitative study	28	32.0 $\bar{x}$	Unspecified	Inhalation	-	Participants reported cannabis reduced crack craving and transient paranoia, improved sleep and appetite, and decreased compulsive crack-seeking, though some disliked reduced “potency”.
Alessi et al. (2011)	Secondary analysis of RCT data	393	36.1 $\bar{x}$	Unspecified	Unspecified	9 months	In Pre-M group, contingency management nearly doubled retention (ST 3.7 vs CM 7.3 weeks); LDA 2.5 vs 4.6 weeks; Month-9 abstinence predicted by CM and LDA.

Authors	Study	Pts	Age	Dose	Delivery	Follow-up	Outcomes
Andrade et al. (2011)	Qualitative study	6	-	Unspecified	Inhalation	-	Reported reduced agitation/cravings, improved appetite, better behavioural control, economic benefits, reduced vulnerability to violence (exploratory).
Chaves et al. (2011)	Qualitative study	92	18-50	Unspecified	Inhalation	-	Participants described multiple non-treatment coping tactics for crack craving; cannabis mentioned contextually in literature, but this study provides thematic, not statistical, findings.
Roux et al. (2011)	Prospective cohort	467	31-37	Unspecified	Unspecified	45 months	Daily cannabis use independently predicted non-medical opioid use during OMT (adjusted coefficient 0.28; p=0.01), alongside cocaine/benzodiazepine use and withdrawal symptoms. Longer time in OMT reduced risk.
Green et al. (2012)	Secondary analysis of RCT data	177	-	Variable	Unspecified	-	Baseline marijuana moderated levodopa/carbidopa response: Bayesian P≈0.96 that more marijuana predicts lower TES with levodopa; 5.4% TES decrease per additional marijuana day vs 4.9% increase on placebo.
Somers & O'Connor (2012)	Retrospective cohort	70	39.0 $\bar{x}$	Unspecified	Unspecified	-	Cannabis-positive urine was associated with increased odds of concurrent cocaine-positive urine (OR = 2.07, 95% CI 1.06–4.04).
Hill et al. (2013)	Secondary analysis of RCT data	152	19.2 $\bar{x}$	Variable	Inhalation	12 weeks	Cannabis use did not significantly impact opioid treatment outcomes, including opioid abstinence.
Lucas et al. (2013)	Cross-sectional survey	404	-	Variable	Oral, Inhalation	-	75.5% reported substituting cannabis for other substances: prescription drugs 67.8%, alcohol 41.0%, illicit substances 36.1%, citing fewer side-effects and better symptom management.
Morgan et al. (2013)	RCT	24	28 $\bar{x}$	400 μ g CBD	Inhalation (CBD)	2 weeks	CBD reduced cigarette consumption by approximately 40% compared to placebo.
Potter et al. (2013)	RCT	1269	37.4 $\bar{x}$	Unspecified	Unspecified	32 weeks	No interaction of opioid type/route with medication on opioid use or attrition; heroin use and injecting predicted worse outcomes; no cannabis-related efficacy signal reported.
Scavone et al. (2013)	Retrospective cohort	91	20-62	Unspecified	Unspecified	9 months	Opiate-positive UDS fell 57.4%→28.2% from induction to stabilization (t(82)=6.58, p<0.001). Cannabis use did not impede induction; exploratory data suggested reduced withdrawal during stabilization.
Lions et al. (2014)	Secondary analysis of RCT data	158	33 $\bar{x}$	Unspecified	Unspecified	12 months	Daily cannabis use during treatment was linked with higher odds of non-prescribed opioid use at 12 months in univariate analyses; multivariable models showed other significant predictors. (Daily cannabis listed among risk factors at M12.)

Authors	Study	Pts	Age	Dose	Delivery	Follow-up	Outcomes
Viola et al. (2014)	Prospective cohort	93	18-45	Unspecified	Unspecified	3 weeks	Compared clinical measures across cannabis-use histories during inpatient treatment; paper focuses on associations rather than intervention effects; no cannabis dosing tested.
Abrahamsson et al. (2015)	Prospective cohort	44	20-55	Unspecified	Unspecified	44 days $\bar{x}$	57% transferred to full OMT; lower baseline AUDIT predicted success (4.4 vs 12.6; $p < 0.001$); trends for less baseline cannabis/heroin use ($p = 0.06$; $p = 0.09$).
Bisaga et al. (2015)	RCT	60	38 $\bar{x}$	30mg	Oral (dronabinol)	8 weeks	Reduced severity of opioid withdrawal during detoxification but no significant effect on treatment retention for naltrexone induction. Only 35% trial completion noted.
Epstein & Preston (2015)	Secondary analysis of RCT data	116	21-59	Variable	Inhalation	10 weeks	No overall difference in withdrawal between users vs non-users; cannabis use did not predict lower next-week withdrawal ($r = 0.01$, 95% CI -0.28 – 0.30 ; $p = 0.69$).
Gonçalves & Nappo (2015)	Qualitative study	27	19-49	Variable	Inhalation	-	Users reported marijuana reduced crack's undesirable effects, craving, and improved sleep/appetite and quality of life; qualitative evidence only.
Lau et al. (2015)	Qualitative study	97	48-68	Variable	Unspecified	-	Participants commonly reported substituting cannabis for alcohol/other drugs to reduce harms; only ~10% reported cannabis-attributed health problems; perceptions favoured cannabis as safer with better self-regulation.
Levine et al. (2015)	Retrospective cohort	290	50.3 $\bar{x}$	Unspecified	Unspecified	1 year	Sex-stratified models examined predictors of ≥ 1 -year retention and opioid abstinence; first-month drug screens (including cannabinoids) entered as predictors; paper does not report a cannabis-efficacy benefit signal.
Mayet et al. (2015)	Prospective cohort	188	32 $\bar{x}$	Variable	Inhalation	12 months	Cannabis use did not significantly impact treatment outcomes. Cannabis use patterns were consistent and associated with underlying health issues rather than methadone treatment itself.
Teixeira et al. (2015)	Qualitative study	5	22-42	Unspecified	Inhalation	-	Using cannabis after crack to calm agitation and support harm-reduction routines (self-care, controlled quantity, pipe hygiene); no quantitative efficacy data.
Lofwall et al. (2016)	RCT	12	31.3 $\bar{x}$	5-30mg	Oral (dronabinol)	5 weeks	Modest withdrawal suppression but also induced side effects like tachycardia at higher doses, suggesting limited efficacy as a standalone treatment for withdrawal.
Proctor et al. (2016)	Retrospective cohort	2410	18-82	Unspecified	Unspecified	12 months	Cannabinoid-positive UDS predicted opioid-positive UDS at some intervals; higher methadone dose predicted opioid abstinence at 9 months.

Authors	Study	Pts	Age	Dose	Delivery	Follow-up	Outcomes
Giasson-Gariépy et al. (2017)	Cross-sectional	28	44.2 $\bar{x}$	Unspecified	Unspecified	72 hours	Cue-induced craving rose in both groups; no between-group difference overall, but time $\times$ group interaction ($F(3,78)=3.3$; $p=0.023$) suggested slower craving decay in cannabis users.
Socias et al. (2017)	Prospective cohort	122	46 $\bar{x}$	Variable	Inhalation	29.1 months $\bar{x}$	Reduced frequency of crack use in subsequent periods after intentional cannabis use to control crack use.
Zielinski et al. (2017)	Prospective cohort	777	38.1 $\bar{x}$	Variable	Unspecified	-	Cannabis use associated with illicit opioid use in women only (OR 1.82, 95% CI 1.18–2.82; $p = 0.007$); no association in men.
Bagra et al. (2018)	Cross-sectional	100	43.9 $\bar{x}$	Unspecified	Oral, Inhalation	-	Current cannabis users had lower buprenorphine dose (7.9 vs 8.9 mg/day; $p=0.04$); no differences in opioid use/craving/withdrawal or QoL; alcohol use $\uparrow$ odds of cannabis (OR 3.43, 95% CI 1.13–11.35).
Hindocha et al. (2018)	RCT	30	28.1 $\bar{x}$	800mg	Oral (CBD)	16 days	After overnight abstinence, CBD reversed attentional bias to cigarette cues ($P=0.007$, $d=0.704$) and reduced cue pleasantness ($P=0.011$); craving/withdrawal unaffected ($BF\approx 7$ for null).
Eastwood et al. (2019)	Prospective cohort	7717	-	Unspecified	Unspecified	5 years	Medicinal cannabis users reported more PTSD symptoms and higher cannabis use than recreational users.
Hurd et al. (2019)	RCT	42	49.8 $\bar{x}$	400-800mg CBD	Oral (CBD)	10 days	CBD significantly reduced cue-induced craving and anxiety acutely and had protracted effects up to 7 days post-administration.
Lucas et al. (2019)	Cross-sectional survey	2032	40.0 $\bar{x}$	Variable	Oral, Inhalation	-	Substitution reported for prescription drugs 69.1% (opioids 35.3% of mentions; 59.3% complete cessation), alcohol 44.5%, tobacco 31.1%, illicit substances 26.6%. Many reported 100% substitution for named illicit drugs.
Oliveira Junior et al. (2019)	Prospective cohort	123	30.2 $\bar{x}$	Variable	Inhalation	6 months	COC+CAN showed worse processing speed, inhibitory control, sustained attention than COC; cannabis did not decrease cocaine relapse at 1/3/6 months.
Shams et al. (2019)	Cross-sectional study	672	38.8 $\bar{x}$	Variable	Unspecified	-	Cannabis use associated with alcohol use (OR 1.46, 95%CI 1.04–2.06) and anxiety disorders (OR 1.75, 1.02–3.02); less heroin use (OR 0.45, 0.24–0.86). No association with pain.
Bergeria et al. (2020)	Cross-sectional survey	200	33.2 $\bar{x}$	Unspecified	Unspecified	-	SOWS total lower on cannabis days (M 16.2 vs 27.8), $t(121)=9.4$, $d=0.84$; VAS 35.3 vs 64.5, $t(121)=11.2$, $d=0.88$; anxiety improved in 76.2%.

Authors	Study	Pts	Age	Dose	Delivery	Follow-up	Outcomes
Karoly et al. (2020)	Cross-sectional survey	533	34.9 $\bar{x}$	Variable	Inhalation	-	Medical-use (CTT) group drank less frequently than non-medical (NCTT); higher THC/CBD associated with more drinks on cannabis-use days and more frequent co-use; low THC/CBD edibles linked to fewer drinks per occasion.
Valleriani et al. (2020)	Qualitative study	23	21-65	Variable	Inhalation	-	Cannabis helped reduce/replace other drugs, manage withdrawal, pain, and sleep, while highlighting access barriers; qualitative evidence only, no effect sizes.
Viola et al. (2020)	Prospective cohort	214	33.4 $\bar{x}$	Unspecified	Unspecified	3 weeks	Cannabis-use frequency groups differed on withdrawal/depression trajectories over 3 weeks (significant group and time effects in mixed models, $p < 0.05$); no experimental cannabis administration.
Karoly et al. (2021)	Prospective cohort	120	33.2 $\bar{x}$	Variable	Inhalation	5 days	CBD-dominant group had fewer drinks per drinking day, fewer alcohol-use days, and fewer co-use days than other groups (all $p < .05$); no difference THC vs CBD+THC.
Liu et al. (2021)	Cross-sectional survey	2968	46.7 $\bar{x}$	Unspecified	Unspecified	-	Cannabis use disorder associated with higher odds of non-medical prescription opioid use (AOR 1.7) and prescription stimulant use (AOR 2.2) among lifetime cocaine users, adjusting for covariates.
Meneses-Gaya et al. (2021)	RCT	31	32.9 $\bar{x}$	300mg CBD	Oral (CBD)	10 days	Time reduced craving, but CBD showed no advantage vs placebo (e.g., MCCS treatment effect $p=0.206$; CCQ-Brief $p=0.116$). No significant group differences in sleep, anxiety, or depression.
Meyer et al. (2021)	Case report	1	30	~400mg CBD	Inhalation (CBD)	12 weeks	With CBD cigarettes (and concurrent aripiprazole + methylphenidate), patient abstained from illicit cannabis and cocaine by discharge; no rehospitalizations reported during early follow-up.
Mok et al. (2021)	Prospective cohort	1936	42 $\bar{x}$	Variable	Unspecified	24 months	22% reported using cannabis for harm reduction at least once; common reasons were substituting for stimulants (50%) and illicit opioids (31%). Descriptive prevalence; no efficacy effect estimates.
Mongeau-Pérusse et al. (2021)	RCT	78	45.9 $\bar{x}$	400-800mg CBD	Oral (CBD)	13 weeks	No benefit vs placebo on cue-induced craving (Δ craving CI -0.33 – 3.04 ; $p=0.069$) or relapse (HR 1.20, 95% CI 0.65–2.20, $p=0.51$).

Authors	Study	Pts	Age	Dose	Delivery	Follow-up	Outcomes
Rosic et al. (2021)	Prospective cohort	2315	36 $\bar{x}$	Variable	Inhalation	1 year	Cannabis use, versus no use, was not significantly associated with differences in opioid use during treatment. Among cannabis users, daily use was linked to lower odds of opioid use compared to occasional use.
Shaw & Marcu (2021)	Case report	1	27	200mg CBD	Oral (CBD)	10 days	Opioid withdrawal improved (COWS 14→5 day 2; 3 day 7); transitioned to naltrexone without precipitated withdrawal or adverse effects.
Bunting et al. (2022)	Secondary analysis of RCT data	474	33.7 $\bar{x}$	Unspecified	Unspecified	4 weeks	Cannabis use increased in first 4 weeks but was not associated with relapse or craving; sedatives showed marginal associations; most polysubstance use not linked to outcomes.
Mongeau-Pérusse et al. (2022)	Secondary analysis of RCT data	78	45.9 $\bar{x}$	400-800mg CBD	Oral (CBD)	13 weeks	No CBD effect on anxiety (BAI $p=0.27$; VAS $p=0.18$), post-stress ($p=0.14$) or post-cue ($p=0.885$) anxiety, or cortisol ($p=0.76$).
Naji et al. (2022)	Prospective cohort	466	39 $\bar{x}$	Variable	Inhalation	1 year	Cannabis use was not protective against opioid relapse, with a hazard ratio close to 1, indicating no significant effect on relapse prevention.
Roser et al. (2022)	Cross-sectional survey	469	40.3 $\bar{x}$	Variable	Inhalation	-	Among >365-day CBD users, >40% reported improved relaxation and sleep; >30% reported less pain/anxiety. Self-reported benefits without control group.
Suzuki et al. (2022)	Open label pilot	5	37.8 $\bar{x}$	600mg CBD	Oral (CBD)	3 days	Cue-induced craving decreased (post-cue 4.6→3.2?; cue-induced craving 3.2→1.2; $p\approx 0.04$); other mood/pain/withdrawal measures not significantly changed.
de Aquino et al. (2023)	RCT	25	47.4 $\bar{x}$	10-20mg THC	Oral (THC)	2 weeks	Oral THC (10–20 mg) increased sedation and cannabinoid-typical subjective effects without reversing methadone's blockade; significant dose-related effects observed on visual analog scales.
Elkrief et al. (2023)	Secondary analysis of RCT data	272	38.9 $\bar{x}$	Variable	Oral, Inhalation	24 weeks	No statistically significant effect of cannabis use on opioid use, craving, or withdrawal symptoms in individuals on opioid agonist therapy.
Karoly et al. (2023)	RCT	36	26.5 $\bar{x}$	30-200mg CBD	Oral (CBD)	3 phases; 1-week wash-out	CBD produced trivial differences in BrAC decline and subjective effects vs placebo; no meaningful changes in stimulation/sedation/craving across conditions.

Authors	Study	Pts	Age	Dose	Delivery	Follow-up	Outcomes
Lake et al. (2023)	Prospective cohort	1389	-	Variable	Inhalation	13 years	Daily cannabis use was associated with a reduced likelihood of illicit opioid use among those on lower methadone doses (30% vs 86%), suggesting cannabis might mitigate withdrawal symptoms at subtherapeutic methadone maintenance treatment levels.
Mok et al. (2023)	Prospective cohort	1936	42 $\bar{x}$	Variable	Unspecified	24 months	Odds of reporting cannabis for harm reduction were higher with daily methamphetamine use (AOR 1.43, 95% CI 1.09–1.89) and treatment barriers (AOR 1.92), and lower with OAT (AOR 0.74) and older age (AOR 0.97/year).
Reddon et al. (2023)	Cross-sectional survey	205	39.9 $\bar{x}$	Variable	Oral, Inhalation	-	Significant association between cannabis use to manage opioid cravings and self-reported reduction in opioid use (aOR: 2.13), mostly in moderate to severe pain (aOR: 4.44) and females (aOR: 8.19).
Suzuki et al. (2023)	RCT	10	45.1 $\bar{x}$	600mg CBD	Oral (CBD)	7 days	CBD reduced cue-induced craving (0.2 vs 1.3; $p = 0.040$) and attentional bias to drug cues (-80.4 ms vs 100.3 ms; $p = 0.041$); other outcomes ns.
Bekier et al. (2024)	Cross-sectional survey	118	42.5 $\bar{x}$	1.3g $\bar{x}$	Inhalation	-	60% reported using cannabis as a substitute for opioids, with self-reported reduction in opioid cravings and perceived effectiveness of cannabis for withdrawal management.
Kudrich et al. (2024)	Cross-sectional survey	550	51.9 $\bar{x}$	Variable	Oral, Inhalation	-	23% reported CBD use; 41.9% for opioid withdrawal, 17.1% to “control addiction.” CBD users held more favourable views of CBD’s therapeutic role (adjusted ORs $\approx$ 1.85–2.05).
Lake et al. (2024)	Prospective cohort	818	42.4 $\bar{x}$	Variable	Inhalation	13 years	Higher methadone dose associated with lower discontinuation risk; cannabis use ($\geq$ daily vs $<$ daily) analyzed as effect modifier in adjusted time-to-event models; specific HRs not reported in text we have.
Reddon et al. (2024)	Cross-sectional survey	297	44.3 $\bar{x}$	Variable	Oral, Inhalation	-	Self-reported reductions in stimulant use, with significant association between cannabis use for craving management and decreased stimulant use (77.6%; aOR: 0.24), particularly among crystal methamphetamine users (aOR: 0.08).
Wolkowicz et al. (2024)	RCT	27	17-70	10-20mg	Oral (dronabinol)	3 days	THC had dose-dependent effects on opioid-cue attentional bias; in high-dose methadone patients, 10 mg increased AB and 20 mg decreased AB (mixed-effects interaction, $p<0.05$).
Hurzeler et al. (2025a)	RCT	22	29.8 $\bar{x}$	800mg CBD	Oral (CBD)	1 month (2 phases; 18-day wash-out)	CBD increased HF-HRV (parasympathetic activity), reduced cue-elicited anxiety and post-cue craving vs placebo; no differences on executive-function tasks.

Authors	Study	Pts	Age	Dose	Delivery	Follow-up	Outcomes
Hurzeler et al. (2025b)	RCT	18	18-62	800mg CBD	Oral (CBD)	-	ROI analyses: no CBD–placebo differences in alcohol-cue activation; exploratory whole-brain: CBD attenuated precuneus activation (cue-nonspecific); no acute effects on craving/mood/cognition.
Kirkland et al. (2025)	RCT	36	17-23	600mg CBD	Oral (CBD)	2 phases; 18-day wash-out	No CBD vs placebo effects on MRS Glx/GABA, fMRI alcohol cue-reactivity, psychophysiology, or short-term alcohol use.
Mueller et al. (2025)	RCT	44	36.1 $\bar{x}$	CBD (<0.3% THC), CBD (0% THC)	Oral (CBD)	24 weeks	Both CBD arms well-tolerated; fsCBD reduced craving and AUD symptoms vs bsCBD/placebo; no change in drinks per drinking day.
Shulman et al. (2025)	Secondary analysis of RCT data	569	34.0 $\bar{x}$	Unspecified	Unspecified	24 weeks	Greater cannabis-use days were associated with lower odds of opioid abstinence and treatment retention, and higher overdose risk (AOR/AHR significant, $p<0.05$).
Zimmermann et al. (2025)	RCT	28	35.8 $\bar{x}$	800mg CBD	Oral (CBD)	1 day	CBD reduced bilateral NAc activation ($t\approx 4.9$, $p<0.001$) and lowered alcohol craving vs placebo ($F_{\text{group}}=4.516$, $p=0.043$; $\text{group}\times\text{time}$ $p=0.025$).

Table 3.21. *Studies evaluating use of medicinal cannabis for drug addiction management.*

In research focusing on polydrug use, Roser et al. (2022) reported a low overall prevalence of frequent CBD use (9%), with benefits reported by frequent users, including improved relaxation, anxiety, sleep, and pain relief. Valleriani et al. (2020) found similar results, with participants reporting reduced pain and cravings, better sleep, more energy, and an overall sense of wellness from using a variable combination of inhaled and edible THC and CBD products. Rizkallah et al. (2022) explored the impact of 800 mg oral CBD administered daily for 13 weeks on individuals with cocaine use disorder. Their study found no significant differences between the CBD and placebo groups in terms of anxiety, as measured by the Beck Anxiety Inventory and the Visual Analogue Scale, nor in stress responses following stressful or cocaine-related scenarios. Furthermore, no differences were observed in cortisol levels or cognitive function between the two groups, suggesting limited efficacy of CBD in this context.

The efficacy of medicinal cannabis in addiction management is a subject of considerable interest, with preliminary findings suggesting a positive impact on reducing drug cravings and withdrawal symptoms. The cases from Lo et al. (2023) involving CBD tincture and cigarettes, provide anecdotal evidence of cannabis's utility in easing the transition away from addictive substances. Similarly, the preclinical findings from Jin et al. (2023) regarding synthetic cannabinoid CIAC001 offer promising insights into the potential mechanisms through which cannabinoids might mitigate addiction-related behaviours. However, the diversity in cannabis formulations, dosages, and routes of administration, combined with the variability in study designs and populations, highlights the need for more standardized and rigorous clinical research. Future studies should aim to elucidate optimal dosing regimens, clarify the roles of various cannabinoids, and establish the long-term safety and efficacy of

medicinal cannabis in addiction treatment contexts. The ongoing research and exploration into medicinal cannabis's role in drug addiction management suggest a cautiously optimistic outlook, with the potential for cannabinoids to complement existing treatments and offer new avenues for reducing the global burden of drug addiction.

3.4.2.12.2. Challenges and limitations in research

The inherent variability in cannabis strains and their chemical compositions presents significant challenges in standardizing research and clinical applications. Different strains of cannabis can vary widely in their concentrations of THC, CBD, and other cannabinoids, leading to inconsistent effects in clinical trials and patient outcomes. Moreover, the administration routes of cannabis, including oral, inhalation, sublingual, and topical applications, can affect the pharmacokinetics and pharmacodynamics of its active compounds, further complicating the establishment of standardized dosing protocols. This variability necessitates a rigorous characterization of cannabis products used in research to ensure reproducibility and comparability of study results (Lo et al., 2023).

Many studies on the clinical use of medicinal cannabis for drug addiction management are limited by their methodologies and sample sizes. Small-scale studies, observational research, and case reports, while valuable for initial insights, may not provide the robust evidence required to guide clinical practice. The lack of large-scale, randomized controlled trials (RCTs) limits the ability to draw definitive conclusions about the efficacy and safety of medicinal cannabis in this context. These methodological limitations highlight the need for well-designed clinical trials with

adequate sample sizes to assess the therapeutic potential of cannabis in a more rigorous and controlled manner (Reddon et al., 2023).

3.4.2.12.3. Research and clinical practice

As evidence for the potential benefits of medicinal cannabis in addiction management grows, integrating cannabis-based treatments into existing protocols will be a critical next step. This integration should be approached cautiously, with a focus on individualized treatment plans that consider the patient's history, the substance of addiction, and any co-occurring disorders. Collaborative efforts between addiction specialists, mental health professionals, and patients will be essential to navigate the complexities of adding medicinal cannabis to the treatment regimen, ensuring that it complements rather than complicates existing therapies (Fehr et al., 2024).

To facilitate the clinical application of medicinal cannabis and address the current challenges related to product variability, the development of standardized, pharmaceutical-grade cannabis products is crucial. These products should undergo rigorous testing for potency, purity, and consistency, meeting the same quality standards as other medications. The availability of such standardized products would not only aid in research and clinical trials but also provide healthcare providers and patients with reliable and safe options for treatment. Regulatory bodies and the cannabis industry must collaborate to establish guidelines and quality control measures that ensure these products meet the required medical standards (Mok et al., 2021).

3.4.2.13. Post-traumatic stress disorder

Post-Traumatic Stress Disorder (PTSD) emerges from exposure to traumatic events such as warfare, natural disasters, serious accidents, or sexual violence. Individuals with PTSD may experience persistent and intense symptoms of distress when reminded of their trauma, avoidance of stimuli associated with the trauma, negative alterations in mood and cognition, and marked changes in arousal and reactivity. Traditional treatments include cognitive behavioural therapy (CBT) and pharmacotherapies such as SSRIs and SNRIs. Despite the availability of these treatments, a significant proportion of individuals either do not respond adequately or cannot tolerate the side effects, highlighting the need for alternative therapeutic options. The primary pharmacological treatments for PTSD involve SSRIs like sertraline and paroxetine, both of which are FDA-approved for PTSD, and SNRIs like venlafaxine. These medications are intended to alleviate symptoms by affecting neurotransmitters involved in mood regulation. However, the efficacy varies, and approximately 20-30% achieve remission, often leading to trials of other medications such as mood stabilizers, atypical antipsychotics, and other off-label prescriptions. The variability in response and potential side effects necessitate ongoing monitoring and adjustments by healthcare providers (Nacasch et al., 2023).

Recent years have seen growing interest in the potential of medicinal cannabis as a treatment for PTSD, largely driven by anecdotal reports and a foundational understanding that the endocannabinoid system may play a role in the pathophysiology of PTSD. Cannabinoids such as THC (tetrahydrocannabinol) and CBD (cannabidiol) have been shown to influence areas of the brain involved in fear

and stress responses, such as the amygdala and prefrontal cortex (Hill et al., 2018; Bonn-Miller et al., 2022).

3.4.2.13.1. Recommended dosages in current literature

The management of PTSD through pharmacological means traditionally involves the use of SSRIs like sertraline and paroxetine. Despite their efficacy in reducing PTSD symptoms for some patients, these treatments often yield incomplete responses and are associated with various side effects that can challenge compliance and long-term usage (Cohen et al., 2020). As a result, there is a growing interest in alternative therapies, including the therapeutic use of medicinal cannabis, which may offer substantial relief with potentially fewer undesirable side effects (LaFrance et al., 2020). Recent advancements in our understanding of the neurobiological underpinnings of PTSD have pointed to the endocannabinoid system as a critical player in modulating fear and anxiety responses (Abizaid et al., 2013). This insight has catalyzed research into how cannabinoids, particularly THC and CBD, might be leveraged to mitigate the core symptoms of PTSD such as hyperarousal, sleep disturbances, and the re-experiencing of traumatic events (Hindocha et al., 2018; Cohen et al., 2020; LaFrance et al., 2020).

Current literature on medicinal cannabis for PTSD, notably from empirical studies and clinical trials, provides varying recommendations on dosages that reflect the nascent stage of this research area (Table 3.22). One notable study indicated that small doses of THC, around 5 mg administered twice daily, can enhance sleep quality and reduce the frequency of nightmares in PTSD patients, thus addressing the persistent hyperarousal often resistant to traditional medications. Similarly, synthetic

cannabinoids like nabilone have been observed to emulate these benefits in controlled dosages, typically mirroring the THC equivalent (Abizaid et al., 2013; LaFrance et al., 2020). Despite promising results, one of the significant challenges in recommending standard dosages of cannabis for PTSD management lies in the variability of individual responses to cannabinoids and the complex nature of cannabis itself, which contains multiple active compounds that may act synergistically. The ratio of THC to CBD can alter therapeutic outcomes and side effect profiles, which necessitates a personalized approach to dosage recommendations. Furthermore, the method of administration, whether inhaled, oral, or sublingual, can significantly affect the bioavailability and efficacy of the treatment, complicating standard dosage determinations. Future research must focus on refining our understanding of how different cannabis constituents interact with the endocannabinoid system specifically altered by PTSD. Longitudinal studies and larger randomized controlled trials are crucial to establish more precise, safe, and effective dosage regimens. Additionally, examining the impact of cannabis on diverse PTSD populations, including variations across different types of trauma exposures and demographic factors such as gender and age, will be essential (Forsythe & Boileau et al., 2013; Muller-Vahl, 2024).

LaFrance et al. conducted an observational study using archival data from the Strainprint® app, involving 404 self-identified PTSD sufferers who logged 11,797 cannabis use sessions over 31 months. This study stands out for its real-time data collection methodology, capturing immediate changes in PTSD symptoms such as intrusions, flashbacks, irritability, and anxiety before and after cannabis use. The participants reported a significant reduction in symptoms, with more substantial reductions associated with higher dosages and prolonged use. This suggests not only the potential symptomatic relief offered by cannabis but also the development of

tolerance or enhanced efficacy over time. The study's reliance on patient-reported outcomes, however, introduces potential biases related to self-reporting and the absence of a placebo control, underscoring the need for more controlled trials to establish causality and minimize placebo effects. Fraser's open-label clinical trial involving 47 PTSD patients examined the effects of nabilone on treatment-resistant nightmares. Participants noted a substantial decrease in nightmare frequency and intensity, along with improvements in sleep quality and reductions in other PTSD symptoms such as daytime flashbacks and night sweats. The study highlights nabilone's potential as an effective intervention for managing specific, persistent PTSD symptoms that are often resistant to conventional treatments. However, the open-label design and reliance on subjective reports limit the generalizability of the findings, emphasizing the need for randomized controlled trials to further validate these outcomes. Reznik and colleagues undertook a naturalistic observational study involving 167 PTSD patients, assessing the impact of medical cannabis on PTSD symptoms, quality of life, and pain scores. This study is particularly relevant for its inclusion of patients with varying PTSD comorbidities, such as clinical depression and chronic pain, reflecting the complex, multifaceted nature of PTSD. Significant improvements were reported in life quality and pain management, with positive changes in PTSD symptoms as well. The study's naturalistic design, while valuable for observing real-world outcomes, lacks the rigorous control of clinical trials, making it difficult to definitively attribute symptom improvements to cannabis use alone.

Jetley et al. (2015) conducted a preliminary randomized, double-blind, placebo-controlled crossover study focused on the use of nabilone, a synthetic cannabinoid, to address PTSD-associated nightmares in Canadian military personnel. This study is noteworthy because it targets a specific, debilitating symptom of PTSD, nightmares,

that often persists despite conventional treatments. The study's crossover design allowed each participant to serve as his own control, enhancing the reliability of the findings. Nabilone was started at a dosage of 0.5 mg and adjusted to a maximum of 3.0 mg based on effectiveness and tolerability. The results indicated a significant reduction in the frequency and intensity of nightmares, with the nabilone group experiencing a greater reduction than the placebo group. While promising, the study's limitations include its small sample size and preliminary nature, which necessitate further validation through larger-scale studies. The review article by Passie et al. (2012), which includes a clinical case report, explores the use of smoked cannabis resin by a 19-year-old male with severe PTSD. This case highlights the self-administered nature of cannabis in managing acute PTSD symptoms like flashbacks and panic attacks. The article discusses the neurobiological rationale for cannabis's effectiveness, focusing on its potential to modulate fear extinction and exert antidepressive effects. These mechanisms are tied to the endocannabinoid system's role in regulating neuroendocrine and behavioural responses to stress. Despite the insightful discussion, the study's reliance on a single case report and the lack of quantified dosage details limit the generalizability and clinical applicability of the findings. Mashiah's (2012) open pilot study presented at the Patients Out of Time Conference examined the use of smoked medical indica cannabis among 29 Israeli combat veterans with chronic, combat-related PTSD. The participants, who were authorized to use no more than 100 grams of cannabis per month, reported significant reductions in PTSD symptoms as assessed by the Clinician-Administered PTSD Scale (CAPS). Improvements in quality of life and a decreased reliance on other medications were also noted. While the study suggests the potential benefits of cannabis for veterans with severe PTSD, its open-label design and lack of a control group mean

that these findings must be interpreted with caution. The study calls for more rigorous trials to confirm the therapeutic value of cannabis in this population.

Shannon and Opila-Lehman's 2016 case report provides a compelling illustration of the potential efficacy of cannabidiol (CBD) oil in treating paediatric PTSD symptoms. The patient, a 10-year-old girl who had experienced significant trauma, exhibited severe anxiety, insomnia, outbursts, and self-destructive behaviours. She was treated with CBD oil, initially receiving 25 mg daily in the evening and subsequently up to 12 mg of CBD spray as needed during the day for anxiety. Over five months, her anxiety symptoms, measured via the Screen for Anxiety Related Disorders (SCARED), and sleep disturbances, assessed using the Sleep Disturbance Scale for Children, improved significantly. This case study underscores the potential anxiolytic and sleep-promoting properties of CBD, which were well-tolerated without significant side effects. The authors attribute these effects to CBD's broad anti-inflammatory and anxiolytic properties, as well as its interaction with neurotransmitter systems influencing anxiety and sleep. While this single case study provides valuable insights, the authors advocate for larger clinical trials to explore the efficacy and safety of CBD in paediatric PTSD patients. Cameron et al. (2014) conducted a retrospective evaluation of nabilone in 104 male inmates at the Secure Treatment Unit of the St Lawrence Valley Correctional and Treatment Centre. The study aimed to evaluate nabilone's effectiveness in treating PTSD-associated insomnia, nightmares, and chronic pain. Participants, who were prescribed nabilone at an initial average dose of 1.4 mg/day (increasing to 4.0 mg/day), reported significant improvements in PTSD symptoms, particularly insomnia and nightmares.

Authors	Study	Pts	Age	Dose	Delivery	Follow-up	Outcomes
Bonn-Miller et al. (2007)	Cross-sectional	103	19.4 $\bar{x}$	-	Unspecified	-	Severity of PTSD symptoms was significantly related to the use of marijuana for coping.
Fraser (2009)	Open label pilot	47	26-68	0.5-6mg	Oral (nabilone)	-	72% experienced either cessation or significant reduction in nightmare intensity.
Klumpers et al. (2012)	RCT	54	18-30	10mg	Oral (THC)	-	Reduced conditioned skin conductance responses but demonstrated no effect two days later.
Mashiah et al. (2012)	Open label pilot	29	-	max. 100g / month	Inhalation (23% THC)	3 years	Reported improvement in PTSD symptoms, especially sleep disturbances and anxiety reduction.
Reznik et al. (2012)	Retrospective cohort	167	-	2-3g / day	Inhalation (23% THC)	3 years	Improvement in quality of life and reduction in PTSD symptoms, particularly in those with comorbid pain or depression.
Das et al. (2013)	RCT	48	18-35	32mg	Inhalation	24 hours	Enhanced consolidation of fear extinction when CBD was administered.
Rabinak et al. (2013)	RCT	29	21-45	7.5mg	Oral (dronabinol)	24 hours	Participants registered lower skin conductance responses to a previously extinguished conditioned stimulus, suggesting improved extinction recall.
Bonn-Miller et al. (2014a)	Cross-sectional	170	41 $\bar{x}$	-	Unspecified	-	Higher PTSD scores were linked to increased cannabis use for sleep improvement and coping.
Bonn-Miller et al. (2014b)	Cross-sectional	217	41.2 $\bar{x}$	6-12 g / week	Inhalation	-	Cannabis was perceived as helpful for alleviating symptoms such as anxiety, chronic pain, and sleep disturbances.
Cameron et al. (2014)	Retrospective cohort	104	32.7 $\bar{x}$	4mg	Oral (nabilone)	-	Significant improvement in PTSD-related insomnia, nightmares, and overall functioning.
Earleywine & Bolles (2014)	Cross-sectional	653	40.1 $\bar{x}$	-	Unspecified	-	Significant correlations between PTSD symptom severity, marijuana use, and expectancies of symptom relief.
Greer et al. (2014)	Retrospective cohort	80	-	-	Inhalation (23% THC)	-	Greater than 75% reduction in PTSD symptom scores was reported during cannabis use compared to non-use.
Roitman et al. (2014)	Open label pilot	10	52.3 $\bar{x}$	10mg / day	Oral (THC)	3 weeks	Improvement in PTSD symptom severity, sleep quality, and reduction in nightmares.
Jetly et al. (2015)	Randomized cross-over	10	18-65	0.5-3mg	Oral (nabilone)	7 weeks / phase; 2-week wash-out	Significant reduction in nightmare frequency and intensity compared to placebo.
Wilkinson et al. (2015)		2276	-	-	Unspecified	4 months	Cannabis use was associated with worse PTSD symptoms and increased violent behaviour.
Johnson et al. (2016)	Cross-sectional	700	-	-	Unspecified	-	No significant difference in PTSD severity between cannabis users and non-users.

Authors	Study	Pts	Age	Dose	Delivery	Follow-up	Outcomes
Shannon & Opila-Lehman (2016)	Case report	1	10	25mg / day (oil); 6-12mg PRN (sublingual)	Oral (CBD)	5 months	Significant reduction in anxiety and improvement in sleep quality.
Tull et al. (2016)	Cross-sectional	202	18-60	-	Unspecified	-	Marijuana dependence moderated emotional reactivity in response to trauma cues, reducing arousal.
Loflin et al. (2017)	Cross-sectional	1971	-	-	Unspecified	-	Medicinal cannabis users reported more PTSD symptoms and higher cannabis use than recreational users.
Elms et al. (2019)	Retrospective case series	11	39.9 $\bar{x}$	33.18mg $\bar{x}$ (wk1) - 48.64mg $\bar{x}$ (wk8)	Oral (CBD)	-	91% of patients experienced a reduction in PTSD symptoms, including decreased nightmares.
LaFrance et al. (2020)	Retrospective cohort	404	-	1-30 puffs	Inhalation	-	Significant short-term reductions in symptoms though long-term symptom severity remained constant, indicating potential development of tolerance.
Bonn-Miller et al. (2021)	Randomized cross-over	80	-	up to 1.8g / day (3 weeks)	Inhalation	3 weeks / phase; 2-week wash-out	No significant difference in symptom reduction between active cannabis and placebo, but all groups showed symptom improvement.
Bonn-Miller et al. (2022)	Prospective cohort	150	50.6 $\bar{x}$	0.3-3g daily	Various	1 year	Users showed greater reductions in PTSD symptom severity over time compared to controls.
Nacasch et al. (2023)	Retrospective cohort	14	32-68	20g / month; inc. by 10g each month if needed	Oral (CBD, THC), Inhalation	6 months - 3 years	Significant improvements in sleep quality and PTSD symptom scores, except for nightmares.
Lynskey et al. (2024)	Prospective cohort	238	-	-	Oral (CBD, THC), Inhalation	3 months	Significant reduction in PTSD symptoms, with greater improvements in individuals with comorbid depression.

Table 3.22. *Studies evaluating use of medicinal cannabis in patients with post-traumatic stress disorder.*

In addition to symptom reduction, the study highlighted the potential of nabilone to reduce polypharmacy by discontinuing other medications like antipsychotics and sedative/hypnotics. nabilone was well-tolerated, with no reports of abuse or significant adverse effects, even in a high-risk population. The findings support the utility of nabilone as a multi-target medication, though prospective, randomized controlled trials are necessary to confirm these outcomes. Roitman et al. (2014) conducted a three-week, open-label study to evaluate the safety and efficacy of Delta-9-Tetrahydrocannabinol (THC) in adult outpatients with chronic PTSD. Participants began with a sublingual dose of 2.5 mg of THC twice daily, increasing to 5 mg twice daily if well-tolerated. The study found that THC significantly improved global symptom severity, sleep quality, nightmare frequency, and hyperarousal symptoms, with mild adverse effects like dry mouth, headache, and dizziness. The study concluded that orally administered THC is safe and well-tolerated in patients with chronic PTSD, highlighting its potential as an add-on treatment. However, the small sample size and open-label design warrant further investigation through larger, randomized controlled trials to determine THC's efficacy in PTSD treatment. Greer et al. (2014) conducted a retrospective chart review of the first 80 PTSD patients evaluated for the New Mexico Medical Cannabis Program. The study aimed to compare PTSD symptoms during periods of cannabis use and non-use using the Clinician-Administered PTSD Scale (CAPS). Patients reported a greater than 75% reduction in CAPS scores during cannabis use, with significant reductions across all PTSD symptom clusters (re-experiencing, avoidance, and hyperarousal). While these findings suggest a significant association between cannabis use and symptom relief, the lack of standardized dosage information and the retrospective nature of the study limit the

ability to draw definitive conclusions. Prospective, placebo-controlled studies are recommended to establish cannabis's therapeutic potential for PTSD.

Elms et al. (2019) conducted a retrospective case series involving 11 adult patients diagnosed with PTSD to evaluate the effectiveness of oral CBD in reducing PTSD symptom severity. Participants were administered CBD either in capsule (22-28 mg) or liquid spray form (1.5 mg per spray). The initial dosage was adjusted based on symptom severity and tolerance, with a median starting dose of 25 mg per day. The primary outcome, PTSD symptom severity, was assessed every four weeks using the PTSD Checklist for the DSM-5 (PCL-5). The study found that 91% of patients experienced a decrease in PTSD symptoms, with the mean total PCL-5 score decreasing by 28% from 51.82 to 37.14 after eight weeks of treatment. Additionally, patients reported subjective improvements in sleep quality and a reduction in nightmares. Importantly, CBD was generally well-tolerated, and no patients discontinued treatment due to adverse effects. The authors highlighted the potential of CBD as a complementary treatment to standard psychiatric care in managing PTSD symptoms. However, the retrospective nature of the study and the lack of a placebo control limit the ability to definitively attribute symptom improvement to CBD. Further, variability in CBD dosing and administration (capsule vs. spray) may have influenced outcomes. Despite these limitations, the study advocates for more rigorous clinical trials to establish the efficacy of CBD in treating PTSD. Klumpers et al. (2012) explored the effects of delta-9-tetrahydrocannabinol (THC) and D-cycloserine (DCS) on fear extinction in 61 healthy volunteers through a controlled experimental study. Participants underwent a three-day conditioning protocol where oral THC (10 mg), DCS (250 mg), or a placebo was administered two hours before extinction training on the second day. Fear-potentiated startle (FPS) measures were used to assess the

retention of fear extinction. The study found that while THC reduced conditioned skin conductance responses during extinction training, this effect did not persist in subsequent tests, suggesting that THC's benefits were limited to its immediate effects and did not influence long-term extinction retention. Similarly, DCS did not significantly affect within-session extinction or extinction retention. These findings indicate that neither DCS nor THC significantly facilitated the extinction of conditioned fear in a lasting manner in healthy humans. The authors emphasized the complexity of translating preclinical findings to human subjects and underscored the need for more targeted interventions that effectively utilize these systems for treating anxiety disorders. Rabinak et al. (2013) investigated the effects of dronabinol on fear extinction in a study involving 29 healthy adults. Participants were randomly assigned to receive either oral dronabinol (7.5 mg) or a placebo two hours before extinction training. Extinction memory recall was tested 24 hours later using a Pavlovian fear conditioning and extinction paradigm, integrating psychophysiological measures (skin conductance response). Compared to the placebo group, the dronabinol group exhibited significantly lower skin conductance responses to extinguished cues, indicating better retention of extinction memory. This finding suggests that dronabinol may prevent the recovery of fear, potentially enhancing the effectiveness of extinction-based therapies for anxiety disorders. The study provides initial evidence that cannabinoid modulation can enhance the retention of extinction learning, offering a new avenue for augmenting therapeutic strategies in the treatment of anxiety disorders like PTSD. Das et al. (2013) conducted a randomized, double-blind, placebo-controlled study to assess the effects of cannabidiol (CBD) on the extinction and consolidation of fear memories in 48 healthy adults. Participants underwent a Pavlovian fear-conditioning paradigm where a coloured box was paired with electric shocks in one context and was extinguished

in a second context. CBD (32 mg) was administered via a vaporizer, either before or after the extinction phase. Skin conductance and shock expectancy were measured as indicators of conditioned responses. The study found that CBD administered post-extinction enhanced the consolidation of extinction learning, as assessed by shock expectancy. CBD administered at either timing also produced a trend-level reduction in the reinstatement of autonomic contextual responding. These findings provide the first evidence of CBD's potential as an adjunct to extinction-based therapies for anxiety disorders due to its effects on memory consolidation. The study concludes that CBD can enhance the consolidation of extinction learning in humans, suggesting its potential utility in therapies for PTSD and related disorders.

Nacasch et al. (2023) conducted a retrospective naturalistic study to assess the impact of medical cannabis on sleep quality and PTSD symptoms among combat veterans with chronic, treatment-resistant PTSD. The study involved 14 participants (12 men, 2 women), aged 32 to 68 years, who had experienced moderate to severe PTSD for at least three years. These individuals were severely symptomatic despite previous conventional treatments and were subsequently given access to up to 20 grams of medical cannabis per month, which they could administer via inhalation (smoking) or sublingual oil. The researchers used the Hebrew versions of the Pittsburgh Sleep Quality Index (PSQI) and the Posttraumatic Diagnostic Scale (PDS) to measure changes in sleep quality and PTSD symptoms every six months as part of treatment follow-up. The findings revealed significant improvements in total sleep scores, subjective sleep quality, and sleep duration. PTSD symptoms also improved, particularly in the areas of intrusiveness, avoidance, and alertness, although the frequency of nightmares remained largely unchanged. Nacasch et al. concluded that medical cannabis treatment was well tolerated and led to improvements in sleep

quality and PTSD symptoms among chronic, treatment-resistant combat veterans. However, the study's retrospective design, lack of a control group, and small sample size limit the ability to draw causal conclusions. Additionally, the specific patient population (mature, treatment-resistant veterans) may restrict the generalizability of the results. Nevertheless, the study contributes to the growing body of evidence suggesting the potential benefits of medical cannabis for managing treatment-resistant PTSD, particularly in reducing symptom severity and improving sleep. In their 2013 editorial, Abizaid et al. discussed the historical use of cannabis for medicinal purposes and explored its potential role in treating PTSD. They highlighted the neurobiological basis of PTSD and the involvement of the endocannabinoid system, particularly the cannabinoid receptor type 1 (CB1) and reduced levels of the endocannabinoid anandamide. The editorial emphasized that while cannabis has been suggested as a potential treatment for PTSD, the efficacy remains under debate due to limited robust clinical data. The authors noted that cannabinoids might modulate the neurobiological pathways involved in PTSD, potentially reducing hyperarousal and facilitating fear extinction. However, they also cautioned against overly optimistic expectations and emphasized the need for systematic scientific studies to distinguish between real therapeutic benefits and "snake oil." Abizaid et al. advocated for high-quality research to determine the safety and efficacy of cannabis for PTSD and called for a balanced, evidence-based approach. Bonn-Miller et al. (2007) conducted a cross-sectional analysis to examine the relationship between posttraumatic stress symptom severity and specific motives for marijuana use among individuals who have experienced traumatic events. The study involved 103 participants (55 women) who were current marijuana users and had experienced at least one traumatic event in their lifetime. The study found that posttraumatic stress symptom severity was significantly related to

copied-motivated marijuana use, even after controlling for the frequency of marijuana use, number of cigarettes smoked per day, and volume of alcohol consumed. Other motives for marijuana use, such as social and enhancement, were not significantly predicted by PTSD symptom severity. These findings highlight that individuals with higher levels of posttraumatic stress symptoms are more likely to use marijuana as a means to cope with their distress. Bonn-Miller et al. emphasized the importance of understanding motivational factors in substance use, particularly among populations with high levels of trauma exposure. The study suggests that interventions targeting these specific motives could help mitigate problematic marijuana use in individuals with PTSD symptoms.

In a 2022 longitudinal, prospective, controlled observational study, Bonn-Miller et al. assessed the impact of cannabis on PTSD symptomatology over one year. The study included 150 participants diagnosed with PTSD, with an average age of 50.67 years and a male predominance (73%). Participants were divided into two groups: those using cannabis obtained from licensed dispensaries (various preparations including flowers, concentrates, edibles, and tinctures) and a control group that did not use cannabis. PTSD symptoms were measured every three months using the Clinician-Administered PTSD Scale for DSM-5 (CAPS-5). Secondary outcomes included psychosocial functioning, sleep quality, and physical activity levels. Cannabis use was tracked through a timeline follow-back diary, accounting for preparation type, frequency, and THC concentration. The study found that cannabis users experienced a significantly greater reduction in PTSD symptoms compared to controls. Additionally, by the end of the study, cannabis users were statistically more likely to no longer meet DSM-5 criteria for PTSD. Improvements in psychosocial functioning, sleep quality, and physical activity were also noted among cannabis users. Importantly, the study

assessed the safety and tolerability of cannabis use, and no significant adverse effects were reported. Bonn-Miller et al. concluded that cannabis obtained from dispensaries may serve as an alternative treatment for PTSD, offering symptom reduction and improved functionality. However, they emphasized the need for randomized, placebo-controlled trials to verify these findings and evaluate the safety and specific effects of different cannabis preparations. In a 2014 observational cross-sectional survey, Bonn-Miller et al. investigated the motivations for cannabis use among patients at a medical cannabis dispensary in California. The study included a convenience sample of 170 participants with an average age of 41 years, 22% of whom were female. Conditions reported included anxiety, chronic pain, stress, insomnia, and depression. The study did not involve a direct cannabis intervention but rather assessed motivations for cannabis use through self-report questionnaires. The results indicated that participants with higher PTSD scores used cannabis more frequently for sleep improvement. Furthermore, higher cannabis use frequency was associated with sleep-related motivations among those with PTSD compared to those without or those who did not use cannabis for sleep. Bonn-Miller et al. concluded that sleep improvement is a significant motivator for cannabis use among individuals with PTSD. They also found a link between PTSD symptom severity and sleep-related cannabis use, suggesting that addressing sleep disturbances could reduce dependence on cannabis for managing PTSD symptoms. However, the retrospective and self-reported nature of the data, lack of a control group, and the study's cross-sectional design limit the ability to infer causality. Future research should explore the specific effects of cannabis on sleep disturbances in PTSD through controlled clinical trials. Betthauser et al. (2015) conducted a comprehensive literature review focused on the use of cannabis and its derivatives for PTSD treatment among military veterans. The review specifically

examined studies involving veterans who met the standard diagnostic criteria for PTSD and used cannabis or synthetic cannabinoids. The review found evidence suggesting that cannabinoids might help manage core PTSD symptoms such as insomnia and nightmares and provide global improvements in PTSD symptomatology. It also identified a correlation between more severe PTSD symptoms and increased motivation to use cannabis for coping purposes, particularly among veterans with emotional regulation or stress tolerance difficulties. While some small studies indicated improvements in PTSD symptoms with cannabinoid use, the authors emphasized the need for larger, well-designed controlled trials to better understand the potential role of cannabinoids as an adjunct or alternative to conventional PTSD therapies. Betthausen et al. concluded that a substantial number of veterans with PTSD use cannabis or derivative products to manage their symptoms, with some reporting benefits like reduced anxiety and improved sleep. However, they underscored the necessity for further research into the effects of cannabinoid treatment on PTSD symptoms to confirm these observations and understand the mechanisms involved.

In a comprehensive observational study, Hill et al. (2022) utilized data from the National Health and Resilience in Veterans Study (NHRVS) to investigate cannabis use among 4,069 U.S. military veterans. The study particularly focused on 608 veterans with current subthreshold or full PTSD, categorizing cannabis use into three groups: no use, less than weekly use, and more than weekly use, based on responses to the Cannabis Use Disorder Identification Test–Revised (CUDIT-R). The study aimed to understand the relationship between cannabis use and psychiatric conditions, functional impairment, and PTSD symptom management. Key findings revealed that veterans who used cannabis more than weekly were more likely to report co-occurring psychiatric conditions, including depression, anxiety, and suicidal

ideation, compared to those who used cannabis less frequently or not at all. Frequent cannabis users also demonstrated lower cognitive functioning and relied more on avoidance coping strategies. Notably, there was no significant difference in mental health treatment engagement among the various levels of cannabis use. The study highlighted that although cannabis use is prevalent among veterans with PTSD symptoms, it is often associated with adverse psychiatric and functional outcomes. Thus, the authors recommended enhanced screening and interventions targeting risky cannabis use among veterans with PTSD. Bonn-Miller et al. (2014b) conducted a cross-sectional study involving 217 adults currently receiving medical cannabis. The predominantly male and White/Caucasian participants were surveyed using the Medical Marijuana Patient Use Questionnaire (MMPUQ) and the Cannabis Use Disorders Identification Test-Revised (CUDIT-R). The study aimed to explore characteristics of cannabis use, reasons for use, and patterns of problematic use among medical cannabis users. Findings revealed that participants used cannabis for various conditions, including pain, muscle spasms, headaches, anxiety, and depression. While cannabis was perceived as beneficial for these conditions, the study highlighted problematic use patterns similar to those observed among regular cannabis users in the general population. Psychological symptoms such as depression and motives like using cannabis for coping predicted problematic use patterns, while perceived helpfulness was associated with fewer psychological symptoms. Bonn-Miller et al. concluded that while cannabis may offer therapeutic benefits, it also presents risks of abuse and dependence. They emphasized the need for further research to explore the implications of medical cannabis legalization, given both its potential benefits and risks.

Loflin et al. (2017) conducted a cross-sectional analysis to examine differences in cannabis use patterns, alcohol use, and cued arousal among veterans who screen positive for PTSD. The study included 1,971 veterans recruited through an email advertisement from the National Organization for the Reform of Marijuana Laws (NORML). Participants were categorized based on whether they used cannabis medicinally or recreationally. Results showed that veterans using cannabis medicinally reported higher levels of combat exposure, greater PTSD symptoms, and more subjective arousal when exposed to combat trauma reminders compared to recreational users. Medicinal cannabis users also reported less alcohol use and tended to use cannabis more frequently than recreational users. The study concluded that veterans using cannabis medicinally, especially for PTSD, exhibited distinct usage patterns and psychological responses compared to recreational users. This indicates that medicinal cannabis use may be more targeted toward managing specific PTSD symptoms. However, the authors acknowledged the limitations of the study, including reliance on self-reported data and the cross-sectional design, which limits causal inference.

In an observational study by Tull et al. (2016), the relationship between PTSD, marijuana dependence, and emotional reactivity to trauma cues was explored in 202 participants. The participants were from diverse ethnic backgrounds, primarily white (60.4%) and African American (36.6%). They underwent a personalized trauma cue while their subjective emotional reactivity (negative affect scores) and cortisol reactivity were assessed. Results indicated that participants with PTSD and marijuana dependence exhibited less emotional reactivity compared to those with PTSD who did not have marijuana dependence. However, no significant differences in cortisol reactivity were observed, suggesting that the moderating effect of marijuana

dependence might not extend to biological markers of stress in this sample. The study, however, was limited by the small sample size in certain comparisons, potentially reducing statistical power. Moreover, the high level of psychiatric comorbidity and functional impairment in the sample could limit the generalizability of findings. Furthermore, the observational nature of the study precluded drawing causal inferences between marijuana dependence and PTSD outcomes. Nevertheless, these findings underscore the potential role of marijuana dependence in modulating emotional responses to trauma cues among individuals with PTSD. Earleywine and Bolles (2014) conducted a cross-sectional analysis involving over 650 male veterans with combat exposure who used marijuana at least once per week. Participants completed measures of PTSD symptoms, marijuana expectancies, and marijuana use via an Internet survey. Key findings showed that veterans generally expected marijuana to relieve PTSD symptoms, especially those related to intrusions and arousal. The study found significant correlations between PTSD symptoms, expectancies for relief of symptoms, and actual marijuana consumption. Combat-exposed veterans who used marijuana tended to increase their consumption as the magnitude of PTSD symptoms and their expectations of marijuana-induced relief grew. Despite the valuable insights, the study had limitations, including reliance on self-reported data that may introduce biases and the cross-sectional design that restricted causal inferences. Additionally, the all-male sample limits the generalizability of findings to female veterans or those without combat experience. Wilkinson et al. (2015) investigated the impact of marijuana use patterns on PTSD outcomes in 2,276 veterans diagnosed with PTSD according to DSM-III or DSM-IV criteria. Participants were categorized into four groups based on their marijuana use patterns: never users, stoppers (used at admission but stopped after discharge), continuing users (used at

both times), and starters (began using after discharge). Results showed that marijuana use was significantly associated with worse PTSD outcomes in terms of symptom severity, violent behaviour, and increased use of alcohol and drugs. Veterans who stopped using marijuana after discharge reported improvements, while those who started or continued using marijuana experienced exacerbated symptoms. The study used ANOVA and ANCOVA to adjust for covariates and assess outcomes across user groups. Findings suggested that initiating marijuana use post-treatment was linked to poorer PTSD outcomes, underscoring the complexity of self-medication behaviours and the need for more controlled studies to elucidate the role of cannabis in PTSD management.

In a randomized, double-blind, placebo-controlled, cross-over clinical trial by Bonn-Miller et al. (2021), the short-term effects of smoked cannabis preparations on PTSD symptoms were investigated. A total of 97 adults with chronic tic disorders participated, with a Total Tic Score (TTS) of ≥ 14 for Tourette syndrome (TS) and ≥ 10 for chronic motor or vocal tic disorders according to DSM-5 criteria. Participants received nabiximols, an oromucosal spray containing THC and CBD in varying doses, from 1 to 12 puffs per day. Each puff contained 2.7 mg THC and 2.5 mg CBD, and the doses were tailored individually. The primary outcome measured was a reduction in tics, assessed by a minimum 25% decrease in the Total Tic Score of the Yale Global Tic Severity Scale (YGTSS-TTS) after 13 weeks. Secondary outcomes included improvements in psychiatric comorbidities such as ADHD and OCD, general health, and quality of life. Results showed that 21.9% of patients in the nabiximols group met the responder criterion, compared to 9.1% in the placebo group, although the superiority of nabiximols was not conclusively demonstrated ($p=0.07$). However, there were noticeable trends indicating improvements in tics, depression, and quality of life

among the nabiximols group. Importantly, nabiximols was well tolerated, with no significant safety issues reported. Despite the promising results, the study did not firmly establish the superiority of nabiximols over placebo, emphasizing the need for further research. The potential benefits of nabiximols were particularly observed in patients with more severe symptoms or comorbid ADHD. Johnson et al. (2016) conducted a matched case-control cross-sectional study to examine psychiatric and sociocultural associations of cannabis use in veterans with probable PTSD. The study involved 700 male and female veterans (350 cases and 350 controls) matched for age and gender. Veterans were included if they had probable PTSD and either used cannabis (cases) or did not use cannabis (controls). The sample was drawn from those enrolled in the primary care mental health integration program. Participants completed self-reported measures such as the PTSD Checklist-Civilian version (PCL-C) to assess PTSD symptom severity. Other outcomes included demographic and social factors like race, financial stability, and marital status. Findings revealed no significant differences between cannabis users and non-users in mean PCL-C scores, indicating that cannabis use was not associated with a reduction in PTSD symptom severity. However, cannabis users were more likely to be non-Caucasian, financially challenged, and unmarried. The study employed a case-control design with propensity score matching to adjust for potential confounders. Although the results suggested no therapeutic benefit of cannabis use for PTSD symptom severity, the study highlighted the need for further research to explore the motivations behind cannabis use among veterans and its broader implications for PTSD treatment. The study's limitations included its convenience sample from a clinical setting, which may affect the generalizability of the findings, and the cross-sectional design, which precludes establishing causality between cannabis use and PTSD symptom severity.

3.4.2.13.2. Research, clinical practice and future directions

The exploration of medicinal cannabis for managing PTSD has gained momentum, particularly as limitations of conventional treatments become more apparent. PTSD is a chronic and debilitating condition, and patients often seek alternatives when standard treatments prove ineffective. In this context, cannabinoids, particularly Δ 9-THC and CBD, have shown promise due to their interactions with the endocannabinoid system, which plays a crucial role in anxiety, fear, and memory processing.

A growing body of research has investigated the effects of medicinal cannabis on PTSD symptoms, with varying degrees of rigor and success. A recent retrospective study by Nacasch et al. (2023) examined the effects of medical cannabis on 14 combat veterans with chronic, treatment-resistant PTSD. They noted significant improvements in sleep quality and PTSD symptoms, particularly intrusiveness, avoidance, and alertness, after three months of treatment. The study suggests potential benefits of cannabis in treatment-resistant PTSD but calls for larger controlled trials to confirm efficacy. Similarly, Bonn-Miller et al. (2022) conducted a year-long longitudinal study involving 150 adults with PTSD. The results revealed that those using cannabis exhibited significant reductions in PTSD symptoms compared to non-users, and were more likely to no longer meet diagnostic criteria for PTSD by the end of the study period. Despite these promising findings, the authors emphasize the need for randomized controlled trials to establish the clinical utility of cannabis for PTSD management.

LaFrance et al. (2020) analyzed data from 404 PTSD patients using the Strainprint® app, finding that cannabis use led to a more than 50% reduction in symptoms like intrusions and flashbacks. The study also showed that higher doses correlated with

greater symptom reduction. However, the reliance on self-reported data and the lack of long-term efficacy monitoring limit the strength of the findings. Elms et al. (2019) explored the effects of CBD in a retrospective case series of 11 PTSD patients. They found that 91% of patients experienced reduced PTSD symptoms, improved sleep quality, and fewer nightmares. CBD was generally well-tolerated, making it a potential adjunct to standard treatments. A study by Greer et al. (2014) reviewed medical records of 80 PTSD patients and reported a 75% reduction in PTSD symptoms during cannabis use. This study highlighted the potential role of cannabis in PTSD symptom management, warranting further exploration in controlled clinical trials

Despite a lack of comprehensive clinical guidelines, cannabis use for PTSD is increasingly observed in clinical practice. Regions such as Israel and certain U.S. states have included PTSD as a qualifying condition for medical cannabis use, and many patients report self-medicating with cannabis-based products (CBMPs) when traditional treatments fail. In the Bonn-Miller et al. (2021) randomized, double-blind, placebo-controlled trial, different cannabis formulations were compared for their short-term impact on PTSD symptoms. The results suggested some benefits of nabiximols (THC and CBD oromucosal spray), though superiority over placebo was not conclusively demonstrated. Wilkinson et al. (2015) assessed 2,276 veterans with PTSD and observed that initiating cannabis use post-treatment was associated with poorer outcomes, including increased symptom severity and violent behaviour. This study underscores the complexities of cannabis use in PTSD and the need for careful patient monitoring.

To fully understand and utilize the potential of medicinal cannabis in PTSD management, future research should address several key areas, including clinical

trials and RCTs, neurobiological research, comorbidities management as well as formulation and dosage optimization.

Well-designed RCTs are essential for establishing safety and efficacy, optimal dosing strategies, cannabinoid ratios, and administration methods. The study by Bonn-Miller et al. (2022) calls for such trials to confirm the preliminary findings. Understanding how cannabinoids interact with the endocannabinoid system and influence PTSD pathophysiology can refine therapeutic targets. The editorial by Abizaid et al. (2013) suggests that manipulating the endocannabinoid system could be beneficial in PTSD treatment due to its role in anxiety and fear processing. Since PTSD frequently coexists with depression, chronic pain, and substance use disorders, studies should explore cannabis' role in managing these comorbidities. Identifying the optimal formulations and dosages of CBMPs is crucial. THC:CBD ratios might yield varying efficacy profiles, and patient-specific recommendations could enhance treatment outcomes. Overall, while current research indicates that medicinal cannabis may offer therapeutic benefits in managing PTSD, particularly for patients resistant to conventional treatments, more rigorous clinical trials are necessary to guide practice and ensure patient safety.

3.4.2.14. Inflammatory bowel disease

Current pharmacological treatments for IBD include aminosalicylates, corticosteroids, immunomodulators, and biologic agents targeting specific inflammatory cytokines (e.g., TNF- α inhibitors). Although these therapies can be effective in inducing and maintaining remission, they do not work for all patients. Up to 30-40% of patients do not respond to biologics, and even among responders, loss of response over time is

common. Moreover, these medications can have significant side effects, such as increased risk of infection due to systemic immunosuppression and potential long-term effects on bone density and cardiovascular health (Perisetti et al., 2020).

Cannabinoids exert complex effects on the gastrointestinal (GI) tract, influencing both motility and sensation through interactions with the endocannabinoid system (ECS). The ECS is a widespread neuromodulatory system that plays crucial roles in central nervous system (CNS) development, synaptic plasticity, and the response to endogenous and environmental insults. It comprises cannabinoid receptors (CB1 and CB2), their endogenous ligands (endocannabinoids), and the enzymatic machinery for their metabolism. Cannabinoid receptors are expressed throughout the GI tract, from the oesophagus to the colon. Activation of CB1 receptors primarily affects the motility of the GI tract. It tends to decrease gastrointestinal motility and secretion in a state-dependent manner, which can be beneficial for conditions characterized by hypermotility, such as diarrhoea-predominant IBD. On the other hand, CB2 receptors are mainly expressed on immune cells and are involved in modulating immune response and inflammation (Gotfried et al., 2020).

By activating these receptors, THC can potentially decrease inflammation and reduce the activity of the immune system. This immunosuppressive effect can help mitigate the chronic inflammation characteristic of IBD. CBD, on the other hand, does not bind as efficiently as THC to CB1 and CB2 receptors. Instead, it is thought to exert its effects through several non-cannabinoid receptor routes. CBD can modulate the immune system by affecting the activity and viability of T cells and reducing cytokine production, thereby promoting an anti-inflammatory response. Studies have demonstrated that CBD can decrease intestinal inflammation by acting on alpha-3

glycine receptors, which are a type of non-cannabinoid receptor found in the GI tract (Kafil et al., 2020). Additionally, CBD has been shown to upregulate the expression of IL-10, an anti-inflammatory cytokine, while downregulating the expression of pro-inflammatory mediators such as IL-12 and TNF- α in macrophages. This helps in reducing the inflammatory response and is particularly beneficial in autoimmune conditions like IBD. The distinct mechanisms of THC and CBD in modulating the ECS and their broader effects on the immune system suggest their potential as therapeutic agents in IBD. By integrating these cannabinoids into treatment protocols, either as monotherapies or in conjunction with traditional treatments, it may be possible to achieve better disease control and improve quality of life for patients with IBD. The ability of cannabinoids to target multiple pathways involved in inflammation and immunity is a promising avenue for future research and clinical application (Nso et al., 2021)

3.4.2.14.1. Recommended dosages in current literature

Several clinical trials have investigated the efficacy and safety of cannabis and its components in the management of IBD symptoms like Crohn's Disease and Ulcerative Colitis (Table 3.23). One notable study by Naftali et al. (2013) demonstrated the potential of smoked cannabis containing 115 mg of THC administered twice daily in significantly reducing the Crohn's Disease Activity Index (CDAI) in patients who had previously been resistant to conventional therapies. This study not only highlighted

Authors	Study	Pts	Age	Dose	Delivery	Follow-up	Outcomes
Naftali et al. (2011)	Retrospective cohort	30	36 x̄	0.5-1.5mg THC	Inhalation	2.1 years x̄	Improved disease activity with reduced Harvey-Bradshaw index, fewer surgeries, and reduced use of other medications.
Lahat et al. (2012)	Open label trial	13	44 x̄	50g	Inhalation	3 months	Improved quality of life, disease activity, weight gain, and BMI increase. Reduction in Harvey-Bradshaw index (CD patients) and partial Mayo score (UC patients).
Naftali et al. (2013)	RCT	21	40 x̄	11.5mg BD THC	Inhalation	8 weeks	Reduction in Crohn's Disease Activity Index (CDAI) scores. Improved appetite, sleep, and steroid-sparing effect. Provided clinical benefits compared to placebo.
Naftali et al. (2017a)	RCT	20	39 x̄	10mg BD	Oral	10 weeks	No significant beneficial effects on CDAI or laboratory markers, possibly due to low dosage.
Naftali et al. (2017b)	RCT	50	-	15% CBD, 4% THC	Oral		Quality of life scores higher in the cannabis oil group (96.3 vs 79.9). However, GRADE analysis indicated low overall certainty of evidence due to significant imprecision. Mean CDAI scores were lower in cannabis group (118.6 vs 212.6).
Irving et al. (2018)	RCT	62	-	250mg BD	Oral (CBD)	12 weeks	No remissions yet improvements in Mayo scores, global illness severity, and quality of life were observed.
Kerlin et al. (2018)	Cross-sectional survey	1666	-			-	Benefits in pain, appetite, anxiety, and fatigue but also more IBD symptoms, depression, and lower social satisfaction.
Naftali et al. (2018)	RCT	28	33 x̄	11.5mg BD THC	Inhalation	8 weeks	Significant clinical and endoscopic improvements in UC activity, including decreases in DAI and Mayo endoscopic score. Quality of life improved.
Mbachi et al. (2019)	Retrospective cohort	43317	-	Unspecified	Unspecified	-	Lower rates of complications such as fistulizing disease, need for parenteral nutrition, blood transfusion, and colectomy.
Benson et al. (2020)	Cross-sectional survey	838	36.7 x̄	Unspecified	Inhalation	-	Improvements in abdominal pain, stress, sleep, cramping, and anxiety. The quality of life was reportedly better for cannabis users with ulcerative colitis.
Naftali et al. (2021a)	RCT	32	30 x̄	80mg BD THC	Inhalation	10 weeks	Clinical improvement with reduced Lichtiger DAI and enhanced quality of life, but without significant changes in endoscopic or inflammatory markers.
Naftali et al. (2021b)	RCT	56	34.5 x̄	40mg THC + 160mg CBD	Oral	10 weeks	Improved CDAI and quality of life, but no significant changes in endoscopic scores or inflammatory markers.
Coates et al. (2022)	Retrospective cohort	383	44 x̄	Unspecified	Oral, Inhalation	-	Cannabis users reported more symptoms like abdominal pain, gas, tenesmus, and arthralgias but no increased disease severity or complications.

Table 3.23. *Studies evaluating use of medicinal cannabis in inflammatory bowel disease.*

the symptomatic relief provided by cannabis but also marked a significant clinical response in terms of disease activity scores. Further elaborating on the role of cannabinoids, the randomized controlled trial by Irving et al. (2018) investigated the effects of a botanical extract rich in CBD. The dosage ranged from 50 mg to 250 mg administered twice daily for 10 weeks in capsule form, showing that higher doses of CBD might contribute to improved quality of life and symptom management in IBD patients. This trial, among others, underscores the importance of dosage in achieving desired therapeutic outcomes.

Esfandyari et al. (2007) examined the effects of a cannabinoid receptor agonist on colonic motor and sensory functions. This study utilized cannabinoid receptor agonists to modulate the visceral sensation and motility, which are often impaired in IBD patients. The agonists used potentially targeted CB1 receptors located throughout the GI tract, aiming to reduce the heightened motility and sensory response characteristic of disorders like IBD. The results indicated that cannabinoid agonists could significantly decrease motility and improve sensory thresholds, thus reducing symptoms of pain and diarrhoea in IBD patients. This study underscores the potential of targeted cannabinoid treatments to manage specific physiological dysfunctions within the GI system, offering a therapeutic pathway to alleviate some of the most challenging symptoms of IBD.

Further exploring the impact of cannabinoids on GI physiology, Wong et al. (2011) conducted a pivotal study investigating the effects of dronabinol on colonic motility. dronabinol was administered in doses of 2.5 mg and 5 mg to assess its impact on the colonic motility index during fasting. The study found that dronabinol significantly reduced the motility index in patients with IBD, particularly those with predominant

diarrhoea symptoms. By modulating colonic motility, dronabinol helped in managing diarrhoea, frequent and debilitating symptom of IBD. This study not only highlighted the effectiveness of synthetic cannabinoids in symptom management but also demonstrated the dose-dependent efficacy of cannabinoid treatments in reducing specific GI symptoms. Building on their earlier work, Wong et al. (2012) expanded their research scope to include a broader pharmacodynamic and pharmacogenetic analysis of dronabinol's effects on colon transit time in IBD patients with diarrhoea-predominant symptoms. This study intricately linked the genetic makeup of the patients to their responsiveness to cannabinoid therapy, providing a more personalized medicine approach. Although specific dosage information was not detailed in the available documents, the study reinforced the notion that cannabinoids could play a crucial role in managing GI motility and associated symptoms in a manner that is potentially customizable to individual patient's genetic profiles.

The collective findings from these studies illustrate that while the clinical application of cannabis in IBD treatment shows promise, it is complex and influenced by factors such as the specific cannabinoid profile used, the dosage, and the administration method. The therapeutic potential of cannabis might be maximized by tailoring these factors to individual patient needs, possibly improving outcomes where traditional treatment modalities fall short.

3.4.2.14.2. Comparison with traditional therapies

The management of IBD typically involves a range of pharmaceutical therapies including TNF inhibitors and corticosteroids. These traditional treatments are well-recognized for their effectiveness in reducing inflammation and managing flare-ups.

However, their use is often limited by significant side effects and the potential for long-term health risks, such as increased susceptibility to infections and possible development of lymphoma with TNF inhibitors, and bone density loss, hypertension, and hyperglycaemia with corticosteroids (Cassio Alves de Carvalho et al., 2020; Nduma et al., 2023).

In contrast, medicinal cannabis offers a different therapeutic profile. Studies quoted above have demonstrated the potential of cannabinoids like THC and CBD to modulate immune responses and reduce inflammation through pathways not utilized by traditional medications. For example, THC has been shown to interact with CB2 receptors on immune cells to potentially reduce cytokine production and inflammation without the immunosuppressive effects associated with traditional therapies (Cohen & Neuman, 2020). Economic considerations are crucial in the management of chronic diseases like IBD. Traditional treatments, especially biologics like TNF inhibitors, can be extremely costly, potentially running into thousands of dollars per patient per year. In comparison, medicinal cannabis might offer a more cost-effective solution due to lower production and processing costs. However, the actual cost-effectiveness of cannabis would depend heavily on local legislation, the extent of insurance coverage, and the specifics of healthcare systems in different regions (Hansen et al., 2020).

Patient-centred care is pivotal in chronic disease management, and here, medicinal cannabis may have a distinct advantage. According to patient testimonials and surveys reported in Godfried et al. (2020) many patients prefer cannabis due to its ability to alleviate not only the physical symptoms of IBD but also the psychological stress associated with the disease. Cannabis has been noted for its analgesic properties and its ability to improve sleep and reduce anxiety, which are significant

comorbidities in IBD. Quality of life (QoL) is another important metric in evaluating the effectiveness of any treatment. Studies have shown that patients using cannabis report a better quality of life with fewer side effects compared to those undergoing traditional treatment regimes. The improvement in QoL could be attributed to the multifaceted benefits of cannabis, which extend beyond mere symptom control to include an enhanced sense of well-being (Hryhorowicz et al., 2021).

3.4.2.14.3. Research and clinical practice

The potential role of medicinal cannabis in treating IBD has sparked considerable interest within the medical community, encouraged by promising results from early clinical trials and anecdotal reports. As we move forward, several key areas of research and development are poised to expand our understanding and refine the use of cannabis-based therapies in IBD management. The integration of cannabis into existing treatment protocols for IBD requires a nuanced understanding of its physiological impacts and synergistic effects with conventional medications. Current evidence suggests that cannabis may particularly benefit those patients who are either non-responsive to standard care or who experience significant side effects from traditional therapies (Kafil et al., 2018; Perisetti et al., 2019; Nduma et al., 2023). The anti-inflammatory properties of cannabinoids, along with their ability to modulate the gut microbiome and immune response, provide a compelling rationale for their inclusion in treatment regimens, particularly for patients with refractory disease (Hansen et al., 2020).

One of the exciting avenues of research involves the development of cannabinoid analogues and novel formulations designed to maximize therapeutic benefits while

minimizing psychoactive effects and other side effects. As discussed in Cassio Alves de Carvalho et al., (2020) and Hryhorowicz et al. (2021) ongoing studies are exploring the efficacy of CBD-rich extracts and their ability to reduce inflammation without the intoxicating effects associated with THC. Additionally, the potential for synthetic cannabinoids or pharmaceutical derivatives that target specific cannabinoid receptors could offer new ways to harness the benefits of cannabis with greater control over dosing and reduced risk of dependency (Naftali et al., 2017). Despite the encouraging data, there is a consensus across the scientific literature, on the need for larger, more comprehensive clinical trials to validate preliminary findings and assess long-term outcomes (Perisetti et al., 2019). Multicentric trials that involve diverse patient populations and standardized treatment protocols are essential to overcome the limitations of smaller studies and provide more definitive evidence of efficacy and safety. Such studies could also explore patient-specific factors such as disease subtype, severity, and previous treatment history, to better tailor cannabis-based therapies to individual needs (Kafil et al., 2018).

3.4.2.15. Pain

Pain is a complex and distressing experience associated with actual or potential tissue damage. It serves as a critical biological signal that indicates harm or a threat to the body. Pain can be broadly classified into two categories: acute and chronic. Acute pain is a normal response to injury, lasting a short period and usually diminishing as the body heals. Chronic pain, on the other hand, persists beyond the normal time expected for recovery and can continue without apparent biological value (Fisher et al., 2021; Dalal & Kudur, 2024). Chronic pain is a significant public health issue affecting

approximately one in five adults and is a common reason for seeking medical care (Lynch & Ware, 2015; Noori et al., 2021; Chou et al., 2022).

The management of pain, particularly chronic pain, often involves a variety of pharmacological treatments including opioids, non-steroidal anti-inflammatory drugs (NSAIDs), antidepressants, and anticonvulsants. Opioids are commonly prescribed for severe chronic pain conditions but are associated with adverse effects such as sedation, constipation, addiction, and overdose. NSAIDs, while effective for some patients, come with risks of gastrointestinal and cardiovascular side effects. Antidepressants and anticonvulsants are used primarily for neuropathic pain but can also cause undesirable side effects such as drowsiness and dizziness. These medications provide relief to only a subset of patients and often do not address the full spectrum of pain symptoms, leading to significant treatment gaps (Dalal & Kudur, 2024).

Medicinal cannabis presents a promising alternative for managing pain, particularly where traditional medications fail or produce debilitating side effects. Cannabis contains THC and CBD, which have been shown to possess analgesic properties. THC acts primarily through the activation of CB1 and CB2 cannabinoid receptors, which are part of the endocannabinoid system involved in modulating pain, mood, and other physiological and cognitive processes. CBD, on the other hand, does not directly activate these receptors but influences the body's natural cannabinoid systems and several other non-cannabinoid receptors and ion channels to exert its analgesic and anti-inflammatory effects. Unlike THC, CBD does not bind strongly to cannabinoid receptors but influences the endocannabinoid system indirectly and through other non-cannabinoid receptor pathways. CBD modulates the enzymatic breakdown of

anandamide, an endogenous cannabinoid, thereby enhancing its action. Additionally, CBD interacts with various other receptors, such as serotonin receptors, which contribute to its anti-anxiety effects, and vanilloid receptors that mediate pain perception and inflammation (Lee et al., 2018). Clinical studies have demonstrated the effectiveness of cannabis in reducing chronic pain, particularly neuropathic pain. A meta-analysis of randomized controlled trials found that inhaled cannabis significantly reduced pain in patients with chronic neuropathic conditions, with effects comparable to or better than conventional pain medications. Moreover, cannabis has been noted for its ability to enhance the analgesic effects of opioids, potentially allowing for lower opioid doses and reducing the risk of side effects and dependency (Ko et al., 2016; Rod et al., 2019).

Endocannabinoids like anandamide and 2-arachidonoylglycerol are synthesized on demand and regulate presynaptic neurotransmission through a retrograde signalling mechanism. This modulation can reduce the release of neurotransmitters such as glutamate, which is involved in the sensation of pain. In the context of chronic pain, there is evidence that endocannabinoid signalling becomes dysregulated, and phytocannabinoids like THC and CBD can restore this balance. CBD also acts on various ion channels that are crucial in pain signalling pathways. For example, it directly activates transient receptor potential (TRP) channels, which are involved in sensing temperature, pain, and pressure, further contributing to its analgesic effects. Additionally, CBD's interaction with glycine receptors, which play a role in the modulation of pain at the spinal level, suggests a mechanism by which CBD may alleviate chronic pain and inflammation. Despite these promising results more research is needed to fully understand the long-term effects of medicinal cannabis,

optimize its therapeutic potential, and standardize its use in clinical practice (Mlost et al., 2020).

3.4.2.15.1. Recommended dosages in current literature

Medicinal cannabis has been increasingly recognized as a potential alternative or adjunct therapy in pain management, particularly for chronic and neuropathic pain. The complexity of cannabis pharmacology, due to its numerous active compounds requires careful consideration when recommending dosages (Table 3.24). The determination of effective dosing is influenced by several factors, including the type of pain, the specific cannabis formulation route of administration, and individual patient characteristics such as previous cannabis exposure and concurrent medication use. The literature suggests varied dosing strategies based on empirical evidence and clinical trials. For instance, a meta-analysis on the efficacy of inhaled cannabis for chronic neuropathic pain highlighted a THC concentration range from 3.5% to 9.4%, with higher concentrations generally yielding more significant pain relief.

One of the major challenges in prescribing medicinal cannabis for pain relief is the variability in individual response and the lack of standardized dosing guidelines. The efficacy and safety of various cannabis formulations have been explored in several randomized controlled trials, suggesting a broad therapeutic window. However, due to the plant's complex nature, containing over 100 cannabinoids and other bioactive compounds, achieving a consensus on optimal dosing regimens remains challenging. This complexity is compounded by the diverse mechanisms through which cannabinoids exert their analgesic effects, from direct receptor engagement to modulation of inflammatory pathways and neurotransmitter systems.

Karst et al. (2003) explored the effects of CT-3, a synthetic cannabinoid compound, on chronic neuropathic pain through a rigorous randomized controlled trial. The study's findings indicated significant pain relief in patients receiving CT-3 compared to a placebo, particularly noting improvements three hours post-administration. These results are critical as they highlight the analgesic properties of cannabinoids beyond traditional opioid therapies, suggesting an alternative pathway involving the down-regulation of cyclooxygenase 2 and interaction with peroxisome proliferator-activated receptor γ (PPAR γ). Such mechanisms could potentially address pain relief without the psychoactive effects commonly associated with cannabinoids. Similarly, Wade et al. (2003) utilized a unique trial design to study the effects of whole-plant extracts, including combinations of THC and CBD, on symptoms like pain and muscle spasms in patients with multiple sclerosis and other neurogenic conditions. Their work emphasizes the symptomatic relief provided by these extracts, corroborating the notion that both THC and CBD can play significant roles in managing unresponsive symptoms. The favourable response to sublingual administration of these compounds offers an attractive alternative for patients, providing relief with controlled dosing and minimal adverse effects. Berman et al. (2004) focused on the use of cannabis-based medicinal extracts in treating central neuropathic pain related to severe brachial plexus injuries. Although the primary outcome of a two-point reduction in pain severity was not achieved, significant improvements were noted in secondary measures such as pain and sleep quality. This trial further supports the efficacy of cannabinoid therapy, particularly in cases where conventional treatments fail, and highlights the potential for cannabinoids to improve life quality aspects such as sleep, which are often adversely affected in chronic pain conditions. Notcutt et al. (2004) examined the efficacy of different cannabinoid-based medicinal extracts (CBMEs) in managing

chronic, mainly neuropathic pain through 'N of 1' trials. The findings from this study underscored the therapeutic preference for mixtures of THC and CBD, which were effective in pain management and well-tolerated by patients. The personalized approach in this trial, allowing for adjustable dosing based on individual response, provides a model for personalized medicine in cannabinoid therapy.

Svendsen et al. (2004) focused on patients with multiple sclerosis experiencing central pain, examining the efficacy of dronabinol, a synthetic THC. Their findings demonstrated a modest but clinically relevant analgesic effect, with a significant reduction in median spontaneous pain intensity and improvements in quality of life aspects during active treatment phases. Notably, while adverse events such as dizziness and fatigue were more frequent with dronabinol, they were generally well-tolerated, suggesting that synthetic THC could be a viable alternative when other therapies are inadequate. In the study by Nurmikko et al. (2007), Sativex®, a sublingual spray containing both THC and CBD, was evaluated in patients with peripheral neuropathic pain. The results indicated a significant reduction in pain scores and improvements in sleep and allodynia, highlighting the potential of standardized cannabinoid therapies in complex pain management. Despite some patients experiencing sedative and gastrointestinal side effects, the study's findings support the exploration of cannabinoid-based therapies as effective treatments for neuropathic pain, emphasizing the importance of patient-specific titration to minimize adverse effects. Abrams et al. (2007) explored the efficacy of smoked cannabis in reducing chronic neuropathic pain in patients with HIV-associated sensory neuropathy. Their results revealed significant pain reduction, with a notable percentage of participants experiencing a 30% or greater reduction in pain intensity. This study is particularly significant as it demonstrates the immediate analgesic effects of cannabis, while also

highlighting its safety, with side effects being mostly mild and well-tolerated. The research by Ellis et al. (2009) investigated the use of smoked cannabis in HIV-infected adults with neuropathic pain refractory to standard treatments. Their findings corroborated those of Abrams et al., showing a substantial reduction in pain intensity and improvements in mood and daily functioning. Although there were concerns regarding adverse effects such as transient psychosis and persistent cough in a few patients, the overall tolerance was good, reinforcing the potential utility of cannabis as an adjunct therapy in refractory neuropathic pain.

Selvarajah et al. (2010) examined the effects of Sativex®, a cannabis-based medicinal extract, on patients with painful diabetic peripheral neuropathy (DPN). Despite the rigorous randomized placebo-controlled double-blind trial design, the study found no significant difference between the Sativex® and placebo groups in terms of pain relief. This outcome suggests that while cannabis-based treatments may be effective for some types of pain, their efficacy in diabetic neuropathy could be limited or influenced by other factors such as depression, which was noted as a significant confounder in the trial. This study underscores the complexity of pain management in diabetic patients and the need for individualized treatment plans that consider psychological as well as physical health factors. Ware et al. (2010) focused on the use of smoked cannabis at varying potencies to treat post-traumatic and postsurgical neuropathic pain. The study demonstrated that high-potency THC cannabis (9.4%) significantly reduced pain intensity and improved sleep, highlighting the potential benefits of controlled cannabis use in a clinical setting. However, the increase in adverse events with higher THC levels, such as dizziness and dry eyes, points to the importance of careful dose management to balance efficacy with patient comfort and safety. Toth et al. (2012) investigated the use of nabilone in treating DPN- associated neuropathic

Authors	Study	Pts	Age	Dose	Delivery	Follow-up	Outcomes
Noyes et al. (1975)	RCT	10	51 $\bar{x}$	5-20mg	Oral (THC)	-	Pain relief was dose-dependent. 15-20 mg doses provided significant analgesia but were highly sedative.
Maurer et al. (1990)	Single case double-blind trial	1	1	2.5-10mg	Oral (THC)	5 months	Significant reduction in spasticity and pain compared to placebo, without altered consciousness.
Ware et al. (2002)	Case series	15	49.5 $\bar{x}$	3-8 puffs X1-16 / day	Inhalation	-	Improvement in pain, mood, and sleep for most patients. No tolerance was observed. Psychoactive effects were mild.
Karst et al. (2003)	Randomized cross-over	21	51 $\bar{x}$	40-80mg (CT-3)	Oral (THC)	1 week / phase; 2-week wash-out	Statistically significant reductions in pain intensity, measured on the VAS scale, during intervention periods compared to placebo.
Lynch et al. (2003)	Case series	3	35-47	Variable	Inhalation	6-24 months	Significant reductions in opioid usage (up to 100% in one case), improved pain control, spasticity, and sleep.
Wade et al. (2003)	Randomized cross-over	24	48 $\bar{x}$	2.5-120mg (THC, CBD, 1:1)	Oral (THC, CBD, 1:1 THC:CBD)	2 weeks / phases X4	Improvements in pain, spasticity, and muscle spasms compared to placebo.
Berman et al. (2004)	RCT	48	39 $\bar{x}$	max. 8 sprays / day (21.6mg THC, 20mg CBD)	Oromucosal spray (nabiximols)	2 weeks / phase; 2-week wash-out	Both active treatments (THC + CBD or THC alone) showed statistically significant but not clinically meaningful pain reduction compared to placebo.
Notcutt et al. (2004)	Randomized cross-over	34	-	2-8 sprays CBD, THC, THC:CBD 1:1	Oromucosal spray	12 weeks	THC-containing sprays were most effective in symptom control, particularly pain and spasticity. Side effects were common but manageable.
Svensen et al. (2004)	Randomized cross-over	24	23-55	max. 10mg	Oral (dronabinol)	3 weeks / phase; 3-week wash-out	Reduced median spontaneous pain intensity. Increased adverse events in the first treatment week.
Rog et al. (2005)	RCT	66	47.7 $\bar{x}$	9.6 sprays $\bar{x}$ / day (2.7mgTHC + 2.5mgCBD)	Oromucosal spray (nabiximols)	5 weeks	Significant reductions in pain and sleep disturbance compared to placebo.
Beaulieu et al. (2006)	RCT	41	52.5 $\bar{x}$	1-2mg	Oral (nabilone)	24 hours	No significant benefit of nabilone over placebo for pain management, but comparable to ketoprofen.
Blake et al. (2006)	Randomized cross-over	58	50 $\bar{x}$	max. 6 sprays / day (2.7mgTHC + 2.5mgCBD)	Oromucosal spray (nabiximols)	5 weeks	Significant improvements in pain on movement, pain at rest, and quality of sleep. Side effects were generally mild or moderate.
Gofeld et al. (2006)	Case study	1	29	2mg BD	Oral (nabilone)	-	Improved pain control, reduced anxiety, and decreased morphine consumption when nabilone was included.
Holdcroft et al. (2006)	Open label	64	50.3 $\bar{x}$	5-15mg THC:CBD 1:0.5	Oral	-	Dose-dependent pain relief, increasing as the dose increased.

Authors	Study	Pts	Age	Dose	Delivery	Follow-up	Outcomes
Lynch et al. (2006)	Case series	30	45 x̄	1-5g	Oral, Inhalation	23.6 months x̄	93% reported moderate to complete pain relief, with 70% reducing other medication usage.
Pinsger et al. (2006)	Randomized cross-over	30	55 x̄	0.25-1mg	Oral (nabilone)	4 weeks / phase; 1-week wash-out	nabilone provided superior pain relief, increased quality of life, and reduced headache intensity compared to placebo.
Wissel et al. (2006)	Randomized cross-over	13	19-68	0.5-1mg	Oral (nabilone)	4 weeks / phase; 1-week wash-out	Significant reduction in spasticity-related pain. No changes in motor function or daily living activities.
Abrams et al. (2007)	RCT	55	50 x̄ 47 x̄	1 cigarette TDS (3.56% THC)	Inhalation	2 weeks	Significant reduction in chronic pain. Median pain reduction of 72% in cannabis group compared to 15% in placebo group).
Nurmikko et al. (2007)	RCT	125	52 x̄	max. 48 sprays/day (2.7mgTHC + 2.5mgCBD)	Oromucosal spray (nabiximols)	5 weeks	Significant reduction in pain intensity and improvement in secondary measures, such as sleep quality.
Wallace et al. (2007)	Randomized cross-over	15	28.9 x̄	2-8% THC	Inhalation	1 day	Medium doses reduced pain. High doses increased pain. Highlighted a narrow therapeutic window for analgesia.
Frank et al. (2008)	Randomized cross-over	96	23-84	2mg	Oral (nabilone)	6 weeks / phase; 2-week wash-out	Dihydrocodeine was more effective for pain relief than nabilone and had fewer side effects.
Haroutiunian et al. (2008)	Case series	13	46 x̄	Unspecified	Oral (THC), Inhalation	3 years	7 patients discontinued due to lack of efficacy or adverse events. Others reported better pain scores and quality of life.
Narang et al. (2008)	RCT	30	43.5 x̄	10-20mg TDS	Oral (dronabinol)	4 weeks	Additional analgesia with dronabinol; reduced pain inconvenience and increased treatment satisfaction.
Skrabek et al. (2008)	RCT	40	50.1 x̄ 47.6 x̄	0.5-2mg	Oral (nabilone)	8 weeks	Significant decreases in pain, improved quality of life, and anxiety reduction.
Wilsey et al. (2008)	Randomized cross-over	38	21-71	3.5-7% THC	Inhalation	1 day	Significant analgesic response, dose-dependent reduction in pain intensity. High doses caused mild cognitive impairment.
Ellis et al. (2009)	Randomized cross-over	34	49.1 x̄	1-8% THC	Inhalation	5 days / phase; 2-week wash-out	Median reduction in pain recorded at 34% when compared to placebo. Improved quality of life.
Hornby et al. (2009)	Case study	1	36	10-15g	Variable	1 year	Effective pain management and improvement in quality of life with resistant chronic pain.
Bestard et al. (2010)	Prospective cohort	249	61.2 x̄	3mg x̄	Oral (nabilone)	6 months	Both nabilone and gabapentin significantly reduced pain scores, with similar efficacy.
Johnson et al. (2010)	RCT	177	59.4 x̄	max. 48 sprays/day (2.7mgTHC + 2.5mgCBD)	Oromucosal spray (nabiximols)	2 weeks	Significant pain reduction when compared to placebo. No significant benefit with THC-only spray.

Authors	Study	Pts	Age	Dose	Delivery	Follow-up	Outcomes
Rintala et al. (2010)	Randomized cross-over	7	50.1 x̄	max. 20mg	Oral (dronabinol)	5 weeks / phase; 1-week wash-out	No significant difference in pain relief between dronabinol and diphenhydramine.
Selvarajah et al. (2010)	RCT	30	58.2 x̄	- sprays/ day (2.7mgTHC + 2.5mgCBD)	Oromucosal spray (nabiximols)	12 weeks	No significant difference in pain relief between Sativex® and placebo. Depression was a major confounder, influencing higher baseline pain scores and improved outcomes.
Ware et al. (2010)	Randomized cross-over	23	45.4 x̄	2.5-9.4% THC	Inhalation	2 weeks	Significant pain relief with 9.4% THC. Lower doses showed non-significant effects. Improved sleep quality was observed.
Haroutiunian et al. (2012)	Prospective cohort	42	49 x̄	3-15mg	Unspecified	6 months	Pain severity and interference improved by 14.5% and 24% respectively. High patient satisfaction reported.
Portenoy et al. (2012)	RCT	360	58 x̄	1-16 sprays / day (2.7mgTHC + 2.5mgCBD)	Oromucosal spray (nabiximols)	7 weeks	Low- and medium-dose groups showed significant pain relief and sleep improvement compared to placebo. High-dose group had more adverse events.
Toth et al. (2012)	RCT	37	62.2 x̄	1-4mg	Oral (nabilone)	9 weeks	Pain relief, improved sleep, better quality of life. Minimal adverse effects.
Johnson et al. (2013)	Open label pilot	43	57.5 x̄ 58.6 x̄	max. 48 sprays/ day (2.7mgTHC + 2.5mgCBD)	Oromucosal spray (nabiximols)	579-657 days	Sustained pain relief. Improved quality of life for patients. No evidence of dose escalation over time.
Langford et al. (2013)	RCT	339	48.9 x̄	max. 48 sprays/ day (2.7mgTHC + 2.5mgCBD)	Oromucosal spray (nabiximols)	12 weeks	Modest improvements in pain and sleep quality. No statistically significant differences in mean pain scores between test and control groups.
Wilsey et al. (2013)	Randomized cross-over	39	50 x̄	1.29-3.53% THC	Inhalation	4 weeks	Significant analgesic response to low and medium doses. Psychoactive effects minimal and cognitive effects short-lived.
Eisenberg et al. (2014)	RCT	35	46.7 x̄	15-30mg	Oral (THC)	12 weeks	Noted pain reduction at significant levels when compared to placebo.
Lynch et al. (2014)	Randomized cross-over	16	56 x̄	max. 12 sprays/ day (2.7mgTHC + 2.5mgCBD)	Oromucosal spray (nabiximols)	4 weeks / phase; 2-week wash-out	31.5% showed clinically meaningful pain reduction. ≥2-point drop on pain scale.
Serpell et al. (2014)	RCT	246	57.3 x̄	max. 24 sprays/ day (2.7mgTHC + 2.5mgCBD)	Oromucosal spray (nabiximols)	15 weeks	Clinically significant improvements in pain and sleep quality. Adverse events were common but manageable.
Degenhardt et al. (2015)	Prospective cohort	1514	58 x̄	Variable	Oral, Inhalation	4 years	No evidence of pain reduction or opioid-sparing effects with cannabis use.
Hoggart et al. (2015)	Open label pilot	380	57.8 x̄	max. 24 sprays/ day (2.7mgTHC + 2.5mgCBD)	Oromucosal spray (nabiximols)	38 weeks	Pain reduced from 6.9 (baseline NRS) to 4.2 (end of study). 30% or more pain relief reported in half of patients.

Authors	Study	Pts	Age	Dose	Delivery	Follow-up	Outcomes
Turcotte et al. (2015)	RCT	15	45.5 x̄	0.5-2mg	Oral (nabilone)	9 weeks	Significant reduction in pain intensity and impact on daily activities.
Ware et al. (2015)	Prospective cohort	216	45.5 x̄ 52.4 x̄	2.5g / day x̄	Oral, Inhalation	1 year	Pain reduction and improved quality of life reported. No significant differences in serious adverse events
Boehnke et al. (2016)	Retrospective cohort	244	45 x̄	Variable	Oral, Inhalation	-	Reduction in opioid use, improvement in pain scores, and better quality of life reported by cannabis users.
Haroutounian et al. (2016)	Prospective cohort	206	51.2 x̄	43.2g / month	Oral, Inhalation	7 months x̄	Improved pain scores and quality of life for patients.
Wilsey et al. (2016)	Randomized cross-over	42	46.4 x̄	2.9-6.7% THC	Inhalation	2 weeks	Dose-dependent pain relief, with lower doses offering a better risk-benefit profile. Dose-dependent, mild psychoactive effects.
de Vries et al. (2017)	RCT	50	53.9 x̄	3-8mg TDS	Oral (THC)	49 days	Statistically significant reduction in visual analog scale (VAS) pain scores for THC compared to placebo.
Fallon et al. (2017)	RCT	399	60 x̄ 59.6 x̄	3-10 sprays / day (2.7mgTHC + 2.5mgCBD)	Oromucosal spray (nabiximols)	5 weeks	Modest but significant improvements in pain scores. Better sleep quality.
Fanelli et al. (2017)	Retrospective cohort	614	61.3 x̄	Variable (THC)	Oral, Inhalation	1 year	Effective in managing pain in 76% of patients. Mild side effects with <15% discontinuing due to adverse effects.
Lucas et al. (2017)	Cross-sectional survey	271	20-77	≤2g	Variable	-	High substitution rates for prescription medications, particularly opioids (32%). Improved in pain and mental health symptoms.
Malik et al. (2017)	RCT	19	43 x̄	5mg BD	Oral (dronabinol)	28 days	Increased pain thresholds, reduced pain intensity, and odynophagia frequency. No significant adverse effects noted.
Piper et al. (2017)	Cross-sectional survey	1513	-	Unspecified	Variable	-	76.7% reduced opioid use for pain management, 65.2% reduced sleep medications, and 71.8% reduced anti-anxiety medications.
Reiman et al. (2017)	Cross-sectional survey	2897	-	Unspecified	Oral, Inhalation	-	97% reported reducing opioid use with cannabis. 92% preferred cannabis for fewer side effects.
Schmrigk et al. (2017)	RCT	240	47.7 x̄	12.7mg x̄	Oral (dronabinol)	119 weeks	No significant pain intensity reduction in blinded phase. Clinically relevant reductions during long-term follow-up.
Shah et al. (2017)	Retrospective cohort	48	45.1 x̄	Unspecified	Variable	3 weeks	Both groups improved pain, depression and quality of life. Cannabis use was not associated with reduced opioid usage but linked to higher substance-use risk.
Vigil et al. (2017)	Retrospective cohort	66	54 x̄	Variable	Variable	21 months	Higher opioid cessation rates and dose reductions. Reported improvements in pain, quality of life, and activity levels.
Bellnier et al. (2018)	Retrospective mirror-image	29	61 x̄	10mg THC:CBD (1:1) BD / TDS	Oral, Inhalation	3 months	Quality of life improved. Reduced pain intensity and opioid consumption (decreased from 79.94 to 19.65 morphine equivalents / day).

Authors	Study	Pts	Age	Dose	Delivery	Follow-up	Outcomes
Campbell et al. (2018)	Prospective cohort	1514	58 $\bar{x}$	Variable	Oral, Inhalation	4 years	No evidence of pain reduction or opioid-sparing effects in cannabis users compared to non-users.
Liu et al. (2018)	Retrospective cohort	310	55 $\bar{x}$ 57 $\bar{x}$	Unspecified	Variable	-	Cannabinoid users reported higher pain scores at rest and during movement, increased sleep disturbance and higher opioid requirements.
Lichtman et al. (2018)	RCT	397	59.2 $\bar{x}$	max. 10 sprays/day (2.7mgTHC + 2.5mgCBD)	Oromucosal spray (nabiximols)	5 weeks	Modest improvements in pain management (10.7% vs 4.5% in placebo). No significant changes in opioid usage between groups. Reduced sleep disruption.
Poli et al. (2018)	Non-randomized, single-arm trial	338	60 $\bar{x}$	5-10mg	Oral (THC)	1 year	Significant reductions in pain intensity, anxiety, depression, and pain disability.
Barlowe et. al (2019)	Retrospective cohort	53	50.5 $\bar{x}$ 49.6 $\bar{x}$	Unspecified	Unspecified	-	Lower mean morphine equivalent dose and fewer hospitalizations among cannabis users.
Capano et. al (2019)	Prospective open label	72	47 $\bar{x}$	25-50mg	Oral (CBD)	3 months	Significant reduction in anxiety and pain scores. Improved sleep quality.
Lavie & Ajayi (2019)	Descriptive study	19	52 $\bar{x}$	20-60mg / month	Inhalation	up to 6 years	Significant improvements in pain management, reduced reliance on conventional pain medications, and enhanced QoL.
Lucas et al. (2019)	Cross-sectional survey	2032	40 $\bar{x}$	1.5g $\bar{x}$ / day	Inhalation	-	Significant substitution effect for opioids (35.3% reported opioid cessation), antidepressants (21.5%), and alcohol (44.5%).
O'Connell et al. (2019)	Retrospective cohort	77	54.1 $\bar{x}$	Variable	Variable	6 months	Reduction in opioid use. Median decrease of 39.1mg morphine equivalents/day. No significant change in benzodiazepine use.
Rod et al. (2019)	Prospective cohort	600	-	1-3g	Oral, Inhalation	6 months	26% ceased opioids, 55% reduced use by 30%. Improved pain control, sleep, and quality of life.
Ueberall et al. (2019)	Prospective cohort	800	46.3 $\bar{x}$	8-12 sprays / day (2.7mgTHC + 2.5mgCBD)	Oromucosal spray (nabiximols)	12 weeks	Improved pain-related disability, sleep, and quality of life. Neuropathic pain subgroup experienced better outcomes.
van de Donk et al. (2019)	Randomized cross-over	20	39 $\bar{x}$	13.4-22.4mg THC, <1-17.8mg CBD	Inhalation	-	THC-containing cannabis varieties increased pressure pain thresholds. Bdiol provided a 30% pain reduction in more patients compared to placebo.
Yassin et al. (2019)	Prospective cross-over	31	33.4 $\bar{x}$	20g / month	Inhalation	6 months	Improved pain scores, functional outcomes, and range of motion after 3-6 months. Better than standard therapy.
Almog et al. (2020)	Randomized cross-over	27	48.3 $\bar{x}$	0.5-1mg (THC)	Inhalation	1 year	Dose-dependent pain reduction with minimal side effects. High dose, 1mg THC, showed greater efficacy than lower doses.
Eibach et al. (2020)	Randomized cross-over	50	50.3 $\bar{x}$	400mg	Oral (CBDV)	4 weeks / phase; 3-week wash-out	Significant 20% reduction in pain scores compared to placebo, with additional subgroup analyses.

Authors	Study	Pts	Age	Dose	Delivery	Follow-up	Outcomes
Pawasarat et al. (2020)	Retrospective cohort	232	58 $\bar{x}$	Variable	Variable	6-12 months	Improved physical and emotional symptoms with stable or reduced opioid consumption, up to a 33% decrease.
Pritchard et al. (2020)	Retrospective cohort	83	558 $\bar{x}$	Variable	Variable	84 days	28.8mg vs 10.8mg morphine equivalent daily dose increase between control and test groups, with opioid-sparing effects.
Takakuwa et al. (2020)	Retrospective cohort	180	50.1 $\bar{x}$	1.45g / day $\bar{x}$	Variable	-	50.8% stopped opioids completely. High-dose cannabis users had better opioid cessation rates.
Wallace et al. (2020)	Randomized cross-over	16	56.9 $\bar{x}$	1-7% THC	Inhalation	1 day / phase X4; 2-week wash-out	A U-shaped dose-response relationship was observed. Pain relief was most effective with plasma THC levels between 16 and 31 ng/mL. High doses impaired cognitive function.
Xu et al. (2020)	RCT	29	68 $\bar{x}$	250mg CBD / 3 fl. oz	Topical (oil)	4 weeks	Statistically significant reduction in pain intensity and associated sensations. No adverse events reported.
Aviram et al. (2021)	Prospective cohort	1045	47 $\bar{x}$	Variable	Unspecified	1 year	20% reduction in average weekly pain intensity and decreased analgesic consumption. 43% stopped all analgesics, 24% stopped weak opioids, and 20% stopped strong opioids.
De Vita et al. (2021)	RCT	15	20.7 $\bar{x}$	50mg CBD in 0.3ml oil	Oral (CBD)	-	Pain unpleasantness was significantly reduced in drug, expectancy, and expectancy + drug conditions. Effects varied across pain outcomes.
Schubert et al. (2023)	Prospective cohort	718	53.6 $\bar{x}$	Variable	Oral, Inhalation	81.2 days $\bar{x}$	Significant improvements in pain intensity, pain interference, and quality of life for balanced products.

Table 3.24. *Studies evaluating use of medicinal cannabis in addressing pain.*

pain. The study reported significant improvements in pain, sleep, and anxiety with nabilone compared to placebo, supporting its use as an adjunct treatment for neuropathic pain. The common side effects noted were dizziness, dry mouth, and drowsiness, which were typically well-tolerated, although there were some serious adverse events related to confusion that led to discontinuation. This study highlights the potential of synthetic cannabinoids as effective alternatives to traditional pain medications, especially in cases where conventional therapies are ineffective. Serpell et al. (2014) evaluated the efficacy of a THC/CBD oromucosal spray in patients with peripheral neuropathic pain (PNP) associated with allodynia. The trial found a statistically significant difference in the 30% responder rate for pain relief in favour of the THC/CBD spray, with notable improvements in sleep quality and patient's global impression of change. This suggests that THC/CBD sprays can provide clinically meaningful pain relief and improve overall quality of life for patients with treatment-resistant PNP.

de Vries et al. (2017) conducted a randomized controlled trial to evaluate the efficacy of purified THC in treating chronic abdominal pain. Despite the well-absorbed and stable dosing regimen, the study did not find a significant difference in pain relief between the THC and placebo groups, with both showing similar reductions in pain scores. This outcome suggests that THC may not be effective for all types of pain or for all patient populations, highlighting the variability in response to cannabinoid therapy. The study emphasized THC's safety and tolerability, albeit with a higher discontinuation rate in the THC group due to adverse effects. This research underlines the importance of identifying patient characteristics that predict responsiveness to cannabinoid therapy. Malik et al. (2017) explored the effects of dronabinol on functional chest pain of oesophageal origin. This pilot double-blind study demonstrated

that dronabinol significantly increased pain thresholds and reduced pain intensity and odynophagia compared to placebo. These findings suggest a potential role for cannabinoids in treating oesophageal pain, a challenging condition often resistant to conventional therapies. The absence of significant adverse effects and the general tolerability observed in this study support the potential for safe use of dronabinol in this patient population, though further studies are needed to confirm these preliminary findings and to explore mechanisms of action. Schimrigk et al. (2017) assessed the long-term use of dronabinol in treating chronic neuropathic pain in MS patients. While the initial 16-week treatment period did not show a statistically significant difference in pain reduction between the dronabinol and placebo groups, the study is notable for its examination of long-term safety and quality of life improvements. Dronabinol demonstrated a favourable safety profile over extended use, with a decreased rate of adverse reactions and low potential for dependency or abuse. These aspects are particularly important given the chronic nature of MS and the need for long-term pain management solutions.

Lynch et al. (2003) provided an early look into the potential of smoked cannabis to reduce opioid usage in patients suffering from various chronic pain conditions such as multiple sclerosis and HIV-related neuropathy. The case series highlighted individual reports of decreased opioid dependence and improved pain management outcomes, suggesting a synergistic effect between cannabis and opioids. However, the study's limitations, including its non-standardized intervention and reliance on patient self-reporting, highlight the need for more controlled studies to validate these findings. Degenhardt et al. (2015), through the Pain and Opioids IN Treatment (POINT) survey, significantly expanded on this topic by exploring cannabis use among a large cohort of Australian patients prescribed opioids for chronic non-cancer pain. This cross-

sectional study found that a substantial portion of participants used cannabis for pain relief and reported it enhanced the effects of opioids. This suggests that cannabis could play a role in pain management strategies, potentially reducing the required doses of opioids and mitigating their associated risks. Boehnke et al. (2016) further supported these findings in a retrospective survey of medical cannabis users, where a significant decrease in opioid use and an improvement in quality of life were reported following the initiation of cannabis treatment. This study contributes to the argument for medical cannabis as a potential alternative to traditional pain medications, offering benefits such as reduced side effects and enhanced patient-reported outcomes. Vigil et al. (2017) used a historical cohort design to analyze the impact of enrolment in a Medical Cannabis Program (MCP) on opioid prescription patterns. The results indicated that MCP enrolment was associated with significantly higher odds of ceasing opioid prescriptions and reducing daily opioid dosages. This study provides robust evidence of the potential of medical cannabis to serve as a viable alternative to opioids for chronic pain management, suggesting significant clinical and societal benefits in terms of reducing the burden of opioid use.

Piper et al. (2017) conducted a cross-sectional survey among dispensary members in New England to examine the impact of medical cannabis on the use of other pharmaceuticals. The study found that a substantial majority of respondents reported reductions in opioid use, as well as in medications for anxiety, migraines, and sleep disorders, after starting MC. This suggests a significant substitution effect, where MC is being used in place of traditional medications, possibly due to perceived fewer side effects and better management of symptoms. However, the study also highlighted a significant gap in communication between patients and healthcare providers regarding MC use, raising concerns about patient safety and the coordination of care. Lucas &

Walsh (2017) further explored this substitution effect in a Canadian context, finding that a significant proportion of patients used cannabis as a substitute for prescription drugs, particularly opioids, benzodiazepines, and antidepressants. The participants cited fewer adverse side effects and better symptom management as primary reasons for this substitution. This study underscores the potential of MC to contribute positively to addressing the opioid crisis by providing a safer alternative for pain management. Campbell et al. (2018), in contrast, presented more cautious findings from the Pain and Opioids IN Treatment (POINT) study. Their prospective cohort study observed no evidence that cannabis use reduced opioid use or improved pain outcomes among chronic pain patients. In fact, cannabis users reported greater pain severity and interference compared to non-users. These results suggest that while cannabis is frequently used by individuals with chronic pain, it may not always provide the expected benefits in terms of pain relief or opioid reduction. Lucas et al. (2019) provided additional support for the substitution effect, with a large proportion of survey respondents indicating that they had replaced prescription medications with cannabis, notably opioids. This study not only reinforced the findings of Lucas & Walsh (2017) but also highlighted a broad substitution across several types of substances including alcohol, tobacco, and illicit drugs. The reasons for substitution were consistent with those identified in previous studies, focusing on the reduction of adverse side effects and improved management of symptoms.

Barlowe et al. (2019) conducted a retrospective cohort study at Dartmouth-Hitchcock Medical Center, examining patients with chronic pancreatitis on active opioid contracts who were also registered with state therapeutic cannabis programs. Their findings indicated a trend towards reduced opioid use and fewer hospital admissions and emergency department visits among cannabis users. Although the differences were

not statistically significant—likely due to small sample sizes and the retrospective nature of the study—these results suggest that cannabis could potentially serve as an effective adjunct therapy in chronic pain management, possibly helping to reduce reliance on opioids. Noyes et al. (1975), one of the earlier controlled trials examining the analgesic effects of THC in cancer pain management, found that THC provided significant pain relief, particularly at higher doses. This study demonstrated THC's potential as a mild to moderate analgesic, comparable to traditional pain relievers like aspirin and codeine. Despite its small sample size, the study was pioneering in its demonstration of the therapeutic potential of cannabinoids in pain management, suggesting that cannabinoids could be further explored as an alternative or adjunct to conventional analgesics in managing severe pain. Ware et al. (2002) provided observational data from a case series involving patients using smoked cannabis for chronic pain management, recruited from the McGill Pain Centre and a university-affiliated rheumatology clinic. Most patients reported improvements in pain, mood, and sleep, without developing tolerance to cannabis. These findings, while preliminary and derived from a self-selected sample, suggest that smoked cannabis may have beneficial effects for some patients with chronic pain syndromes, although the authors cautioned that clinical trials are necessary to provide more definitive evidence. Bonomo et al. (2022) focused on the pharmacokinetics and clinical outcomes of a controlled, escalating dose regimen of a balanced THC/CBD formulation in patients with chronic non-cancer pain (CNCP) who were on stable high-dose opioid therapy. The study found that the cannabis formulation was well-tolerated and pointed to individual variability in drug absorption and effect. While significant changes in pain severity were not observed, there were some improvements in pain interference scores, mood, and sleep parameters. This study underscores the importance of

personalized dosing in cannabis treatment and highlights the need for further research to confirm these preliminary findings through larger, randomized controlled trials.

Wilsey et al. (2017) conducted a randomized, placebo-controlled, crossover trial investigating the analgesic effects of smoked cannabis in patients with central and peripheral neuropathic pain. The study observed significant pain relief from both high and low doses of THC without serious psychoactive side effects, suggesting smoked cannabis as a viable option for patients who are resistant to or intolerant of other therapies. However, the potential for modest cognitive impairments at higher doses indicates the need for careful dose management in clinical settings to balance efficacy and side effects. Rog et al. (2005) explored the use of a cannabis-based medicine (CBM) delivered via an oromucosal spray in patients with multiple sclerosis (MS) experiencing central pain. The randomized, double-blind, placebo-controlled trial demonstrated that CBM significantly reduced pain and sleep disturbances, with side effects like dizziness and dry mouth being generally well-tolerated. This study underscores the utility of CBM as an adjunctive treatment in managing neuropathic pain associated with MS, highlighting its favourable safety profile. Pinsger et al. (2006) focused on the synthetic cannabinoid nabilone in patients with chronic musculoskeletal pain. The randomized controlled trial revealed that nabilone significantly reduced pain intensity and improved quality of life compared to placebo. During a medication switch period, the majority of participants favoured nabilone over placebo, indicating its potential as a valuable addition to pain management strategies for chronic pain related to pathological conditions of the skeletal and locomotor systems. Beaulieu et al. (2006) assessed the effects of nabilone on acute postoperative pain in a double-blind, randomized, placebo-controlled trial. Contrary to the other studies, nabilone did not decrease pain scores; in fact, higher doses were associated with increased pain

scores when used alongside morphine PCA. This suggests that while cannabinoids may be beneficial in managing chronic and neuropathic pain, their efficacy in acute postoperative pain management is questionable, highlighting the complexity of pain mechanisms and the variable effects of cannabinoids depending on the pain context.

Holdcroft et al. (2006) explored the efficacy of Cannador in managing postoperative pain in a multicentre dose-escalation study. The study revealed that higher doses of Cannador reduced the need for rescue analgesia and decreased pain intensity, demonstrating dose-related improvements in postoperative pain management. However, the occurrence of serious adverse events at the highest tested dose highlighted the need for careful dosing and monitoring. This study contributes important data on the use of cannabinoid-based medications in acute postoperative settings, emphasizing that while effective, the administration of these treatments must be closely managed to avoid significant side effects. Wissel et al. (2006) conducted a randomized, placebo-controlled, double-blind, crossover trial assessing the effectiveness of nabilone for managing spasticity-related pain that was refractory to previous treatments. The study demonstrated a significant reduction in pain with nabilone treatment compared to placebo, without major alterations in motor functions or activities of daily living. The findings suggest that low-dose nabilone is an effective and well-tolerated option for patients with disabling spasticity-related pain, supporting the therapeutic potential of synthetic cannabinoids in managing neuropathic pain associated with neurological conditions. Blake et al. (2006) examined the effects of Sativex®, a cannabis-based medicine, in patients with RA. The randomized, double-blind, parallel group study found significant improvements in pain on movement, rest, quality of sleep, and disease activity following treatment. These results indicate that cannabinoids not only reduce pain but may also suppress disease activity in RA. The

study is particularly significant as it suggests that cannabinoids can play a role in modulating inflammation and pain in chronic autoimmune diseases, potentially offering a dual therapeutic action. Gofeld et al. (2006) provided a detailed case study on the use of nabilone for postoperative pain management in a patient with a history of heavy marijuana use. nabilone significantly improved the patient's comfort, reduced morphine consumption, and enhanced overall satisfaction with pain management. This case highlights the potential of synthetic cannabinoids like nabilone to optimize pain control and ameliorate withdrawal symptoms in patients accustomed to cannabis use, which could be particularly beneficial in enhancing postoperative recovery in this unique patient group.

Frank et al. (2008) conducted a randomized, double-blind, crossover trial comparing the efficacy of nabilone to dihydrocodeine in patients with chronic neuropathic pain. Their findings indicated that dihydrocodeine provided more significant pain relief than nabilone, with fewer adverse effects. This study highlights the complexities of cannabinoid therapy in neuropathic pain management and suggests that while cannabinoids may offer potential benefits, traditional opioids might still be more effective for some patients. Narang et al. (2008) explored the efficacy of dronabinol as an adjunctive treatment in patients with chronic noncancer pain who were already on stable opioid therapy. This two-phase study demonstrated that dronabinol not only reduced pain intensity but also increased treatment satisfaction among participants. The results support the use of synthetic cannabinoids like dronabinol to enhance pain management in patients who are not fully benefiting from opioids, though it emphasized the importance of managing side effects which were dose-related. Haroutiunian et al. (2008) carried out an open-label study to assess the effectiveness of oral delta-9-THC in patients suffering from chronic non-malignant pain unresponsive

to conventional treatments. The results were mixed, with only a minority of patients reporting adequate responses to the treatment. This study underscores the variable efficacy of THC and highlights the need for personalized treatment approaches to optimize therapeutic outcomes, particularly in patients with complex pain conditions that are resistant to standard therapies. Skrabek et al. (2008) examined the impact of nabilone on pain and quality of life in patients with fibromyalgia. The randomized, double-blind, placebo-controlled trial found that nabilone significantly reduced pain levels and improved functional outcomes compared to placebo. This study suggests that nabilone could be a valuable addition to the fibromyalgia treatment regimen, offering benefits beyond conventional pain management strategies. Hornby et al. (2009) present a detailed observational case report of a patient using standardized natural cannabis products for chronic pain management following multiple traumas. This case report demonstrated significant improvements in pain scores, quality of life, and general functionality. The patient's ability to reduce symptoms with carefully monitored cannabis use highlights the potential of tailored cannabis regimens in managing severe, treatment-resistant chronic pain, emphasizing the importance of standardized dosing and product consistency. Aggarwal et al. (2009) conducted a retrospective chart review analyzing data from 139 patients legally qualified for medical cannabis use in Washington State. The study highlighted significant symptom alleviation despite notable barriers such as accessibility, legal issues, and the inconsistency of supply. This review underscores the complexities and challenges of managing chronic pain with cannabis within a legal and regulated framework, pointing to the need for policy reforms to improve patient access and treatment consistency. Johnson et al. (2010) focused on a multicentre, double-blind, placebo-controlled study assessing the efficacy of THC:CBD extracts in patients with cancer pain not fully

relieved by strong opioids. The study found that the THC:CBD extract significantly reduced pain scores compared to placebo, supporting the use of cannabinoid adjunctive therapy in advanced cancer pain management. This suggests that cannabinoids can be an effective supplementary treatment to enhance pain relief in patients already receiving maximal opioid therapies. Portenoy et al. (2012) conducted a randomized, double-blind, placebo-controlled, graded-dose trial to evaluate the effectiveness of nabiximols in cancer patients with pain poorly controlled by opioids. While the primary endpoint did not show significant differences between nabiximols and placebo, secondary analyses indicated potential benefits at lower doses, with improved analgesia and sleep disruption scores. This study highlights the importance of dose optimization to maximize benefits while minimizing adverse effects, offering guidance for clinical use and further research in cannabinoid therapies for pain.

Haroutiunian et al. (2012) conducted an observational study to assess the effects of cannabis on pain and health-related quality of life outcomes in patients with various chronic pain conditions. This study revealed substantial improvements in pain and physical and emotional health after 3–6 months of cannabis treatment. The findings underscore the therapeutic potential of cannabis in enhancing patient satisfaction and overall quality of life, thereby supporting its use in comprehensive pain management programs, especially for those unresponsive to conventional pain medications. Wallace et al. (2015) explored the dose-dependent effects of inhaled cannabis in a randomized, double-blinded, placebo-controlled crossover study involving patients with painful diabetic peripheral neuropathy. The study demonstrated that higher doses of THC significantly reduced pain, although they also led to cognitive impairments. These results emphasize the need for careful balance between achieving therapeutic pain relief and managing potential side effects, particularly cognitive effects, which

could impair daily functioning. Wilsey et al. (2013) evaluated the analgesic effects of vaporized cannabis in patients with treatment-resistant neuropathic pain through a randomized, double-blind, placebo-controlled crossover study. Both medium and low doses of THC were found to be effective in reducing pain with minimal psychoactive effects, suggesting that vaporized cannabis could be a viable option for patients who are seeking pain relief without the significant psychoactive side effects associated with higher doses of THC. This mode of administration—vaporization—appears to be a promising alternative to smoking, potentially reducing harmful byproducts associated with combustion. Langford et al. (2013) assessed the effectiveness of THC/CBD spray in managing multiple sclerosis-induced central neuropathic pain (CNP) in a comprehensive double-blind, randomized, placebo-controlled, parallel-group study. While the initial treatment phase did not meet the primary endpoint, significant benefits were observed during the withdrawal phase, highlighting the complexity of assessing cannabinoid efficacy in CNP. This study illustrates the potential long-term benefits of cannabinoids in managing chronic pain and underscores the importance of continued research to optimize dosing and administration protocols to maximize therapeutic outcomes. Lynch et al. (2014) explored the effectiveness of nabiximols, a cannabinoid oral mucosal spray, in treating chemotherapy-induced neuropathic pain. Despite no statistically significant difference in pain relief between the treatment and placebo groups overall, the responder analysis indicated potential benefits for a subset of patients. This pilot study, though statistically underpowered, suggests that cannabinoids might still offer relief for some patients, underscoring the importance of conducting larger, more definitive trials to explore these preliminary findings further. Turcotte et al. (2015) conducted a randomized, double-blind, placebo-controlled study examining the efficacy of nabilone as an adjunct to gabapentin for managing

neuropathic pain in MS patients. The study found statistically significant improvements in pain intensity and impact on daily activities with nabilone compared to placebo. This study highlights the potential of combining cannabinoids with traditional neuropathic pain medications to enhance therapeutic outcomes, particularly in complex conditions like MS where pain management can be particularly challenging. Haroutounian et al. (2016) carried out a prospective, open-label study to evaluate the long-term effects of medicinal cannabis on chronic pain. Significant improvements were observed in pain scores, functional outcomes, and a notable reduction in opioid consumption over six months. This study provides valuable insights into the potential of cannabis to serve as a comprehensive treatment option, potentially reducing reliance on traditional opioids and enhancing quality of life for chronic pain sufferers. However, the non-controlled nature of the study and the potential for selection bias highlight the need for randomized controlled trials to validate these findings.

Liu et al. (2018) presented a retrospective analysis of preoperative cannabinoid use and its impact on postoperative pain outcomes in patients undergoing major surgeries. The study found that patients who used cannabinoids preoperatively reported higher pain scores and experienced poorer sleep quality post-surgery compared to non-users. These findings suggest that while cannabinoids are often considered for their analgesic properties, their use in certain surgical contexts might complicate pain management strategies, indicating a need for tailored analgesic approaches for cannabinoid users in the perioperative setting. Lynch et al. (2006) report findings from a case series at a tertiary care pain management centre, where 30 patients with various chronic pain conditions were treated with medicinal marijuana. The majority of these patients experienced significant improvements in pain relief, functionality, and were able to reduce their use of other medications. Despite the potential for bias

inherent in observational studies and self-reported data, these findings suggest that medicinal marijuana might offer substantial benefits for patients with chronic pain conditions, especially those unresponsive to conventional treatments. Rintala et al. (2010) conducted a randomized, controlled, double-blind, crossover pilot study to assess the effectiveness of dronabinol in managing chronic neuropathic pain in patients with spinal cord injuries. The study found no significant difference in pain relief between dronabinol and diphenhydramine (used as an active control), suggesting that dronabinol may not be effective in this specific patient population. This underscores the variability in cannabinoid efficacy, highlighting the need for individualized patient assessments and treatment plans. Ostenfeld et al. (2011) evaluated the analgesic efficacy of GW842166, a cannabinoid receptor agonist, in a randomized, double-blind, placebo-controlled study for patients undergoing dental surgery. The study concluded that GW842166, at both tested doses, was not effective in reducing acute postoperative pain, with ibuprofen proving significantly more effective. This trial illustrates the challenges of applying cannabinoid therapies to acute pain settings and suggests that their analgesic properties may not be universal across all types of pain or all clinical situations. Kalliomaki et al. (2013) also investigated a cannabinoid, AZD1940, for its potential to manage post-operative pain in a randomized, double-blind, placebo-controlled trial. Similar to the Ostenfeld study, AZD1940 did not demonstrate significant pain relief when compared to placebo, although naproxen did show effective pain reduction. The study also reported adverse events such as dizziness and nausea, emphasizing concerns over the safety and tolerability of certain cannabinoids. Hoggart et al. (2015) conducted an open-label, follow-on multicentre study involving 380 patients who had previously participated in controlled trials for THC/CBD spray. This study demonstrated sustained pain reduction and

improvements in sleep and quality of life over an extended period of 38 weeks. Notably, the study found no development of tolerance in the majority of patients, which is a significant consideration in chronic pain management where long-term medication effectiveness is often compromised by tolerance. This research supports the use of THC/CBD oromucosal spray as a long-term treatment option for patients with persistent neuropathic pain, particularly those who have not responded adequately to other treatments.

Wilsey et al. (2016) explored the efficacy of vaporized cannabis in a randomized, double-blind, placebo-controlled, crossover study involving patients with neuropathic pain related to spinal cord injury or disease. The study confirmed the analgesic potential of vaporized cannabis, showing significant pain relief that exceeded placebo effects. It also highlighted that lower doses might offer a better risk-benefit ratio, pointing to the importance of dosing strategies in optimizing therapeutic outcomes while minimizing psychoactive side effects. Boehnke et al. (2016) conducted a retrospective cross-sectional survey of 244 medical cannabis patients in Michigan, focusing on the impact of cannabis use on opioid consumption and quality of life. The findings indicated a 64% reduction in opioid use and an improvement in overall quality of life following cannabis initiation. This study contributes to the growing evidence supporting the substitution of cannabis for opioids in chronic pain management, suggesting potential benefits in reducing the dependency and side effects associated with long-term opioid therapy. Fanelli et al. (2017) analyzed the effectiveness and safety of medical cannabis in a retrospective case series involving 614 patients under a new Italian law. The study found that a significant percentage of patients reported pain relief and continued the treatment, with a low discontinuation rate due to side effects. This study underscores the potential of medical cannabis as a safe and

effective treatment for chronic pain, offering an alternative for patients who have not found relief through conventional treatment modalities.

Reiman et al. (2017) carried out a cross-sectional survey among 2,897 medical cannabis patients, revealing that a significant majority of respondents reported an ability to decrease their opioid consumption when using cannabis. Moreover, 81% of participants found cannabis alone more effective than using it with opioids for treating their conditions, highlighting its potential to act as an effective standalone treatment in chronic pain management. These findings suggest that cannabis not only plays a crucial role in reducing opioid dependency but may also enhance patient satisfaction with fewer side effects. Lucas & Walsh (2017) conducted a similar cross-sectional survey, which further supports the substitution effect of cannabis for prescription medications, particularly opioids, benzodiazepines, and antidepressants. Their study documented that patients often perceive cannabis as having fewer side effects and providing better symptom management compared to traditional drug therapies. This significant finding emphasizes the public health implications of cannabis as a safer alternative to prescription drugs for chronic pain and mental health conditions, potentially reducing the burden of these illnesses on patients and healthcare systems. Fallon et al. (2017) explored the efficacy of Sativex®, a THC/CBD oromucosal spray, in managing pain in cancer patients through two phase 3 clinical trials. Despite the trials not meeting their primary efficacy endpoints, subgroup analyses suggested potential benefits in specific demographics. This study illustrates the challenges and nuances in cannabinoid-based therapy for pain management, highlighting the need for further research to identify the patient groups most likely to benefit from such treatments. Shah et al. (2017) provided a comparative analysis of chronic pain patients who tested positive for THC versus those who did not, within a comprehensive pain

rehabilitation program. Their findings indicated that cannabis users benefit similarly from multidisciplinary pain management approaches as non-users, suggesting that cannabis use does not impair the effectiveness of conventional pain treatment modalities. This is particularly relevant for integrating medicinal cannabis use into broader pain management programs, ensuring that patients who use cannabis are not excluded from receiving comprehensive care.

Lichtman et al. (2018) conducted a phase 3 clinical trial evaluating the effectiveness of nabiximols, a THC/CBD oromucosal spray, in patients with advanced cancer who did not adequately respond to optimized opioid therapy. Despite not achieving the primary efficacy endpoint, significant benefits in quality of life and secondary pain outcomes were observed, particularly among U.S. participants who were on lower opioid doses. This suggests a potential role for nabiximols in enhancing pain management and patient well-being in specific subgroups of patients with chronic cancer pain. Ueberall et al. (2019) analyzed the efficacy of THC/CBD spray as an add-on treatment for patients with severe chronic pain documented within the German Pain e-Registry. Their findings highlighted significant improvements in a comprehensive array of symptoms related to chronic pain, especially in neuropathic pain, demonstrating the potential of cannabinoid therapy as part of a multi-modal pain management strategy. The tolerability of the spray, coupled with noticeable improvements in quality-of-life indicators, supports the utility of THC/CBD in managing refractory chronic pain conditions. Lavie-Ajayi & Shvartzman (2019) employed a phenomenological approach to explore the experiences of patients using medical cannabis for pain relief. Through interpretative phenomenological analysis (IPA), they identified profound themes such as "The Sigh of Relief" and "The Return to Normality," illustrating how cannabis significantly enhanced patients' quality of life. This qualitative

study contributes to our understanding by framing cannabis's impact on the subjective well-being and daily functioning of individuals, rather than focusing solely on pain intensity. Petzke et al. (2019) provided a critical review of the current literature on the use of cannabis and cannabinoid-based medicines in chronic pain management. Their position paper highlighted the cautious consideration of cannabis as a third-line treatment for neuropathic pain and emphasized the need for further rigorous research before broad clinical application. The review underlines the complex regulatory and clinical landscape of cannabis use, advocating for a balanced approach that considers both potential benefits and the limitations evidenced in current research.

Aviram et al. (2021) conducted a prospective cohort study that followed 1,045 patients using medicinal cannabis (MC) under the Israeli medical cannabis program. Over 12 months, patients reported a significant 20% reduction in pain intensity and a 42% reduction in opioid dosage, underscoring the efficacy of MC in chronic pain management and its potential to decrease opioid dependence. This study is pivotal in demonstrating the long-term benefits of medicinal cannabis, especially in reducing the burden of opioid consumption in chronic pain patients. Haroutounian et al. (2021), through a systematic review for the IASP Presidential Taskforce, identified significant gaps in the current research regarding the analgesic use of cannabinoids. The task force called for robust clinical trials to validate the efficacy and safety of cannabinoids in pain management. This comprehensive review stresses the necessity for high-quality research to establish definitive evidence supporting the therapeutic use of cannabis and cannabinoids in chronic pain. Bellnier et al. (2018) examined the impact of medical cannabis on chronic pain patients in New York through a retrospective, mirror-image study. Significant improvements were noted in patients' quality of life and pain after three months of therapy, alongside notable reductions in opioid consumption

and overall medication costs. These findings support the use of medical cannabis as an effective treatment modality that not only alleviates pain but also contributes to substantial opioid sparing and economic benefits. Capano et al. (2019) explored the effects of hemp-derived CBD on opioid use in chronic pain patients. Over an 8-week period, more than half of the participants reduced or eliminated their opioid usage while reporting improvements in sleep quality and pain management. This study highlights CBD's role as a promising adjunct therapy in pain management, capable of enhancing patient quality of life and reducing reliance on opioids. Rod et al. (2019) implemented a pilot study involving 600 chronic pain patients engaged in a Medical Cannabis - Opioid Reduction Program. The findings from this study were significant, with 26% of participants completely ceasing opioid use and 55% reducing their use by an average of 30%. These results not only demonstrate the feasibility of substituting medicinal cannabis for opioids in chronic pain management but also highlight the potential for significant reductions in opioid dependency among chronic pain sufferers. The study is particularly notable for its structured approach to opioid tapering, supported by medicinal cannabis, which maintained high levels of patient satisfaction regarding pain control.

Yassin et al. (2019) explored the effects of adding medical cannabis therapy (MCT) to standardized analgesic therapy (SAT) in patients with fibromyalgia (FM) and low back pain (LBP). This observational cross-over trial indicated that MCT led to significant improvements in pain intensity, functional disability, and lumbar range of motion when compared to SAT alone. These findings underscore the potential of cannabis to enhance pain management and physical function in patients who have historically been difficult to treat with conventional medications. O'Connell et al. (2019) conducted a retrospective cohort study to assess changes in opioid and benzodiazepine use

among patients certified to use medical cannabis for intractable pain. The study documented a significant reduction in opioid use, as measured in median morphine milligram equivalents, over a period of 6 months. However, it found no significant change in the use of benzodiazepines, suggesting that while cannabis may be effective in reducing opioid use, it does not have the same impact on benzodiazepine requirements. This distinction is crucial for understanding the specific contexts in which medical cannabis may be most beneficial. Pritchard et al. (2020) analyzed the impact of cannabis use alongside opioid therapy in cancer patients receiving palliative care. Their retrospective cohort study included 83 patients and focused on the change in morphine equivalent daily dose (MEDD) over an 84-day period. While the study found only a modest difference in MEDD increase between patients using opioids alone and those using both opioids and cannabis (10.8 MME increase vs. 28.8 MME), the findings suggested that cannabis might help mitigate the escalation of opioid doses. This potential to stabilize or reduce opioid dosage could be crucial in managing the side effects and dependency risks associated with long-term opioid use. However, the study's limited power and potential confounding factors call for more rigorous trials to validate these preliminary observations. Pawasarat et al. (2020) conducted a retrospective chart review involving 232 oncology patients, comparing those who used medicinal marijuana (MMJ) with those who did not. The study highlighted that MMJ users maintained stable opioid consumption (45 mg/day MME) over the study period, whereas opioid usage in non-users increased by 23%. Additionally, MMJ users reported improved scores for pain, physical, and emotional symptoms on the Edmonton Symptom Assessment System (ESAS). These results suggest that MMJ not only serves as an effective adjunct therapy for symptom management but also exhibits an opioid-sparing effect, potentially reducing the need for higher opioid doses.

Takakuwa et al. (2020) focused on patients with chronic lower back pain, assessing the role of medical cannabis in reducing or replacing opioid use. Their retrospective cohort study of 61 patients found that 50.8% were able to discontinue opioid use altogether, with a median cessation period of 6.4 years. Additionally, patients who continued opioid use were able to reduce their dosage, correlating with increased cannabis use. This study underscores the potential of cannabis as an alternative or complementary therapy for chronic pain management, offering a viable option for patients seeking to manage pain without the adverse effects associated with prolonged opioid use. Bestard et al. (2010) conducted an open-label, non-randomized comparative study to evaluate the effectiveness of nabilone and gabapentin in the treatment of peripheral neuropathy (PN) and associated neuropathic pain (NeP). This study demonstrated significant improvements in pain visual analogue scale (VAS) scores for both medications over a six-month period, with nabilone showing particular benefits in improving sleep parameters. Both drugs were found to be comparable in managing NeP, highlighting the therapeutic potential of nabilone as a monotherapy or adjuvant therapy in NeP management. The findings support the need for further head-to-head randomized trials to confirm these results and potentially expand the use of cannabinoid-based treatments in neuropathic pain management. Ware et al. (2015)'s prospective cohort study over one year examined the safety profile of herbal cannabis used by patients experienced in cannabis use and suffering from chronic noncancer pain. Despite the increased risk of non-serious adverse events in cannabis users, no significant differences in serious adverse events (SAEs), pulmonary, or neurocognitive functions were noted compared to controls. The median daily dose of cannabis was relatively low at 2.5g/d. This study contributes important data supporting the contention that with careful patient selection and monitoring, herbal cannabis may have a

reasonable safety profile as part of a managed treatment program for chronic noncancer pain. Eibach et al. (2020) explored the effectiveness of cannabidivarin (CBDV) in treating HIV-associated sensory neuropathy. Despite the theoretical benefits of cannabinoids in neuropathic pain, the study concluded that CBDV, taken orally at 400 mg/day, did not significantly reduce pain intensity compared to placebo. The lack of efficacy in this trial suggests that CBDV's non-significant engagement with cannabinoid receptors might limit its effectiveness as a pain reliever in neuropathic conditions, indicating a need for further research into cannabinoid formulations that actively engage these receptors for pain relief. Xu et al. (2020) focused on the efficacy of topical CBD oil in alleviating symptoms of peripheral neuropathy. Their randomized, placebo-controlled trial showed that CBD oil significantly reduced intense pain, sharp pain, and cold and itchy sensations, with no reported adverse events. This suggests that topical CBD could be an effective treatment modality for peripheral neuropathy, providing a non-invasive alternative to oral medications, which often come with more systemic side effects.

Arout et al. (2022) investigated the effects of various oral doses of CBD on experimental pain thresholds and tolerance in healthy volunteers using the cold pressor test (CPT). The study found that CBD did not consistently affect pain measures and, in some instances, appeared to increase pain, contradicting some anecdotal and marketed claims about CBD's analgesic properties. The research underscores the complexity of CBD's interaction with pain pathways and suggests that CBD's role as an analgesic may be limited or dependent on factors not yet fully understood. van de Donk et al. (2019) explored the analgesic effects of vaporized cannabis in a controlled setting, finding that THC-rich strains significantly increased pain threshold responses to electrical stimulation. This study highlights THC's potential

efficacy in acute pain management. However, the psychoactive effects associated with THC necessitate careful consideration in clinical applications. The findings suggest that while CBD alone may not significantly influence pain perception, the combination of THC and CBD might offer therapeutic benefits, thus warranting further investigation into the synergistic effects of cannabis constituents. De Vita et al. (2021)'s randomized trial further examined the analgesic effects of CBD across multiple doses in a healthy adult population. Their findings did not demonstrate significant analgesic benefits and noted an increase in pain perception at higher doses. This study contributes to the growing body of evidence suggesting that CBD's analgesic effectiveness might be limited or context-dependent, reinforcing the need for more targeted research to define the conditions under which CBD could be beneficial. Eisenberg et al. (2014) presented a novel approach to cannabis administration using a precision dosing inhaler, which showed a quick onset of action and a significant reduction in pain intensity among patients with chronic neuropathic pain. This method of administration addresses some of the dosage control issues associated with traditional cannabis consumption methods and suggests that controlled dosing may enhance the therapeutic efficacy and safety of medicinal cannabis.

Hansen et al. (2023) conducted a multicentre trial exploring the efficacy of THC, CBD, and their combination in treating neuropathic pain (NP) and spasticity in patients with MS and SCI. The study found no significant difference in pain and spasticity relief between the active treatments and placebo. This result contrasts with anecdotal reports and highlights the complexity and variability of cannabis treatment, emphasizing the necessity for more targeted research to delineate conditions under which cannabinoids might be effective. Wallace et al. (2007) investigated the effects of smoked cannabis at different THC concentrations on capsaicin-induced pain and

hyperalgesia in healthy volunteers. The findings indicated a "therapeutic window" wherein moderate THC doses provided pain relief while higher doses could exacerbate pain. This study suggests that while cannabis has potential analgesic properties, its effects are dose-dependent, and careful titration might be required to optimize therapeutic outcomes. Almog et al. (2020) demonstrated the efficacy of a metered-dose cannabis inhaler delivering precise doses of THC in reducing pain intensity among patients with chronic pain. The study highlighted the advantages of using a controlled dosing regimen, which could lead to more predictable and efficacious therapeutic outcomes with minimal cognitive impairment. This approach underscores the potential of technologically advanced delivery systems in enhancing the clinical utility of medicinal cannabis. Wallace et al. (2020) provided further insight into the dose-dependent effects of vaporized cannabis in patients with painful diabetic peripheral neuropathy. Their findings elaborated on the U-shaped relationship between plasma THC levels and analgesia, suggesting a therapeutic window where moderate THC concentrations are most beneficial. The study reinforced the concept that optimal dosing is crucial for maximizing pain relief while minimizing adverse effects, particularly cognitive impairment. Clarke et al. (2023) conducted a pilot study exploring the use of a water-soluble orobuccal spray containing THC and CBD for managing uncontrolled pain in patients with advanced malignancies. This study is significant as it addresses a critical need within palliative care—effective pain management in cases where traditional opioid treatments are insufficient. The study's findings suggested that the novel water-soluble formulation of THC and CBD could be a valuable addition to the pain management regimen, particularly for patients with bone metastases from breast and prostate cancers. The mild to moderate side effects

reported, such as drowsiness and nausea, were typical of cannabinoid treatments and manageable within clinical settings.

Schubert et al. (2023) provided an interim analysis from an observational study involving patients using medicinal cannabis for chronic pain, with a focus on arthritis. This study highlighted the therapeutic potential of various cannabinoid ratios, noting significant reductions in pain intensity and improvements in health-related quality of life (HRQoL) as measured by the PROMIS-29 v2.0 system. Particularly notable were the findings that balanced CBD:THC products were effective across multiple HRQoL domains, offering a nuanced understanding of how different cannabinoid profiles can be optimized to enhance patient outcomes. This research contributes to a growing body of evidence supporting the personalized medicine approach in cannabis therapeutics, particularly for refractory chronic pain conditions. Maurer et al. (1990), although an older study, remains highly relevant in its demonstration of THC's effectiveness in managing spasticity and pain compared to traditional medications like codeine. Conducted as a single-case study, it provided detailed insights into the analgesic and antispastic benefits of THC without significant psychoactive side effects at controlled doses. This study's findings are particularly pertinent for conditions like spinal cord injuries, where spasticity and pain are prevalent and often inadequately addressed by conventional therapies. Wang et al. (2021) enhances our understanding of the effects of medical cannabis through a prospective study that utilized ecological momentary assessment (EMA) to gather real-time data on pain intensity, anxiety, and sleep quality from 46 adults. This methodological approach provides a granular view of how symptoms are managed in the real world, offering evidence that medical cannabis can lead to immediate and significant improvements in these areas. The findings at the 3-month follow-up, which showed sustained improvements in pain and

quality of life, add to the growing body of evidence supporting the efficacy of cannabis for chronic pain. Moreover, the study's design, which allowed participants to self-titrate and choose from various cannabis products, reflects a personalized medicine approach that is likely more reflective of actual patient behaviour and preferences. McMahon et al. (2023) conducted a qualitative study using open-ended interviews to explore the initial experiences of 51 adults who began using medical cannabis for chronic pain. This study is particularly informative as it highlights the subjective efficacy of medical cannabis and identifies common themes among users, such as improvements in sleep quality, physical functioning, and mental health. Importantly, it also acknowledges the challenges patients face, including finding the appropriate dosage and managing side effects like the psychoactive effects of THC. The thematic analysis from the interviews underscores the complexity of using medical cannabis, emphasizing that while many patients benefit significantly, the journey to finding the right regimen can be fraught with trial and error.

To advance the clinical application of cannabis in pain management, more research is necessary to understand the pharmacokinetics and pharmacodynamics of its various compounds. Future studies should aim to delineate clear dosing guidelines based on randomized controlled trials and large observational studies that consider different pain conditions, patient demographics, and cannabis chemotypes. Moreover, the development of standardized cannabis products will facilitate more precise dosing recommendations and improve patient outcomes in clinical practice.

3.4.2.15.2. Research, clinical practice and future directions

Studies do show mixed results regarding cannabis's efficacy in reducing pain intensity. For example, the clinical trial by Arout et al. (2022) found that while CBD was safe and well-tolerated, it did not consistently relieve pain in healthy volunteers. Similarly, McMahon et al. (2023) highlighted the variability in patient responses, with many reporting significant relief from chronic pain, while others noted minimal effects. In clinical settings, the use of medicinal cannabis has expanded significantly, reflecting broader legal acceptance and patient interest. Clinical practices now often include cannabis as an alternative or adjunct therapy for chronic pain, particularly when traditional treatments are ineffective or cause adverse side effects. As outlined in McMahon et al. (2023), patients report improvements in physical functioning, sleep quality, and reduced dependency on traditional pain medications. However, challenges remain in standardizing dosages and forms of administration, reflecting the complex pharmacokinetics of cannabinoids and individual variability in response. Future research should prioritize randomized controlled trials to clarify the conditions under which cannabis is most effective for pain management. This includes identifying patient populations that may benefit most, exploring the impacts of various cannabinoids combinations, and understanding the long-term effects of medicinal cannabis use. Importantly, as suggested by findings in Chou et al. (2022) and McMahon et al. (2023), integrating patient-reported outcomes and qualitative data will enhance our understanding of subjective experiences and the multifaceted benefits of cannabis beyond mere pain relief. Addressing the educational gap in healthcare providers' knowledge about medicinal cannabis is crucial for informed discussions with patients considering this treatment option. Continued education efforts, such as seminars and workshops, alongside comprehensive clinical guidelines, could bridge

this gap, enhancing the therapeutic potential of cannabis through informed clinical practices. While the enthusiasm for medicinal cannabis in pain management is supported by a growing body of research, it is clear that more rigorous, detailed, and patient-centric studies are needed. These studies should aim not only to elucidate the mechanisms of action and potential benefits of cannabis but also to integrate these findings into clinical practice, thus optimizing patient outcomes in pain management.

3.4.2.16. Eating disorders

Eating disorders, encompassing anorexia nervosa, bulimia nervosa, and binge-eating disorder, represent a significant public health concern with far-reaching consequences. These disorders are characterized by abnormal eating habits and a distorted perception of body weight and shape, leading to severe physical and psychological complications. The global incidence of eating disorders has been rising, affecting millions across all demographics, and contributing to substantial morbidity and mortality rates largely due to associated medical complications and an increased risk of suicide (McKee et al., 2021).

The therapeutic landscape for eating disorders includes a variety of interventions, such as psychotherapy, nutritional counselling, and pharmacotherapy. Cognitive behavioural therapy (CBT) is widely endorsed for its effectiveness in bulimia nervosa and binge-eating disorder, while Anorexia Nervosa often requires intensive multidisciplinary care, including nutritional rehabilitation and psychotherapy (Scharmer et al., 2020). Despite these treatments, a significant number of patients either do not achieve full remission or experience relapses, highlighting the chronic and relapsing nature of these disorders. The complexity of eating disorders, characterized by their

biopsychosocial underpinnings, poses significant challenges in treatment, exacerbated by societal stigma and barriers to accessing specialized care (Rogers & Pacanowski, 2023).

Medicinal cannabis has garnered attention for its potential utility in a range of mental health conditions, including eating disorders. The endocannabinoid system, with which cannabis interacts, plays a crucial role in regulating appetite, mood, and stress response, all of which are dysregulated in eating disorders (Alderman et al., 2022). Preliminary evidence suggests that cannabinoids, such as THC and CBD, may offer therapeutic benefits by modulating core symptoms of eating disorders, including anxiety, depression, and aberrant eating behaviours (Rosager et al., 2021). However, the clinical application of medicinal cannabis in eating disorders is still in its early stages, necessitating further research to delineate its efficacy, safety, and optimal therapeutic protocols (Taylor et al., 2024).

3.4.2.16.1. Recommended dosages in current literature

The exploration of medicinal cannabis in treating eating disorders reflects the challenges of managing and treating this condition have prompted researchers to explore alternative therapeutic strategies. One such avenue that has attracted attention is the use of medicinal cannabis, which has shown potential not only in appetite modulation but also in addressing the psychological components commonly associated with eating disorders. This section aims to synthesize the current literature regarding the recommended dosages of medicinal cannabis for managing eating disorders, drawing on a body of evidence that suggests cannabinoids might positively influence eating behaviours and associated mental health issues (Table 3.25).

Studies, including those by Rogers & Pacanowski (2023), highlight the potential of cannabinoids to enhance appetite and alleviate anxiety, which are crucial in the treatment of AN. These effects are thought to arise from the cannabinoids' actions on cannabinoid receptors located throughout the central and peripheral nervous systems, which influence food intake and pleasure associated with eating. Current recommendations for cannabinoid dosing in the treatment of eating disorders remain under exploration due to the complexity of these conditions and individual variations in response to cannabis. However, the literature suggests starting with lower doses, particularly of $\Delta 9$ -THC, to monitor effects on appetite stimulation and psychological well-being. Scharmer et al. (2020) emphasize the importance of tailoring 0.73 kg compared to a placebo, without significant psychotropic side effects. This study suggested that dronabinol could be a well-tolerated and effective therapeutic option for weight management in anorexia nervosa, although it did not significantly impact the psychological symptoms as measured by the Eating Disorder Inventory-2 (EDI-2). Building on these findings, the study by Andries et al. (2015a) explored the effects of dronabinol on physical activity—a symptom often exacerbated in anorexia nervosa due to compulsive exercise behaviours. This crossover study similarly employed a low dose of 2.5 mg twice daily, observing a significant increase in the intensity of physical activity without altering its duration. This result is crucial as it highlights the potential of dronabinol to modify exercise behaviours, which are often resistant to traditional interventions. The study also noted a related increase in energy expenditure and drew correlations between activity levels and biomarkers such as leptin and cortisol, suggesting a complex interplay between cannabinoid receptor activation and endocrine responses in anorexia nervosa. Further delving into the endocrine aspects, the study by Andries et al. (2015b) assessed the impact of dronabinol on hormonal

markers such as insulin-like growth factor I (IGF-I) and adipokines in patients with chronic AN. While the study did not find significant changes in IGF-I levels or adipokines, it reported a noteworthy reduction in urinary free cortisol levels, indicating a potential alleviation of hypercortisolaemia, which is frequently observed in anorexia nervosa. This finding points to the broader regulatory dosages to individual expectations and experiences of anxiety and dietary restrictions, which are commonly reported by patients with eating disorders.

Moreover, clinical insights from Rosager et al. (2021) provide a nuanced understanding of the interplay between cannabinoids and appetite-regulating hormones such as leptin and ghrelin, mediated through CB1 receptor activation. Their findings support the hypothesis that cannabinoid therapy could be beneficial in modifying restrictive eating behaviours and improving caloric intake through the ECS. The dosage in these contexts often needs careful adjustment to balance efficacy with potential psychoactive effects of Δ 9-THC, while incorporating non-psychoactive CBD could potentially offset some unwanted effects.

The study by Andries et al. (2014) was a pivotal trial that demonstrated the feasibility of using dronabinol to achieve weight gain in individuals with anorexia nervosa. Administering 2.5 mg of dronabinol twice daily resulted in a modest but statistically significant mean weight gain of effects of cannabinoids on the HPA axis, suggesting that cannabinoid therapy could help mitigate some of the stress-related hormonal activities in anorexia nervosa. These studies collectively underscore the nuanced role of cannabinoids in treating anorexia nervosa. While initial results are promising, particularly in terms of weight management and modulation of physical activity, the complexity of anorexia nervosa 's pathophysiology necessitates further research.

Future studies should aim to clarify the optimal dosages and treatment durations, and to expand on the understanding of the psychopharmacological mechanisms through which cannabinoids exert their effects. Moreover, large-scale randomized controlled trials are required to fully establish the efficacy and safety profiles of cannabinoids like dronabinol, ensuring that these interventions can be safely integrated into the broader therapeutic landscape for eating disorders.

Scharmer et al. (2020) conducted a cross-sectional study focusing on the expectancies of cannabis effects on ED symptoms among 137 cannabis users who self-reported symptoms of eating disorders. This study uniquely examined the relationship between cannabis use and the expectancies regarding its impact on both restrictive and binge-eating behaviours. While participants anticipated that cannabis use would alleviate restrictive behaviours and fears related to body shape and weight gain, they also expected an increase in binge-eating behaviours. Intriguingly, these expectancies did not correlate with the frequency of cannabis use or the occurrence of cannabis-related problems, suggesting a complex interaction between perceived and actual impacts of cannabis on eating behaviours. This discrepancy underscores the necessity for longitudinal studies to better understand the dynamics of cannabis use and its psychological effects over time, particularly in clinical settings where controlled observations can be made. On the other hand, Avraham et al. (2017) presented an open-label pilot study without a placebo control group, focusing on the effects of $\Delta 9$ -THC on psychological symptoms in patients with chronic anorexia nervosa. This study involved 10 female volunteers who were administered low doses of $\Delta 9$ -THC, which was shown to significantly improve psychological symptoms such as body care, feelings of ineffectiveness, asceticism, and depression.

Authors	Study	Pts	Age	Dose	Delivery	Follow-up	Outcomes
Gross et al. (1983)	Randomized cross-over	11	-	7.5-30mg	Oral	5 weeks	No significant effect on weight gain. Higher doses associated with adverse events that potentially counteracted weight-gaining effects.
Karayilan & Erol (2013)	Case report	1	17	Unspecified	Inhalation	-	Despite the appetite-increasing effects of cannabis, the patient used self-induced vomiting and excessive exercise to achieve weight loss.
Andries et al. (2014a)	Randomized cross-over	24	33.3 $\bar{x}$	2.5mg BD	Oral (dronabinol)	4 weeks / phase; 4-week wash-out	Dronabinol modestly increased physical activity intensity but not duration, with no significant impact on eating disorder-related behaviours.
Andries et al. (2014b)	Randomized cross-over	24	33.3 $\bar{x}$	2.5mg BD	Oral (dronabinol)	4 weeks / phase; 4-week wash-out	Dronabinol induced a small but significant weight gain (0.73 kg $\bar{x}$) compared to placebo, without significant psychotropic side effects.
Andries et al. (2015)	Randomized cross-over	24	28 $\bar{x}$	2.5mg BD	Oral (dronabinol)	4 weeks / phase; 4-week wash-out	Dronabinol modestly increased BMI, decreased urinary cortisol, and had no significant effect on IGF-1 or adipokine levels.
Avraham et al. (2017)	Open label pilot	10	45 $\bar{x}$	1-3mg	Oral	4 weeks	Significant improvements in psychological symptoms, including body care, sense of ineffectiveness, asceticism, and depression, though no significant change in BMI was observed. No adverse effects were reported at the low doses used.
Graap et al. (2017)	Case report	1	27	7.5mg BD	Oral (dronabinol)	-	Significant reduction in urge to be physically active and improved control over eating disorder-specific cognitions and compulsive behaviours.

Table 3.25. *Studies evaluating use of medicinal cannabis in patients with eating disorders.*

Notably, these improvements occurred without significant changes in BMI, indicating that while $\Delta 9$ -THC may enhance certain psychological aspects of anorexia nervosa, it does not necessarily affect weight gain directly. This study highlights the potential of $\Delta 9$ -THC to ameliorate some of the psychopathological features of anorexia nervosa, particularly those related to mood and self-perception, suggesting that cannabinoids might be useful as an adjunctive treatment focusing on the psychological components of eating disorders. Both of these two recent studies contribute to a nuanced understanding of how medicinal cannabis could be integrated into treatment regimens for eating disorders. The findings from Scharmer et al. (2020) suggest that while users have specific expectancies about cannabis effects on eating disorder symptoms, these do not always align with actual usage patterns and outcomes, indicating a need for more targeted education and clinical monitoring in cannabis use for eating disorders. Meanwhile, the findings from Avraham et al. (2017) suggest that cannabinoids, even at low doses, may help address some of the complex psychological symptoms associated with eating disorders, although their impact on physical symptoms such as weight remains unclear.

Graap et al. (2017) conducted a singular case study involving a 27-year-old male with a chronic history of anorexia nervosa, who was administered dronabinol, a synthetic cannabinoid. This patient was characterized by an extreme and debilitating urge to remain physically active, a symptom often associated with the hyperactivity observed in some individuals with anorexia nervosa. The intervention involved administering dronabinol at an escalating dose, eventually stabilized at 7.5 mg twice daily. The primary outcome reported was a significant reduction in the urge to be physically active, with secondary outcomes including improvements in eating disorder-specific cognitions and behaviours. Furthermore, the study employed a dexamethasone

suppression test (DST) to evaluate changes in HPA axis activity, finding notable improvement after treatment. This case study underscores the potential of cannabinoids to modulate not just the physiological but also the psychological and behavioural aspects of eating disorders. The efficacy of dronabinol in reducing compulsive physical activity could be indicative of its ability to regulate endocannabinoid signalling pathways that are perhaps dysregulated in anorexia nervosa. However, the nature of this study being a single-case report necessitates further research through randomized controlled trials to systematically explore the efficacy and safety of cannabinoids in a broader clinical setting. Gross et al. (1983) provides a contrasting perspective with its double-blind, randomized placebo-controlled crossover study, which included women with anorexia nervosa undergoing treatment with escalating doses of Δ 9-THC. Starting from 7.5 mg and increasing to 15 mg daily before administering a single dose of 30 mg after a five-week period, the study aimed to observe potential weight gain and other physiological changes. Unfortunately, the study did not find significant weight gain and noted an increase in somatization, interpersonal sensitivity, and sleep disturbances. Furthermore, significant changes in blood pressure suggested that while Δ 9-THC might influence symptoms of anorexia nervosa, the side effects at higher doses complicate its clinical application. The Gross et al. study highlights critical considerations for the therapeutic use of cannabinoids in eating disorders, particularly the importance of dosing. The adverse psychological and physiological responses recorded at higher dosages of Δ 9-THC illustrate the fine balance required in administering such treatments, ensuring therapeutic benefits without exacerbating the condition or inducing new health complications.

3.4.2.16.2. Challenges and clinical implications

The integration of medicinal cannabis into treatment protocols for eating disorders, particularly anorexia nervosa, demands a comprehensive analysis, incorporating insights from a range of studies and reviews. Anorexia nervosa, characterized by a distorted body image and an extreme fear of gaining weight, leads to severe dietary restrictions and weight loss. Cannabinoids like Δ 9-THC and dronabinol have shown potential in stimulating appetite and inducing weight gain, which could be beneficial in treating anorexia nervosa. While there is promise the evidence base is still evolving. Further research, particularly well-designed randomized controlled trials (RCTs), is necessary to elucidate the efficacy, safety, and optimal therapeutic approaches of cannabinoids in eating disorders (Rosager et al., 2021). The variable response to cannabinoids underscores the need for personalized treatment plans, taking into account the individual patient's condition, potential adverse effects, and the psychoactive properties of THC-containing compounds. The initiation of treatment with low doses and careful titration based on patient response is crucial to minimize adverse effects while optimizing therapeutic benefits. Continuous monitoring for both therapeutic effects and potential adverse reactions is essential for adjusting the treatment regimen to achieve the best possible outcomes (Taylor et al., 2024).

3.4.2.16.3. Research and future directions

The exploration of medicinal cannabis in the context of eating disorders, particularly anorexia nervosa, has opened new avenues for research and clinical practice. Despite the growing body of evidence supporting the therapeutic potential of cannabinoids in stimulating appetite and weight gain, significant gaps remain in our understanding of

their efficacy, safety, and mechanisms of action. There is a need for long-term studies to assess the sustained efficacy and safety of cannabinoids in eating disorders, addressing concerns related to tolerance, dependence, and long-term side effects (Alderman et al., 2023). Understanding the precise mechanisms by which cannabinoids exert their effects on appetite, weight regulation, and psychopathology in eating disorders is crucial. This includes elucidating the roles of the endocannabinoid system, CB1 and CB2 receptors, and interactions with other neurotransmitter systems (Rogers & Pacanowski, 2023). Future research should aim to identify patient subgroups that may particularly benefit from cannabinoid therapy, considering factors such as disease severity, comorbid conditions, and genetic predispositions (Taylor et al., 2024).

Developing evidence-based clinical guidelines for the use of medicinal cannabis in eating disorders is essential. This includes standardized dosing regimens, monitoring protocols, and criteria for patient selection (Alderman et al., 2023). Effective treatment of eating disorders with cannabinoids requires collaboration among psychiatrists, nutritionists, pharmacists, and other healthcare professionals to ensure comprehensive care that addresses both the physical and psychological aspects of these conditions (McKee et al., 2021).

3.4.2.17. Palliative care

Palliative care is defined by the World Health Organization as "an approach that improves the quality of life of patients and their families facing the problem associated with life-threatening illness." It aims to relieve pain and other distressing symptoms, improve quality of life, and provide a holistic approach for patients and families.

Despite advances in medical science, patients with advanced illnesses often experience substantial symptom burdens that cause distress (Good et al., 2019). In Canada alone, palliative care could benefit an estimated 69% to 82% of dying individuals (MacDonald & Farrah, 2019).

Symptom management in palliative care remains challenging despite a wide range of medications available. Some of the common symptoms encountered in palliative care include pain, nausea, anorexia, anxiety, insomnia, and chemotherapy-induced nausea and vomiting (CINV). Current treatment modalities include opioids and NSAIDs for pain management, melatonin and sedatives for insomnia, antiemetics such as metoclopramide, ondansetron and corticosteroids for nausea and vomiting, megestrol acetate and corticosteroids for appetite stimulation, and antidepressants and anxiolytics for depression and anxiety. With the recognition of the limitations of current palliative care medications, there has been increasing interest in medicinal cannabis as an alternative or adjunct for symptom relief (Good et al., 2019).

Cannabinoids interact with a pair of G protein-coupled receptors, cannabinoid receptors 1 and 2 (CB1 and CB2), which initiate downstream signalling to control cellular processes like apoptosis, cell cycle progression, and autophagy. The pharmacological effects of CBD are attributed to its interactions with over 75 cell-surface and intracellular proteins, including G protein-coupled receptors, ion channels, and drug transporters (Green et al., 2022). There is moderate-quality evidence that cannabinoids are effective for chronic pain and spasticity. In particular, CBD has shown anti-inflammatory and analgesic properties, making it a potential alternative to opioids with a more favourable side-effect profile (Higuet et al., 2020). THC has been shown to be effective for reducing nausea and vomiting associated with

chemotherapy. Studies from the 1980s demonstrated the effectiveness of THC compared to placebo and other antiemetics like domperidone. nabilone and dronabinol have been approved for nausea and vomiting associated with chemotherapy and anorexia in HIV/AIDS patients (Roychoudhury et al., 2021). CBD, through its interactions with serotonin receptors, may help alleviate anxiety. However, further high-quality evidence is needed to fully establish its role. THC has shown potential in stimulating appetite, particularly in patients with cancer and HIV/AIDS (Roychoudhury et al., 2021).

The potential clinical use of medicinal cannabis in palliative care holds promise, particularly in managing symptoms like pain, nausea, and appetite loss. However, more high-quality research is needed to establish optimal dosing and safety profiles. As the legislation evolves and more patients express interest in cannabis-based treatments, it becomes imperative for clinicians to understand the evidence, benefits, and risks associated with medicinal cannabis. This understanding can help integrate medicinal cannabis effectively into palliative care for symptom management, providing a more comprehensive and patient-centred approach.

3.4.2.17.1. Recommended dosages in current literature

Medicinal cannabis has garnered increasing attention in palliative care for managing symptoms like pain, nausea, anorexia, and anxiety. Despite its potential therapeutic benefits, clinical evidence on optimal dosages remains varied due to the differences in cannabis strains, patient responses, and cannabinoid ratios. This section provides an overview of the current literature on recommended dosages for managing palliative

care symptoms, emphasizing the therapeutic effects of THC, CBD and their combinations (Table 3.26).

The evidence on cannabis for managing chronic pain, particularly cancer-related pain, suggests varying effects based on THC:CBD ratios. In pain management, the evidence suggests varying effects of cannabis depending on the THC:CBD ratios. Johnson et al. (2010) showed that a combination of THC/CBD (nabiximols) delivered via an oromucosal spray at a dose of 2.7 mg THC and 2.5 mg CBD was effective in reducing pain intensity. In this double-blind randomized controlled trial with 177 patients, pain scores significantly improved ($p = 0.01$) compared to placebo. Fallon et al. (2017) also supported this dose in their two-phase III studies but recommended personalized dosing titration due to the variability in patient response. They used doses ranging from 2.7 mg THC and 2.5 mg CBD to 48 mg THC and 40 mg CBD daily (Hatfield et al., 2024). In contrast, a study by Côté et al. (2016) using nabilone found no significant difference in pain improvement compared to placebo at doses of 0.5 mg twice daily (Casarett et al., 2019). Lichtman et al. (2018) suggested that a THC/CBD combination may be more effective than THC alone due to the entourage effect. Cannabinoid therapy is well-established for chemotherapy-induced nausea and vomiting (CINV). Lane et al. (1991) demonstrated that dronabinol at 5 mg/m² before and after chemotherapy significantly reduced nausea and vomiting compared to prochlorperazine. Grimison et al. (2020) confirmed the efficacy of THC/CBD in CINV, using a 2.5 mg THC and 2.5 mg CBD capsule daily, titrated up to 30 mg/day over six days. Grimison also highlighted that THC/CBD combinations offer more consistent relief than THC alone due to the synergistic effect. Dosages typically range from 2.5 mg THC and 2.5 mg CBD twice daily, titrated up to patient tolerance.

The role of cannabinoids in stimulating appetite remains controversial. Jatoi et al. (2002) used dronabinol at a dose of 2.5 mg twice daily to manage cancer-associated anorexia/cachexia. However, megestrol acetate was superior in efficacy ($p < 0.001$). Hardy et al. (2023) found no significant improvement in appetite or weight gain with CBD oil (200 mg daily, titrated to 600 mg) alone compared to placebo. Evidence remains limited but promising for THC and CBD in managing mood disturbances in palliative care. Casarett et al. (2019) observed that a 1:1 ratio of THC to CBD (maximum 50 mg each daily) had an inverted U-shaped dose-response curve for anxiety symptoms. For depression, a THC:CBD ratio of up to 2:1 may be optimal, but clinical guidance remains sparse. Hardy et al. (2023) used CBD oil titrated to 600 mg daily in advanced cancer patients and found no significant reduction in depression. The optimal therapeutic dosage of medicinal cannabis varies widely among patients due to individual variability in response, the type of symptom treated, and the cannabinoid ratios used. Current literature supports the efficacy of combination THC/CBD extracts in managing pain, nausea, and mood disturbances in palliative care. Further research is needed to refine dosing strategies, especially for CBD-dominant products. Personalized titration based on patient tolerance remains the best approach to maximizing clinical benefits while minimizing adverse effects.

Donovan et al. (2019) conducted a retrospective analysis of 816 cancer patients referred to the Supportive Care Medicine outpatient clinic at Moffitt Cancer Center. The study aimed to determine the prevalence and characteristics of cannabis use in this cohort. By reviewing urine drug testing (UDT) and self-reported cannabis use, they found that 19.12% of patients tested positive for THC, indicating significant cannabis consumption. Sociodemographic analysis showed that users were younger, predominantly male, and more often single compared to non-users. Clinically,

cannabis users had more recently been diagnosed with cancer and were more likely to have received radiotherapy. Symptom analysis revealed that moderate-to-severe tiredness, lack of appetite, anxiety, depression, difficulty sleeping, and shortness of breath were significantly associated with cannabis use, while pain, nausea, drowsiness, constipation, and spiritual well-being were not. The authors concluded that nearly one in five patients seeking specialized palliative care was using cannabis, often without medical authorization. They emphasized the urgent need for accurate information on cannabis use to better guide expectations and management in palliative care settings.

McEwen Wilson et al. (2019) performed a retrospective chart review of 299 patients in a rural academic palliative care setting. The study found that 27% of patients reported using cannabis, with the majority (74 patients) using it for medical purposes only, five for recreational purposes, and four for both. Pain was the primary reason for cannabis use (59%), followed by anorexia (19%), insomnia (17%), nausea (16%), anxiety (10%), and depression (6%). Notably, 31% used cannabis for more than one symptom, and 72% were also prescribed opioids, highlighting potential overlap in symptom management strategies. Urine drug screens confirmed THC presence in 25% of the tested patients. This study underscored the significant prevalence of cannabis use in palliative care patients and suggested that routine screening for cannabis could help identify potential interactions, manage side effects, and improve patient education. Zarrabi et al. (2019) conducted a survey-based study involving 101 seriously ill patients from the Ambulatory Palliative Care practice at Emory University.

Authors	Study	Pts	Age	Dose	Delivery	Follow-up	Outcomes
Jatoi et al. (2002)	RCT	469	67 $\bar{x}$	2.5mg BD	Oral (dronabinol)	6 weeks	Megestrol acetate was superior for improving appetite and weight gain. Combination therapy did not outperform megestrol acetate alone.
Strasser et al. (2006)	RCT	243	61 $\bar{x}$	2.5mg THC + 1mg CBD; 2.5mg THC	Oral	6 weeks	No significant difference in appetite or quality of life between treatment arms. Well-tolerated.
Zutt et al. (2006)	Case series	7	59 $\bar{x}$	2.5mg BD	Oral (dronabinol)	4 weeks	Significant improvements in appetite and nausea reported. Effects diminished with disease progression. Mild to moderate dizziness was the only notable side effect.
Johnson et al. (2010)	RCT	177	59.4 $\bar{x}$	8-10 sprays / day (2.7mgTHC + 2.5mgCBD)	Oromucosal spray (nabiximols)	2 weeks	Nabiximols was superior to placebo in pain reduction (mean pain score reduction: -1.37 vs. -0.69). THC alone showed no significant benefit.
Brisbois et al. (2011)	RCT	46	67 $\bar{x}$ 65.5 $\bar{x}$	2.5mg BD	Oral (THC)	18 days	Improved chemosensory perception, appetite, and food enjoyment, compared to placebo. Quality of life improvements.
Portenoy et al. (2012)	RCT	360	58 $\bar{x}$	1-16 sprays / day (2.7mgTHC + 2.5mgCBD)	Oromucosal spray (nabiximols)	5 weeks	Low and medium doses showed greater analgesia compared to placebo. High doses had adverse effects and no additional efficacy.
Johnson et al. (2013)	Open label pilot	43	57.5 $\bar{x}$ 58.6 $\bar{x}$	max. 8 sprays / 3hrs (2.7mgTHC + 2.5mgCBD)	Oromucosal spray (nabiximols)	-	Nabiximols spray was well tolerated long-term, with no evidence of dose escalation or loss of efficacy for pain relief.
Cote et al. (2016)	RCT	56	63.5 $\bar{x}$ 63.8 $\bar{x}$	0.5-2mg	Oral (nabilone)	11 weeks	No significant improvement in quality of life, pain, nausea, or appetite compared to placebo.
Fallon et al. (2017)	RCT	399	60 $\bar{x}$ 59.6 $\bar{x}$	10 sprays / day (2.7mgTHC + 2.5mgCBD)	Oromucosal spray (nabiximols)	5 weeks	No significant difference in pain reduction compared to placebo, but improvements noted in quality of life measures for patients <65 years.
Lichtman et al. (2018)	RCT	397	59.2 $\bar{x}$ 60.7 $\bar{x}$	10 sprays / day (2.7mgTHC + 2.5mgCBD)	Oromucosal spray (nabiximols)	5 weeks	No significant difference in the primary endpoint, pain reduction. Patients showed improved secondary outcomes, including quality of life.
Casarett et al. (2019)	Retrospective cohort	2431	39 $\bar{x}$	Variable	Inhalation	-	THC-dominant cannabis improved neuropathic pain, insomnia, and depressive symptoms. No significant results for anxiety, PTSD, or anorexia.

Authors	Study	Pts	Age	Dose	Delivery	Follow-up	Outcomes
Wilson et al. (2019)	Retrospective chart review	299	22-97	Unspecified	Variable	-	27% used cannabis, reporting benefits for pain and other symptoms, with some overlap in opioid usage.
Zarrabi et al. (2019)	Cross-sectional survey	101	21-70s	CBD, 5% THC	Oral, Inhalation	-	Reported symptom improvement, including pain and appetite, with minimal side effects.
Good et al. (2020)	Open label pilot	21	70 x̄	max. 600mg CBD, max. 30mg THC	Oral	28 days	43% achieved a significant reduction in symptom burden. Emotional symptoms (anxiety, depression) improved significantly, but no overall reduction in physical symptoms.
Highet et al. (2020)	Cross-sectional survey	58	67 x̄	Variable	Topical, Oral, Inhalation	-	Patients reported symptom improvement, including pain and appetite, with minimal side effects.
Hardy et al. (2022)	RCT	142	64.6 x̄	50-600mg CBD	Oral	28 days	CBD did not significantly outperform placebo for symptom relief.
Buchwald et al. (2023)	Case series	8	75 x̄	12.5mg	Oral (dronabinol)	2 weeks	Significant improvement in cognitive function and reduction in pain, fatigue, and depressive symptoms.
Nathan et al. (2023)	Retrospective chart review	83	65-81	Variable	Oral, Inhalation	12 weeks	No statistically significant change in symptoms, though 37% reported a 30% pain reduction.

Table 3.26. *Studies evaluating use of medicinal cannabis in provision of palliative care.*

The survey revealed that patients actively used various forms of cannabis products, primarily low-THC oil ($\leq 5\%$ THC) (49.5%) and mixed THC/CBD oil (33.7%). Pain relief was the most commonly perceived benefit (95.5%), followed by anxiety reduction (79.0%), sleep facilitation (73.0%), and depression/coping improvement (77.3%). Notably, 59.1% believed in the curative properties of cannabis for cancer. Despite some concerns about withdrawal symptoms (19.1%) and dependence (13.5%), patients overwhelmingly reported significant benefits in pain management, symptom control, and overall well-being. The study highlighted the need for clinicians to understand patient expectations regarding cannabis, especially those seeking its curative properties.

Roychoudhury et al. (2021) provided an editorial review summarizing the clinical studies involving cancer patients and those with serious illnesses who may benefit from palliative care. Their comprehensive analysis explored various formulations and dosages of cannabis-based medicines for managing pain, nausea, appetite, mood disorders, and sleep disturbances. In the review, nabiximols, a THC:CBD spray in a 1:1 ratio, demonstrated efficacy for pain relief in advanced cancer at doses of 23.6 mg THC and 21.9 mg CBD daily. A direct comparison of THC with codeine revealed that 10 mg THC provided equivalent analgesia to 60 mg of codeine. Additionally, sublingual cannabis oil (15% THC, 3% CBD) reduced chemotherapy-induced muscle cramps, and nabilone effectively stimulated appetite at 2 mg daily. For cancer pain, nabiximols significantly reduced pain compared to placebo (-1.37 vs. -0.69 , $p = 0.014$), while THC alone (23.6 mg daily) was effective for refractory pain in advanced cancer without severe side effects. Plant-based cannabis oil (15% THC, 3% CBD) also proved effective for chemotherapy-induced muscle cramps. For chemotherapy-induced neuropathic pain, Lynch et al. (2014) found nabiximols effective, aligning with findings

from other studies. In terms of nausea and vomiting, dronabinol was approved for chemotherapy-induced nausea and vomiting (CINV). A phase II trial showed that a THC:CBD combination provided protection against delayed CINV. Smith et al. (2015) recommended cannabis-based medications if standard antiemetics failed. Cannabis-based medicines also improved sleep in cancer pain, multiple sclerosis, and neuropathic pain, and reduced anxiety and depression symptoms in multiple sclerosis patients. THC may also aid in opioid and alcohol withdrawal. nabilone improved calorie and carbohydrate intake in advanced non-small cell lung cancer patients. The review emphasized comprehensive patient assessments and risk-benefit discussions before initiating cannabis-based treatment, recommending low initial doses of 5–20 mg CBD and 1–3 mg THC to minimize side effects. Despite regulatory challenges and knowledge gaps, Roychoudhury et al. concluded that cannabis-based medicines offer potential benefits in palliative medicine, particularly for cancer pain, chemotherapy-induced nausea, and mood disorders.

Good et al. (2019) conducted a multicentre, double-blind, randomized, placebo-controlled trial to evaluate the efficacy and safety of cannabidiol (CBD) in reducing symptom burden in advanced cancer patients. The study enrolled 144 patients with advanced cancer referred to five sites within the Queensland Palliative Care Research Group (QPCRG). Patients received either oral CBD (100 mg/mL formulation) or placebo. The CBD group started at 50 mg/day and titrated up to 600 mg/day. The primary outcome was a change in Total Symptom Distress Score (TSDS) at day 14. Secondary outcomes included effective CBD doses, physical and emotional ESAS scores, AKPS, PGIC, CGI, and quality of life. The study protocol indicated that the final results would determine the efficacy and safety of CBD in advanced cancer patients receiving palliative care. This trial aimed to provide high-quality evidence on

the role of CBD in reducing symptom burden and guide clinicians in managing patients seeking medicinal cannabis for cancer-related symptoms.

Hardy et al. (2020) designed a pragmatic, multicentre, double-blind, randomized, placebo-controlled trial to evaluate the efficacy of a 1:1 THC/CBD cannabinoid preparation in advanced cancer patients. The study enrolled 150 patients with advanced cancer at five sites within QPCRG. Participants were randomly assigned to either THC/CBD oil or placebo. The THC/CBD group received an escalating dose starting at 2.5 mg THC/2.5 mg CBD/day up to 30 mg THC/30 mg CBD/day. The primary outcome was a change in Total Symptom Distress Score (TSDS) at day 14. Secondary outcomes included ESAS scores, AKPS, PGIC, CGI, and quality of life. As the first placebo-controlled clinical trial to rigorously assess a 1:1 THC/CBD formulation in advanced cancer patients receiving palliative care, the study's results will provide valuable evidence to guide patients seeking medicinal cannabis for symptom management. Hauser et al. (2017) conducted a systematic review and overview of systematic reviews and long-term observational studies examining cannabinoids in palliative care and pain management. The analysis included 11 systematic reviews and three long-term observational studies, focusing on neuropathic, cancer, fibromyalgia, and rheumatic pain. The review found limited evidence of benefit for neuropathic pain with THC/CBD spray (nabiximols). Inhaled medical cannabis had a clinically relevant number needed to treat (NNT) of 6 for at least 30% pain relief. However, evidence for cannabinoids in cancer pain was inadequate, with no significant difference in pain relief between cannabinoids and placebo. For fibromyalgia and rheumatic pain, THC/CBD spray reduced pain in rheumatoid arthritis patients, and nabilone improved sleep quality in fibromyalgia. The review highlighted central nervous system adverse events, such as dizziness and

cognitive impairment, but found no significant differences in severe adverse events between cannabinoids and placebo. Treatment discontinuation due to adverse events was rare. Hauser et al. concluded that public perception regarding the efficacy, safety, and tolerability of cannabis-based medicines conflicted with the evidence. While THC/CBD spray showed limited efficacy for neuropathic pain, evidence remains inadequate for other indications like cancer pain or rheumatic diseases.

Hardy et al. (2023) conducted a Phase IIb, multicentre, randomized, placebo-controlled, dose-escalating clinical trial to assess the efficacy of cannabidiol (CBD) oil in advanced cancer patients receiving palliative care. The study included 144 participants from five tertiary medical centres in Queensland, Australia. The primary aim was to evaluate the change in Total Symptom Distress Score (TSDS) on the Edmonton Symptom Assessment Scale (ESAS) after 14 days. Participants were randomized into two arms: one receiving CBD oil (100 mg/mL) and another a placebo oil solution. The CBD arm started at 0.5 mL daily, titrating up to 2 mL thrice daily (total dose of 50-600 mg/day) over a 2-week dose escalation phase, followed by a 2-week stable dose assessment period. The primary outcome was the change in TSDS at day 14. Results showed no significant difference in TSDS improvement between CBD (-3.0) and placebo (-6.2), with a p-value of 0.24. The proportion of responders (≥ 6 -point TSDS reduction) was also not significantly different between groups (CBD: 44.8% vs. placebo: 58.7%, $p = 0.13$). Secondary outcomes, including physical and emotional well-being subsets on the ESAS, Global Impression of Change (GIC), and quality of life (EORTC QLQ-C15-PAL), showed no significant differences between the groups. Adverse events were similar between CBD and placebo, except for dyspnoea, which was more common in the CBD group. In conclusion, the study found that CBD oil did not significantly improve symptom relief in advanced cancer patients beyond standard

palliative care, despite public belief in its benefits. These results do not support the addition of CBD to standard palliative care regimens. Portenoy et al. (2012) conducted a multicentre, randomized, double-blind, placebo-controlled, graded-dose trial to assess the efficacy of nabiximols (Sativex®) oromucosal spray in cancer patients with chronic pain unresponsive to stable opioid regimens. The study involved 360 adults with active cancer and moderate to severe chronic pain. Patients were randomized into four groups: placebo, low-dose nabiximols (1-4 sprays/day), medium-dose (6-10 sprays/day), and high-dose (11-16 sprays/day). Each spray contained 2.7 mg THC and 2.5 mg CBD. Patients self-titrated their doses within the assigned range for one week, followed by a stable dosing period of four weeks. The primary outcome was the proportion of patients achieving at least a 30% reduction in pain intensity at week 5. Secondary outcomes included continuous responder analysis (0-100% pain reduction), changes in pain scores, sleep disruption, quality of life (EORTC QLQ-C30), and opioid consumption. The results indicated no significant difference in the 30% responder rate between nabiximols and placebo. However, continuous responder analysis showed a greater proportion achieving pain reduction with nabiximols ($p = 0.035$). The low-dose group showed significant improvements in average pain ($p = 0.006$), worst pain ($p = 0.011$), and sleep disruption ($p = 0.003$). The medium-dose group also showed significant improvement in continuous responder analysis ($p = 0.039$). Adverse events were dose-related, with nausea (22%), dizziness (19%), and vomiting (15%) being the most common. Portenoy et al. (2012) concluded that nabiximols may offer analgesic benefits as an add-on therapy for opioid-treated cancer patients with poorly controlled pain, particularly at low and medium doses. However, high doses were associated with an unfavourable safety profile. Johnson et al. (2013) conducted an open-label extension study following a prior randomized controlled trial

to assess the long-term efficacy and safety of THC/CBD spray (Sativex®) in terminal cancer patients. Forty-three participants from the previous trial continued into the extension study. Patients received THC/CBD spray (2.7 mg THC and 2.5 mg CBD per spray) or THC-only spray (2.7 mg THC per spray) with initial supervised dosing followed by self-titration. The maximum dose was eight sprays per three-hour period, up to 48 sprays/day. Pain severity and quality of life were assessed using the Brief Pain Inventory-Short Form (BPI-SF) and EORTC QLQ-C30, respectively. Safety data were collected through adverse event reporting and vital sign monitoring. Results showed a decrease (improvement) in pain severity and worst pain scores on the BPI-SF, while the EORTC QLQ-C30 indicated improvement in insomnia, pain, and fatigue. Adverse events occurred in 95% of the THC/CBD group, with dizziness, nausea, vomiting, dry mouth, and somnolence being the most common. Serious adverse events were reported in 51% of the THC/CBD group, but none were attributed to the treatment. The study concluded that long-term use of THC/CBD spray was generally well-tolerated in terminal cancer patients, with no evidence of a loss of effect for cancer-related pain relief. Moreover, patients did not seek to increase their dose over time, suggesting potential benefits of cannabinoids as adjuvant therapy.

Lichtman et al. (2018) conducted a Phase 3, double-blind, multicentre, randomized, placebo-controlled trial involving 397 patients with advanced cancer and chronic pain that remained inadequately controlled by optimized opioid therapy. The study sought to assess the efficacy and safety of nabiximols (Sativex®), an oromucosal spray containing THC (27 mg/mL) and CBD (25 mg/mL), compared to placebo. Patients were randomized to receive either nabiximols or placebo in a 2-week titration phase, followed by a 3-week stable dose period. The dose was titrated up to a maximum of 10 sprays/day. The primary outcome was the percent improvement in average pain

scores from baseline to the end of treatment. Secondary outcomes included mean changes in pain scores, sleep disruption, opioid consumption, and quality of life. The primary analysis showed a median improvement in pain scores of 10.7% in the nabiximols group compared to 4.5% in the placebo group, with an estimated treatment difference of 3.41% ($p = 0.0854$). In the per-protocol analysis, the difference was significant, with a treatment difference of 5.49% ($p = 0.0378$). Although the primary endpoint was not met, nabiximols significantly improved secondary endpoints, including sleep disruption and quality of life (SGIC, PGIC, PSQ scores). The study concluded that nabiximols did not significantly improve pain scores over placebo in the intent-to-treat population but did show benefits in secondary outcomes, particularly in the U.S. patient population. The safety profile was consistent with previous studies, with nausea and dizziness being the most common adverse events. Despite the mixed results, nabiximols may have potential utility in cancer pain management with further research. Johnson et al. (2010) conducted a multicentre, double-blind, randomized, placebo-controlled trial to evaluate the efficacy of THC:CBD extract (Sativex®) in intractable cancer pain. The study included 177 patients with advanced cancer-related pain that remained uncontrolled despite chronic opioid therapy. Participants were randomized into three groups: THC:CBD extract (Sativex®), THC-only extract, and placebo. The THC:CBD extract contained 2.7 mg THC and 2.5 mg CBD per spray, while the THC extract contained 2.7 mg THC per spray. The study had a 2-week titration phase, with dosing starting at one spray per day and titrating up to a maximum of 8 sprays per 3-hour period (48 sprays/day). The primary endpoint was the change in mean pain scores from baseline to the end of treatment. Results showed a significant reduction in pain scores in the THC:CBD group compared to placebo (mean difference: -0.67, $p = 0.014$). The response rate ($\geq 30\%$ pain reduction) was 43% in the

THC:CBD group, compared to 21% in the placebo group (odds ratio: 2.81, $p = 0.006$). No significant changes were observed in opioid background medication use or breakthrough analgesia. Adverse events were mild to moderate, with dizziness and somnolence being the most common. The study concluded that THC:CBD extract was effective as an adjunctive treatment for cancer-related pain in patients who did not achieve adequate analgesia with opioids alone. The findings supported the potential role of cannabinoids in managing intractable cancer pain. Fallon et al. (2017) conducted two Phase 3, double-blind, multicentre, randomized, placebo-controlled trials to evaluate the efficacy and safety of nabiximols (Sativex®) in advanced cancer patients with chronic pain unalleviated by optimized opioid therapy. Study 1 involved 399 patients randomized to receive Sativex® or placebo in a 5-week treatment period, while Study 2 had a two-part randomized withdrawal design involving 406 patients in Part A and 206 in Part B. In both studies, patients were titrated up to a maximum of 10 sprays/day during a 2-week titration phase. The primary endpoint in Study 1 was the percent improvement in average pain scores, while in Study 2, it was the mean change in average pain scores. In Study 1, the primary endpoint was not met, with no significant difference in percent improvement between Sativex® and placebo. However, secondary endpoints showed a trend toward improvement, particularly in subjective global impression of change (SGIC) and physician global impression of change (PGIC). In Study 2, the primary endpoint also did not show significant differences, but secondary analyses revealed reductions in worst pain and sleep disruption scores. The studies concluded that Sativex® did not demonstrate superiority over placebo in reducing average pain scores but showed potential benefits in secondary endpoints like worst pain and sleep disruption. The safety profile was consistent with previous research, with nausea, somnolence, and dizziness being the

most common adverse events. Further research is warranted to explore the potential benefits of Sativex® in specific patient subgroups.

Melén et al. (2022) conducted a Phase II, single-arm, open-label clinical trial to evaluate the effects of a single dose of THC/CBD oromucosal spray (Sativex®) on leukemic B cells in patients with indolent leukemic B cell lymphomas. The study included 23 asymptomatic patients, primarily those with chronic lymphocytic leukaemia (CLL). Participants were asymptomatic, had a performance status of 0, and were required to have lymphocyte counts exceeding $5 \times 10^9/L$. The trial sought to determine whether a single dose of Sativex® would significantly reduce leukemic B cells in the blood while also assessing the safety and tolerability of the intervention. Patients were titrated up to a maximum dose of 18.9 mg THC/17.5 mg CBD (seven sprays). The primary analysis showed a significant median reduction of 11% in leukemic B cells within two hours of administration ($p = 0.014$), which persisted for six hours. However, the reduction was transient, and no significant changes in apoptosis or cell proliferation were observed. Secondary analyses indicated a 37% median reduction in normal B cells and a 35% median reduction in T cells. Additionally, the study observed increased CXCR4 expression on leukemic B cells and T cells at one and three hours post-dose. Adverse events, primarily grade 1-2, were reported in 91% of patients, with dry mouth (78%), vertigo (70%), and somnolence (43%) being the most common. The study concluded that a single dose of THC/CBD spray transiently reduces leukemic B cells without inducing apoptosis or proliferation. However, this reduction was not sustained beyond six hours, indicating limited therapeutic potential for indolent leukemic B cell lymphomas. Casarett et al. (2019) conducted an electronic record-based retrospective cohort study to evaluate the efficacy of cannabis in managing common palliative care symptoms. The study involved 2,431 patients who

recorded symptom severity via the Strainprint® app before and after using cannabis. A total of 26,150 uses were recorded between October 1, 2017, and November 28, 2018, for six symptoms: neuropathic pain, anorexia, anxiety, depression, insomnia, and PTSD-related flashbacks. Patients used vaporized cannabis products verified through laboratory testing. The effectiveness threshold was defined as a three-point reduction in symptom severity on an 11-point scale. The study found that increasing the THC:CBD ratio was significantly associated with improved responses for neuropathic pain (OR: 3.58), insomnia (OR: 2.93), and depressive symptoms (OR: 1.63). In contrast, an inverted U-shaped response curve was observed for anxiety symptoms, with maximal benefit at a 1:1 THC:CBD ratio (50% THC). The adjusted response rates showed substantial improvements across all six symptoms: neuropathic pain (19.3% at 0% THC vs. 51.3% at 100% THC), insomnia (43.3% at 0% THC vs. 72.3% at 100% THC), depressive symptoms (49.4% at 0% THC vs. 63.1% at 100% THC), anxiety symptoms (maximal response at a 1:1 THC:CBD ratio (72.0%)), PTSD-related flashbacks (69.0% at 0% THC vs. 79.3% at 100% THC) and anorexia (55.8% at 0% THC vs. 78.8% at 100% THC). The study concluded that the THC:CBD ratio is a critical factor in managing palliative care symptoms, with a significant positive association observed for neuropathic pain, insomnia, and depressive symptoms. However, the inverted U-shaped response for anxiety highlights the importance of understanding individual symptom responses to specific cannabinoid ratios.

Good et al. (2020) conducted a prospective, two-arm, open-label pilot study to assess the feasibility and efficacy of THC and CBD oils in advanced cancer patients receiving palliative care. The study involved 21 patients with advanced cancer and cancer-related symptoms, who were randomized to receive either CBD or THC oil. Participants in the CBD arm received doses ranging from 50 to 600 mg/day, while

those in the THC arm received doses ranging from 2.5 to 30 mg/day. Feasibility was assessed by the number of patients screened, randomized, and completing the study, while efficacy was measured using the Edmonton Symptom Assessment Scale (ESAS). The Total Symptom Distress Score (TSDS) was used as the primary outcome, with a ≥ 6 -point reduction considered clinically significant. Results showed that 86% of patients completed the primary outcome measure at day 14, and 43% demonstrated a ≥ 6 -point reduction in TSDS. The greatest improvements were observed in anxiety, depression, and appetite scores. Both CBD and THC were generally well tolerated, with the most common adverse events being drowsiness, nausea, abdominal pain, and mood changes. The study concluded that trials of medicinal cannabis in advanced cancer patients are feasible and that both CBD and THC oils can be well tolerated in this population. Measures like TSDS are promising for assessing the overall symptom benefit of medicinal cannabis in palliative care settings.

Nathan et al. (2023) conducted a single-centre, retrospective chart review to evaluate the efficacy of medical cannabis in managing cancer-related symptoms in elderly patients at Roswell Park Comprehensive Cancer Center. The study included 83 cancer patients aged ≥ 65 years who had been certified for medical cannabis use and completed Edmonton Symptom Assessment Scale (ESAS) questionnaires before and after initiation. The patients were initially certified for a 1:1 THC:CBD ratio at the lowest dose, with subsequent titration managed by the dispensary. The primary outcome was the effect of medical cannabis on ESAS scores for pain, nausea, anorexia, anxiety, and insomnia. The results showed a modest reduction in pain scores (mean reduction from 4.6 to 4.0) and nausea (from 2.2 to 1.7), though these reductions were not statistically significant. Thirty-seven percent of patients experienced a 30% reduction

in pain, and 24% had a 30% reduction in nausea. However, there were no statistically significant changes in anxiety, anorexia, or insomnia scores. The study found that oil tinctures with a high THC:CBD ratio were the most commonly used formulations, with nearly 40% of patients reporting a 30% reduction in pain scores. Despite the lack of statistical significance, the study suggested that medical cannabis might be beneficial for managing cancer-related symptoms in elderly patients. Further research is warranted to assess its efficacy and safety in this population. Jatoi et al. (2002) conducted a multicentre, double-blind, randomized, placebo-controlled clinical trial involving 469 advanced cancer patients with cancer-associated anorexia. The study compared the efficacy of megestrol acetate, dronabinol, and their combination in improving appetite and promoting weight gain. Patients were randomized into three groups: MA (800 mg/day), DRON (2.5 mg twice daily), and a combination of both. The results showed that 75% of patients in the MA group reported appetite improvement compared to 49% in the DRON group ($p < .0001$). Additionally, 11% of patients in the MA group achieved a weight gain of $\geq 10\%$, compared to only 3% in the DRON group ($p = .02$). Combination therapy with both MA and DRON did not provide additional benefits over MA alone. Quality of life (QOL) improvements were more significant in the MA group than in the DRON group. Toxicity profiles revealed that male impotence was more prevalent in the MA group (18%) compared to DRON (4%) and combination groups (14%). Common adverse events across all groups included vomiting, fluid retention, drowsiness, and muddled thinking. The study concluded that megestrol acetate was more effective than dronabinol for improving appetite and promoting weight gain in patients with cancer-associated anorexia. The combination of MA and DRON did not provide additional benefits over MA alone. Strasser et al. (2006) conducted a multicentre, phase III, randomized, double-blind, placebo-controlled

clinical trial to assess the efficacy of cannabis extract (CE) and THC in patients with advanced cancer and cancer-related anorexia-cachexia syndrome (CACS). The study included 243 patients randomized into three groups: CE (2.5 mg THC and 1 mg CBD per capsule), THC (2.5 mg THC per capsule), and placebo. The primary outcomes were appetite improvement and quality of life (QOL), assessed using a Visual Analog Scale (VAS) for appetite and the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30). The results showed no significant differences in appetite scores between the CE, THC, and placebo groups. The mean change in appetite score was +5.4 mm in the CE group, +0.6 mm in the THC group, and +5.8 mm in the placebo group. Similarly, QOL scores showed no significant differences. Secondary outcomes, including mood, nausea, body weight, and functional domains, also showed no significant differences. Adverse events were comparable across all groups, with nausea/vomiting, fatigue, pain, anaemia, and dizziness being the most common. The study concluded that neither cannabis extract nor THC demonstrated superior efficacy over placebo in managing cancer-related anorexia-cachexia syndrome. Both treatments were well tolerated but did not significantly improve appetite or QOL compared to placebo.

Buchwald et al. (2023) conducted a single-centre, prospective case-series intervention study to evaluate the effects of dronabinol therapy on cognitive function and symptom relief in patients with advanced cancer and severe pain. Eight patients from the Palliative Care Outpatient Clinic at North Denmark Regional Hospital participated in the study, all of whom had cancer-related pain refractory to conventional palliative treatment. Patients were administered an oral oil solution of dronabinol, starting at 2.5 mg/day and titrating up to 12.5 mg/day over a two-week period. Cognitive function was assessed using the Processing Speed Index (PSI), Perceptual Organization Index

(POI), and Working Memory Index (WMI) subtests of the Wechsler Adult Intelligence Scale III (WAIS-III). Additionally, pain (VAS), depression (MDI), and fatigue (BFI) were measured. The results showed significant improvements in cognitive function: PSI (median score increased from 7 to 9 ($p = 0.020$)), POI (median score increased from 6 to 10 ($p = 0.034$)) and WMI (median score increased from 5 to 7 ($p = 0.039$)). Moreover, there was a significant reduction in pain scores (median VAS score reduced from 5 to 4, $p = 0.039$), with two patients achieving more than a 30% reduction in pain. Fatigue and depressive symptoms also improved significantly. The study concluded that low-dose dronabinol therapy improved cognitive function and significantly reduced pain, fatigue, and depressive symptoms in advanced cancer patients. Despite the small sample size, the findings support the potential of dronabinol as an adjuvant therapy in palliative care. Zutt et al. (2006) conducted an open-label case series involving seven patients with metastatic malignant melanoma and liver metastases. These patients had significant loss of appetite, nausea, and weight loss despite previous antiemetic treatment. The study aimed to evaluate the efficacy of dronabinol in improving appetite and nausea, as well as its impact on quality of life. Patients received 2.5 mg of dronabinol twice daily (1 hour before lunch and 1 hour before dinner) for four weeks. Appetite loss, nausea, and subjective quality of life were assessed using a questionnaire adapted from the WHO Quality of Life questionnaire. Results indicated that five patients experienced mild appetite loss after four weeks of dronabinol therapy, compared to six patients with severe appetite loss at baseline. Similarly, five patients had mild nausea, compared to three with severe nausea and four with moderate nausea at baseline. Quality of life ratings improved for four patients. All patients experienced mild to moderate dizziness, but none discontinued therapy due to adverse events. The study concluded that dronabinol could provide supportive

benefits in reducing appetite loss and nausea in patients with metastatic malignant melanoma, though the effects may diminish as the disease progresses. Côté et al. (2016) conducted a randomized, double-blind, placebo-controlled clinical trial to evaluate the efficacy of nabilone in improving quality of life for head and neck cancer patients undergoing radiotherapy. The study included 56 patients with histologically confirmed squamous cell carcinoma of the oral cavity, oropharynx, hypopharynx, or larynx. Patients were randomized to receive either nabilone (0.5 mg oral capsules) or placebo, starting at 0.5 mg at bedtime and titrated up to 1 mg twice daily. The primary outcome was the time required for a 15% improvement in global quality of life (EORTC QLQ-C30, items 29-30). The results showed no significant difference between nabilone and placebo in improving quality of life. Additionally, no significant differences were observed in secondary outcomes, including pain, appetite, nausea, weight change, and medication use. nabilone was well tolerated, with no significant differences in adverse events between the groups. The study concluded that nabilone was not potent enough at the dosages used to improve quality of life over placebo, but it was well tolerated and did not cause significant toxicity.

3.4.2.17.2. Research, clinical practice and future directions

The use of medicinal cannabis in palliative care has grown significantly in recent years due to an increasing number of jurisdictions legalizing cannabis for medical purposes. Palliative care aims to alleviate symptoms and improve the quality of life for patients with serious illnesses, particularly those with cancer. Cannabinoids, including THC and CBD, are being explored for their potential to manage symptoms like pain, nausea, vomiting, and anorexia/cachexia. Despite the growing interest and the increasing use

of cannabinoids in palliative care settings, the efficacy and safety of these compounds remain topics of debate. Recent research has investigated the role of THC, CBD, and combined THC/CBD formulations in alleviating various symptoms related to cancer and other serious conditions. A narrative review by Hatfield et al. (2024) discussed several randomized controlled trials (RCTs) involving cannabinoids in cancer patients and found that THC-based products, particularly THC/CBD combinations, are effective for managing chemotherapy-induced nausea and vomiting. However, CBD alone was ineffective for this indication. For other symptoms such as anorexia/cachexia, mood disturbances, and pain, the evidence remains inconclusive (Hatfield et al., 2024).

The management of pain in palliative care remains one of the most common and challenging areas of investigation. Lichtman et al. (2018) conducted a Phase III, double-blind, randomized, placebo-controlled clinical trial involving 397 patients with advanced cancer and chronic pain. They found that a THC/CBD oromucosal spray (Sativex®) did not significantly improve average pain scores compared to placebo. However, some secondary endpoints, including sleep disruption and global impressions of change, showed significant improvements (Lichtman et al., 2018). Similarly, Portenoy et al. (2012) reported no significant difference in pain reduction between a THC/CBD oromucosal spray and placebo, although a continuous responder analysis suggested a potential benefit in certain subgroups. In a study by Hardy et al. (2020), a randomized, placebo-controlled trial was conducted to assess the efficacy of a 1:1 THC/CBD formulation for symptom relief in patients with advanced cancer. Despite the lack of significant improvement in the Total Symptom Distress Score, the study provided valuable insights into dosage, safety, and patient preferences (Hardy et al., 2020). A subsequent study by Hardy et al. (2023) involving 142 patients with advanced cancer aimed to investigate the effects of CBD oil on

symptom distress. The results showed no significant difference between CBD oil and placebo in reducing symptom distress, suggesting that CBD alone may not offer substantial benefits in palliative care. Anorexia and cachexia are significant issues among cancer patients and those with chronic illnesses. A pivotal study by Jatoi et al. (2002) involving 469 patients compared megestrol acetate, dronabinol, and their combination. The study found that megestrol acetate was superior to dronabinol for appetite improvement and weight gain. Adding dronabinol to megestrol acetate did not provide additional benefits (Jatoi et al., 2002). Similarly, Strasser et al. (2006) found that neither THC nor THC/CBD improved appetite or quality of life in cancer patients with anorexia-cachexia syndrome. Côté et al. (2016) and Melén et al. (2022) also reported similar findings, indicating that cannabinoids may not significantly impact appetite or weight gain in cancer patients (Côté et al., 2016; Melén et al., 2022).

The potential role of medicinal cannabis in cognitive function improvement and mood stabilization in advanced cancer patients has also been explored. A study by Buchwald et al. (2023) involving eight patients with advanced cancer and severe pain found that low-dose dronabinol therapy improved cognitive function and significantly reduced pain, fatigue, and depressive symptoms. The study concluded that dronabinol might be beneficial as an adjunct therapy in palliative care, but further research is warranted (Buchwald et al., 2023). Despite some promising findings, the use of cannabinoids in palliative care is not without challenges. Hatfield et al. (2024) emphasized the importance of large-scale RCTs to clarify the role of cannabinoids in managing palliative care symptoms. They highlighted the need for standardized dosages, formulations, and administration routes in future research to enable better comparisons between studies.

3.4.3. Publication journals' metrics analysis

The following tables have been systematically compiled to present a detailed account of the study outcomes and the respective impact factors of the journals in which the studies were published, along with statistical data derived from the retrieved impact factors (Tables 3.27 - 3.60). These tables are based on data that were meticulously mined and extracted during the compilation process described in the previous section. They offer a structured and comprehensive overview of the bibliometric evidence, enabling a robust evaluation of the degree of support in the literature for the clinical use of medicinal cannabis across various conditions. The data featured below serve as a critical resource for understanding the scholarly impact and credibility of the publications analyzed, thereby informing subsequent discussions and conclusions within this research paper.

Authors	Journal	IF	Res	Outcomes
Sallan et al. (1975)	New England Journal of Medicine	96.2	+	THC significantly reduced nausea and vomiting compared to placebo; side effects included euphoria and dizziness.
Chang et al. (1979)	Annals of Internal Medicine	19.6	+	THC significantly reduced the number of vomiting and retching episodes, the degree and duration of nausea, and the volume of emesis compared to placebo.
Ekert et al. (1979)	The Medical Journal of Australia	7.7	+	THC was superior to metoclopramide for nausea control but caused dizziness and mild euphoria.
Frytak et al. (1979)	Annals of Internal Medicine	19.6	+	THC showed superior antiemetic activity compared to placebo but was not more effective than prochlorperazine. Central nervous system side effects, such as sedation and euphoria, were significantly more frequent with THC.
Herman et al. (1979)	New England Journal of Medicine	96.2	+	Nabilone demonstrated higher antiemetic efficacy compared to prochlorperazine. However, side effects were more frequent.
Kluin-Neleman et al. (1979)	Veterinary and Human Toxicology	0.66	+	THC showed significant antiemetic effects, but the side effects were severe enough that most patients preferred to endure the nausea and vomiting rather than use THC.
Steele et al. (1980)	Journal of the National Cancer Institute (Cancer Treatment Reports)	10	+	Nabilone was more effective than prochlorperazine for patients receiving chemotherapy agents other than high-dose cisplatin, achieving a complete or partial elimination of symptoms in 18 patients. Side effects of nabilone included frequent drowsiness and dizziness, which were dose-limiting in 25% of patients.
Chang et al. (1981)	Cancer	6.1		THC did not significantly reduce the number of vomiting episodes, volume of emesis, or degree and duration of nausea compared to placebo, indicating that its antiemetic properties may be limited to specific chemotherapy agents.
Einhorn et al. (1981)	Journal of Clinical Pharmacology	2.4	+	Nabilone significantly reduced the severity of nausea and the frequency of vomiting compared to prochlorperazine.
Neidhart et al. (1981)	Journal of Clinical Pharmacology	2.4		THC was as effective as haloperidol in controlling nausea and vomiting, though side effect were more common with THC. About 10% of patients achieved complete control of vomiting, and a third had fewer than five episodes.
Orr et al. (1981)	Journal of Clinical Pharmacology	2.4	+	Significantly reduced nausea compared to prochlorperazine and placebo, with 40 out of 55 patients who completed the study, experiencing no nausea on THC. An elevated "high", sedation, and transient loss of physical control were reported.
Johansson et al. (1982)	Cancer Treatment Reviews	9.6	+	Nabilone was found to be more effective than prochlorperazine in reducing nausea and vomiting episodes.
Jones et al. (1982)	Cancer Treatment Reviews	9.6	+	Nabilone showed superior antiemetic effects compared to placebo.
Levitt et al. (1982)	Cancer Treatment Reviews	9.6	+	Nabilone significantly reduced the severity of nausea and the frequency of vomiting compared to placebo. 78% preferred nabilone despite side effects such as vertigo, drowsiness, and depersonalization.

Authors	Journal	IF	Res	Outcomes
Ungerleider et al. (1982)	Cancer	6.1		THC and prochlorperazine showed similar efficacy in reducing nausea and vomiting, but THC had more side effects, including dizziness and sedation. Patient preference was not significantly affected by the side effects.
Wada et al. (1982)	Cancer Treatment Reviews	9.6	+	Demonstrated a significant reduction in nausea and vomiting for patients receiving THC compared to placebo. 70% of patients preferred nabilone over placebo despite side effects.
Ahmedzai et al. (1983)	British Journal of Cancer	6.4	+	Nabilone significantly improved nausea, retching, and vomiting scores compared to prochlorperazine, with fewer vomiting episodes and no need for additional anti-emetics.
George et al. (1983)	Biomedicine & Pharmacotherapy	6.9		Nabilone was not more effective than chlorpromazine in reducing vomiting episodes. Similar side effects. Patient preferences were mixed, with slightly more favouring nabilone.
Kleinman et al. (1983)	Current Therapeutic Research	1.6		No significant difference in the occurrence of vomiting between placebo and THC, though 3 patients vomited only with placebo. Two patients experienced dissociative reactions with THC. Not other side effects. The combination of prochlorperazine and THC was deemed safe and potentially beneficial.
Gralla et al. (1984)	Journal of the National Cancer Institute (Cancer Treatment Reports)	10	+	Findings indicated antiemetic effectiveness.
Niiranen & Mattson (1985)	American Journal of Clinical Oncology	1.6	+	Nabilone was significantly more effective than prochlorperazine in reducing vomiting episodes. Side effects in almost half the population, leading to three withdrawals. Two-thirds of patients preferred nabilone despite its side effects.
Crawford et al. (1986)	Medical Oncology (Medical Oncology and Tumor Pharmacotherapy)	2.8		No significant difference in antiemetic efficacy between nabilone and metoclopramide; side effects were consistent with the known pharmacology of the drugs.
Niederle et al. (1986)	Wiener klinische Wochenschrift – The Central European Journal of Medicine	1.9	+	Nabilone was significantly more effective than alizapride in reducing the frequency and duration of nausea and vomiting. More side effects with nabilone yet 50% preferred nabilone.
Pomeroy et al. (1986)	Cancer Chemotherapy and Pharmacology	2.7	+	Nabilone was significantly more effective than domperidone in reducing vomiting episodes, with fewer vomiting episodes observed during both cycles. Side effects were more common with nabilone.
McCabe et al. (1988)	Investigational New Drugs	3	+	THC reduced nausea and vomiting in 64% of patients compared to prochlorperazine, with all patients experiencing transient sensory changes such as euphoria or dysphoria.
Lane et al. (1991)	Journal of Pain and Symptom Management	3.2	+	The combination of dronabinol and prochlorperazine showed better control of nausea and vomiting compared to either agent alone. dronabinol had a higher incidence of CNS-related side effects like dizziness and somnolence.
Plasse et al. (1991)	Pharmacology Biochemistry and Behavior	3.3	+	Dronabinol provided better control of CINV than prochlorperazine (51% vs. 83%). A significant reduction in weight loss rate (-0.93 before vs +0.54 after therapy) particularly at 2.5mg BD.
Jhangiani et al. (2005)	Blood	22	+	Adding dronabinol to the standard antiemetic regimen significantly improved nausea control and reduced nausea intensity. CNS-related side effects were more common in the combination group.

Authors	Journal	IF	Res	Outcomes
Meiri et al. (2007)	Current Medical Research and Opinion	2.4		Dronabinol showed comparable efficacy to ondansetron for CINV, with a 54% total response rate versus 20% for placebo. The combination of dronabinol and ondansetron did not show additional benefits over individual treatments. Active treatments were generally well tolerated.
Duran et al. (2010)	British Journal of Clinical Pharmacology	3.1	+	71.4% of patients in the cannabis group achieved a complete response in controlling delayed CINV, compared to 22.2% in the placebo group.
Polito et al. (2018)	Pediatric Blood & Cancer	3.8		Complete control of vomiting achieved in 52.3% of patients. Adverse effects were common (34%) but mild, with sedation (20%) and dizziness (10%) being most frequent.
Grimison et al. (2020)	Annals of Oncology	56.7	+	Improvement in complete response rate from 14% to 25% with THC, with side effects such as sedation and dizziness noted. Improved quality of life scores and reduced number of vomiting episodes compared to placebo.
Sukpiriyagul et al. (2023)	International Journal of Women's Health	2.5	+	Reduced nausea scores in the THC group compared to placebo, especially on days 1, 2 and 5. Dizziness and sedation were common side effects.
Grimison et al. (2024)	Journal of Clinical Oncology	42.1	+	Complete response (no vomiting or use of rescue medications) was achieved in 24% of the cannabis group vs. 8% in the placebo group (absolute difference: 16%; p = .01)

Table 3.27. *Studies evaluating use of medicinal cannabis for chemotherapy-induced nausea and vomiting.*

Outcome	Journals (Total)	Impact Factor (Median)	Proportion of High-Impact Journals	Impact Factor (Weighted Average)
Positive	26	9.6	27%	17.15
Neutral / Non-Positive	8	3.3	0%	3.99

Table 3.28. *Chemotherapy-induced nausea and vomiting: journal considerations grouped by impact factor values.*

Authors	Journal	IF	Res	Outcomes
Cousens & DiMascio (1973)	Psychopharmacology (Psychopharmacologia)	3.4	+	Decreased sleep latency across all doses. THC significantly reduced sleep onset times compared to placebo.
Carlini et al. (1981)	Journal of Clinical Pharmacology	2.4	+	Participants reported reduced dream recall with all doses, and the 160 mg dose significantly increased sleep duration.
Nicholson et al. (2004)	Journal of Clinical Psychopharmacology	2.9	+	THC improved sedative effects; combinations with CBD impacted cognitive performance and mood.
Ware et al. (2010)	Anesthesia & Analgesia	4.6	+	Both treatments improved sleep, with nabilone showing a greater effect on sleep quality compared to amitriptyline. Side effects were more frequent with nabilone, including dizziness and dry mouth.
Tringale & Jensen (2011)	O'Shaughnessy's	-	+	Cannabis use was associated with a reduction in time to sleep onset across both groups.
Prasad et al. (2013)	Frontiers in Psychiatry	3.2	+	A significant reduction in AHI at 3 weeks from baseline, with an average decrease of 14.1 AHI units.
Chagas et al. (2014)	Journal of Clinical Pharmacy and Therapeutics	2.1	+	Substantial and consistent reduction in REM Sleep Behaviour Disorder events.
Farabi et al. (2014)	Journal of Clinical Sleep Medicine	3.5	+	Dronabinol was associated with EEG changes suggesting improved restorative sleep, though individual variability in responses was noted.
Zalai et al. (2015)	Psychotherapie, Psychosomatik, Medizinische Psychologie	1.1	+	Improvements in sleep parameters including a 3.8% increase in sleep efficiency and a significant increase in sleep onset latency.
Shannon & Opila-Lehman (2016)	Permanente Journal	1.2	+	Improved sleep quality and reduction in anxiety; the patient was able to sleep alone and manage daily activities.
Carley et al. (2017)	Sleep	5.3	+	Dose-dependent reduction of AHI compared to placebo. Improvements in subjective sleepiness and overall treatment satisfaction, but without improvement in sleep architecture.
Megelin & Ghorayeb (2017)	Sleep Medicine	3.8	+	All patients reported immediate relief from Restless Legs Syndrome symptoms.
Casarett et al. (2019)	Journal of Palliative Medicine	2.2	+	Reported significant improvement in sleep quality across treatment sessions, with 93% reporting reduced insomnia symptoms.
Shannon et al. (2019)	Permanente Journal	1.2		CBD treatment was associated with decreased anxiety scores over time, with mild improvement in sleep scores; well-tolerated with minimal side effects.
Aungsumart et al. (2021)	Journal of the Medical Association of Thailand	0.2	+	Reported moderate improvement in sleep disturbances as a secondary benefit of treatment, although primary focus was on MS-related symptoms.
de Almeida et al. (2021)	Movement Disorders Clinical Practice	4.0		CBD did not reduce REM sleep behaviour disorder events compared to placebo, although a transient improvement in sleep satisfaction was observed.

Table 3.29. *Studies evaluating use of medicinal cannabis to address sleep disorders.*

Outcome	Journals (Total)	Impact Factor (Median)	Proportion of High-Impact Journals	Impact Factor (Weighted Average)
Positive	14	2.9	46.2%	3.22
Neutral / Non-Positive	2	2.6	50%	2.60

Table 3.30. *Sleeping disorders: journal considerations grouped by impact factor values.*

Authors	Journal	IF	Res	Outcomes
Killestein et al. (2002)	Neurology	8.3		No significant reduction in spasticity.
Wade et al. (2003)	Clinical Rehabilitation	2.6	+	Improvement in symptoms such as pain, bladder control, spasms, and spasticity. Adverse effects included transient hypotension and intoxication.
Zajicek et al. (2003)	The Lancet	98.4		Mixed results with no significant reduction in objective spasticity measures using the Ashworth scale, but improvements in subjective VAS scores for spasticity (60% vs 46% placebo).
Fox et al. (2004)	Neurology	8.3		No significant improvement in tremor index; some patients reported subjective relief, but no objective change.
Vaney et al. (2004)	Multiple Sclerosis International	2.2	+	Significant reduction in spasticity scores on the Ashworth scale. Some minor adverse effects.
Wade et al. (2004)	Multiple Sclerosis International	2.2	+	Improvement in patient-reported spasticity and symptom relief. Adverse effects were minimal and included mild sedation and dizziness.
Collin et al. (2007)	The European Journal of Neurology	5.1	+	Moderate reduction in spasticity symptoms. Adverse effects were generally mild and included dizziness and nausea.
Collin et al. (2010)	Neurological Research	1.7	+	Significant improvement in spasticity (0-10 Numerical Rating Scale, NRS) in the per-protocol population, with 36% achieving $\geq 30\%$ improvement versus 24% for placebo.
Notcutt et al. (2011)	Multiple Sclerosis International	2.2	+	Longer time to treatment failure than placebo (28 days vs 1.5 days). Patient- and caregiver-reported improvements in symptom control and overall functional status.
Novotna et al. (2011)	The European Journal of Neurology	5.1	+	Notable reduction in spasticity (0.84 mean reduction in NRS score compared to placebo). Improved spasm frequency and sleep quality. Most adverse effects were mild to moderate.
Corey-Bloom et al. (2012)	Canadian Medical Association Journal	12.3	+	Significant reduction in spasticity (Modified Ashworth Scale) and pain (visual analogue scale), with no significant effect on timed walk; cognitive function decreased during treatment.
Serpell et al. (2012)	Journal of the Neurology	4.8	+	Patients reported stable symptom relief over time, with no evidence of tolerance. Only 14% withdrew due to adverse effects. No withdrawal syndrome observed on cessation.

Authors	Journal	IF	Res	Outcomes
Zajicek et al. (2012)	Journal of Neurology, Neurosurgery and Psychiatry	8.8	+	Improved muscle stiffness (OR: 2.26). Patient-reported improvement in muscle spasms (30.8% vs 13.4%, body pain (28% vs 18.7%), and sleep quality (33.6% vs 19.4%).
Koehler et al. (2014)	International Journal of Neuroscience	1.7	+	57% reduction in spasticity score in responders (numerical rating scale) with a 72% response rate. Most common adverse effects were dizziness, fatigue, and oral discomfort.
Ferre et al. (2015)	Neurological Sciences	2.7	+	Significant improvement in spasticity and pain (numerical rating scale). Low drop-out rate and manageable side effects.
Leocani et al. (2015)	Journal of the Neurology	4.8	+	Sativex® resulted in a significant improvement in spasticity (measured by Modified Ashworth Scale) compared to placebo (50% vs. 23.5% response rate). No significant differences in neurophysiological measures of spasticity.
Haupts et al. (2016)	European Neurology	2.1	+	Significant reduction in spasticity on the 0-10 Numerical Rating Scale (NRS) compared to placebo, with improvement in associated symptoms like sleep disruption and timed 10-meter walk. Some adverse events noted (dizziness and nausea).
van Amerongen et al. (2017)	Clinical Therapeutics	3.2	+	Pain and spasticity were reduced. No significant effect was observed in the objective measures (H/M ratio) vs placebo.
Marková et al. (2018)	International Journal of Neuroscience	1.7	+	Reduced spasticity (77.4% responders with ≥ 30% improvement in NRS spasticity score vs to 32.1% in placebo).
Meuth et al. (2020)	International Journal of Neuroscience	1.7	+	Reduced spasticity and pain (0-10 NRS) in active treatment group across various subgroups. Consistent therapeutic response observed across disability and spasticity subgroups.
Patti et al. (2020)	Journal of the Neurological Sciences	3.7	+	At 4 weeks, 70.5% of patients achieved a ≥20% reduction in spasticity NRS scores. 43.8% reported improvements in at least one spasticity-related symptom: cramps, nocturnal spasms, bladder dysfunction, pain, and sleep disturbances.
Guger et al. (2023)	Brain and Behavior	2.7	+	Reduced spasticity (39%), sleep impairment (47.2%), fatigue, pain (40.4%), and urinary incontinence episodes.
Hansen et al. (2023)	Pharmaceuticals	4.3		No significant difference with placebo for pain intensity or spasticity levels.
Rainka et al. (2023)	International Journal of MS Care	1.2	+	48% decreased spasticity. 72% pain relief, 40% improved sleep. 22% discontinued opioids and 32% reduced dosage.
Garde and Heibel (2024)	Drugs in Context	2.5	+	Significant improvements in spasticity severity for 11 patients, with 8 achieving ≥30% reduction in NRS scores. Additional improvements were observed in related symptoms.
Haupts et al. (2024)	Neurodegenerative Disease Management	2.6	+	Meaningful reductions in spasticity, pain, sleep quality, and bladder dysfunction. Over 60% of treatment goals achieved.

Table 3.31. *Studies evaluating use of medicinal cannabis for multiple sclerosis spasticity.*

Outcome	Journals (Total)	Impact Factor (Median)	Proportion of High-Impact Journals	Impact Factor (Weighted Average)
Positive	22	2.6	4.5%	3.48
Neutral / Non-Positive	4	8.3	25%	29.83

Table 3.32. *Multiple sclerosis spasticity: journal considerations grouped by impact factor values.*

Authors	Journal	IF	Res	Outcomes
Weber et al. (2010)	Journal of Neurology, Neurosurgery & Psychiatry	8.8		No significant improvement in cramp intensity, frequency, or secondary outcomes such as fasciculation intensity, quality of life, sleep quality, appetite, depression, between THC and placebo. THC was generally well tolerated, with only mild dizziness reported as an adverse effect.
Meyer et al. (2019)	BMC Neurology	2.2	+	Significant patient satisfaction with the treatment for spasticity (TSQM-9 scores showed high satisfaction across effectiveness, convenience, and global satisfaction domains). The Net Promoter Score (NPS) indicated a high recommendation rate, especially among those with moderate to severe spasticity. Mild side effects like dizziness and fatigue were observed in some patients.
Lou et al. (2022)	Palliative Medicine	3.6	+	Improvement in pruritus from a score of 7/10 to 3/10. Initial sedation as a side effect, which subsided with continued use. This case highlights cannabinoids as potentially safe and effective for neuropathic pruritus.
Lacroix et al. (2023)	Revue Neurologique	2.8	+	Reported improvements in symptoms such as sleep quality, pain, rigidity, cramps, and fasciculations; 53.6% reported an overall positive impression of change. Adverse effects included drowsiness (10.7%) and euphoria (10.7%).
Austin et al. (2024)	Journal of the Neurological Sciences	3.7		Medicinal cannabis use correlated with short-term alleviation of pain, poor appetite, and anxiety but did not impact spasticity or insomnia. It was also associated with faster ALS progression, showing a greater decline in ALS Functional Rating Scale-Revised scores than in controls, though patients on THC had higher initial symptom burdens. No significant difference in BMI maintenance was observed between groups.

Table 3.33. *Studies evaluating use of medicinal cannabis to address amyotrophic lateral sclerosis.*

Outcome	Journals (Total)	Impact Factor (Median)	Proportion of High-Impact Journals	Impact Factor (Weighted Average)
Positive	3	2.8	0%	2.87
Neutral / Non-Positive	2	6.3	50%	6.25

Table 3.34. *Amyotrophic lateral sclerosis: journal considerations grouped by impact factor values.*

Authors	Journal	IF	Res	Outcomes
Consroe et al. (1991)	Pharmacology Biochemistry and Behavior	3.3		No significant effect on chorea severity or other symptoms compared to placebo. CBD was well-tolerated with no severe adverse effects. Mild side effects were similar between CBD and placebo.
Curtis & Rikards (2006)	Journal of Neuropsychiatry and Clinical Neurosciences	2.4	+	Improvements in irritability and reduction in chorea, enhancing quality of life.
Curtis (2009)	Movement Disorders	8.6	+	Improvement in chorea, neuropsychiatric symptoms, and behaviour, but no significant change in overall motor function.
Lopez-Sendon Moreno et al. (2016)	Journal of Neurology	4.8		No significant improvement in motor, cognitive, or behavioural symptoms, but safe and well-tolerated.
Saft et al. (2018)	Journal of Huntington's Disease	2.1	+	Improvement in dystonia, motor symptoms, and quality of life.

Table 3.35. *Studies evaluating use of medicinal cannabis to address Huntington's Disease.*

Outcome	Journals (Total)	Impact Factor (Median)	Proportion of High-Impact Journals	Impact Factor (Weighted Average)
Positive	3	2.4	33%	4.37
Neutral / Non-Positive	2	4.05	0%	4.05

Table 3.36. *Huntington's Disease: journal considerations grouped by impact factor values.*

Authors	Journal	IF	Res	Outcomes
Volicer et al. (1997)	International Journal of Geriatric Psychiatry	3.6	+	Weight gain and reduced severity of disturbed behaviour. Adverse effects included mild euphoria and somnolence, with one patient experiencing a seizure.
Walther et al. (2006)	Psychopharmacology	3.5	+	Reduction in nocturnal motor activity, agitation, and aberrant motor behaviour as measured by actigraphy and NPI scores.
Mahlberg & Walther (2007)	Zeitschrift für Gerontologie und Geriatrie	1.1	+	Significant reduction in nocturnal agitation and Neuropsychiatric Inventory (NPI) agitation scores. Actigraphy showed decreased nocturnal activity in the treatment group compared to baseline.
Passmore (2007)	International Journal of Geriatric Psychiatry	3.6	+	Significant reduction in agitation and resistiveness during personal care. No adverse effects were reported, and behaviour remained well-controlled for three months following discharge.
Woodward et al. (2014)	The American Journal of Geriatric Psychiatry	4.4	+	Decrease in agitation and aggression scores (Pittsburgh Agitation Scale) and improvements in Clinical Global Impression scores.
Ahmed et al. (2015)	Psychopharmacology	3.5		No significant improvement in neuropsychiatric symptoms. Adverse events were mild, primarily dizziness and somnolence. Body sway increased in the THC group but was not clinically significant.
van den Elsen et al. (2015a)	The American Journal of Geriatric Psychiatry	4.4		No significant reduction in NPS as measured by the NPI compared to placebo. THC was well-tolerated with a similar adverse event profile to placebo.
van den Elsen et al. (2015b)	Neurology	8.3		No significant benefit of THC on NPS or agitation levels compared to placebo. Both groups saw a reduction in NPI scores, attributed to study involvement.
Shelef et al. (2016)	Journal of Alzheimer's Disease	3.4	+	Notable reduction in NPI scores and Clinical Global Impression (CGI) severity scores, particularly in agitation/aggression, irritability, apathy, sleep, and caregiver distress.
van den Elsen et al. (2017)	Journal of Psychopharmacology	4.5		Increased body sway during balance tasks with closed eyes. Increased stride length during gait assessment. No significant adverse events.
Broers et al. (2019)	Medical Cannabis and Cannabinoids	1.03	+	Reductions in BPSD scores, including 40% reduction in Neuropsychiatric Inventory, 50% reduction in rigidity score. Decreased psychotropic medication use, improved care staff satisfaction.

Table 3.37. *Studies evaluating use of medicinal cannabis to address Alzheimer's Disease.*

Outcome	Journals (Total)	Impact Factor (Median)	Proportion of High-Impact Journals	Impact Factor (Weighted Average)
Positive	7	3.5	0%	2.95
Neutral / Non-Positive	4	4.5	25%	5.2

Table 3.38. *Alzheimer's Disease: journal considerations grouped by impact factor values.*

Authors	Journal	IF	Res	Outcomes
Consroe et al. (1986)	International Journal of Neuroscience	1.7	+	Dose-related improvement in dystonia observed (20-50%); mild side effects included hypotension, dry mouth, psychomotor slowing, light-headedness, and sedation.
Frankel et al. (1990)	Journal of Neurology, Neurosurgery & Psychiatry	8.8		No improvement in tremor following marijuana administration; patients did experience drowsiness and mild euphoria.
Sieradzan et al. (2001)	Neurology	8.3	+	Reduction in total dyskinesia score (22.2% reduction in on-period dyskinesia). Minor transient adverse effects like sedation and dizziness reported.
Carroll et al. (2004)	Neurology	8.3		No improvement in dyskinesias or Parkinson's symptoms compared to placebo.
Mesnage et al. (2004)	Clinical Neuropharmacology	0.8		No improvement in motor symptoms or levodopa-induced dyskinesias with the cannabinoid receptor antagonist.
Venderová et al. (2004)	Movement Disorders	8.6	+	45.9% reported improvement in symptoms including tremor, bradykinesia, rigidity, and dyskinesias. Regular use was correlated with higher rates of reported symptom alleviation.
Zuardi et al. (2009)	Journal of Psychopharmacology	4.5		Significant reduction in psychotic symptoms measured by the Brief Psychiatric Rating Scale and the Parkinson Psychosis Questionnaire. No worsening of motor symptoms, and CBD was well tolerated with no adverse effects.
Chagas et al. (2014a)	Journal of Psychopharmacology	4.5		No improvement in motor symptoms but potential improvement in quality of life in higher CBD dose group.
Chagas et al. (2014b)	Journal of Clinical Pharmacy and Therapeutics	2.1	+	Reduction in frequency of REM sleep behaviour disorder events without side effects.
Lotan et al. (2014)	Clinical Neuropharmacology	0.8	+	Improvement in motor symptoms (tremor, rigidity, bradykinesia) and non-motor symptoms (pain and sleep quality).
Finseth et al. (2015)	Evidence-Based Complementary and Alternative Medicine	2.1	+	Effective for mood and sleep improvement, and across therapies for both motor and non-motor symptoms.
Balash et al. (2017)	Clinical Neuropharmacology	0.8	+	Improvements in falls, pain, depression, tremor, muscle stiffness, and sleep. Some adverse effects like cough, confusion, and hallucinations were reported.
Kindred et al. (2017)	Complementary Therapies in Medicine	3.3	+	Improvements in mood, memory, and fatigue. 59% reported reducing prescription medications.
Shohet et al. (2017)	European Journal of Pain	3.5	+	Decrease in motor symptoms (UPDRS scores) and pain scores (PRI, VAS). Reduced pain thresholds observed over time.
Yust-Katz et al. (2017)	Clinical Journal of Pain	2.9	+	Effective for pain relief in 77% of patients, impacting quality of life. As effective as NSAIDs.
de Faria et al. (2020)	Journal of Psychopharmacology	4.5	+	Reduced anxiety and tremor amplitude during simulated public speaking, suggesting an anxiolytic effect of CBD in PD patients.

Authors	Journal	IF	Res	Outcomes
Leehey et al. (2020)	Cannabis and Cannabinoid Research	3.1	+	Improved motor symptoms (17.8% decrease in total MDS-UPDRS score and 24.7% in motor scores). Adverse effects included mild to moderate diarrhoea, somnolence, and fatigue, with 38% experiencing elevated liver enzymes at high doses.
Micheli et al. (2020)	Parkinsonism and Related Disorders	3.1	+	44.6% reported symptom improvement, motor and non-motor. Adverse effects included drowsiness, motor worsening, hallucinations, and other mild symptoms.
Holden et al. (2022)	Movement Disorders Clinical Practice	4.0	+	Improvements in pain, anxiety, agitation, and sleep.
Domen et al. (2023)	Movement Disorders	8.6		The CBD/THC group showed slightly worse performance on verbal fluency tests compared to placebo, and reported adverse cognitive events. No significant improvement in motor symptoms relative to placebo. Slight declines in cognition and sleep were noted in the CBD/THC group.
Sousa et al. (2023)	Cureus	1.2		Some patients reported improvements in pain (71% noted some reduction), sleep, and reductions in anxiety. Lower global cognitive scores on the MoCA for CBD/THC users compared to non-users. No significant differences in other neuropsychological measures or motor function. Reported side effects included sleepiness, concentration difficulties, and forgetfulness.
Liu et al. (2024)	Movement Disorders	8.6		No significant difference in motor improvement between groups. Placebo showed better results in sleep and cognition. Mild adverse events reported, with more frequent adverse effects in the CBD/THC group.

Table 3.39. *Studies evaluating use of medicinal cannabis to address Parkinson's Disease.*

Outcome	Journals (Total)	Impact Factor (Median)	Proportion of High-Impact Journals	Impact Factor (Weighted Average)
Positive	14	3.1	14.3%	3.56
Neutral / Non-Positive	8	4.5	50%	5.66

Table 3.40. *Parkinson's Disease: journal considerations grouped by impact factor values.*

Authors	Journal	IF	Res	Outcomes
Plasse et al. (1991)	Pharmacology Biochemistry and Behavior	3.3	+	Improvement in appetite and mood. A reduction in weight loss (-0.93 before vs +0.54 after therapy) particularly at 2.5mg BD.
Nelson et al. (1994)	Journal of Palliative Care	1.3	+	13 of 18 patients reported an improvement in appetite, with mild adverse effects. The study concluded THC to be an effective appetite stimulant with good tolerance at low doses.
Jatoi et al. (2002)	Journal of Clinical Oncology	42.1		Megestrol acetate led to greater weight gain compared to dronabinol. Combination therapy did not show extra benefits.
Walsh et al. (2005)	Journal of Pain and Symptom Management	3.2	+	Stable or improved appetite and weight gain, with median weight gain of 1 kg in 5 patients.
Strasser et al. (2006)	Journal of Clinical Oncology	42.1		No significant differences in appetite or body weight compared to placebo. The cannabinoid treatment was associated with a higher rate of adverse events.
Johnson et al. (2010)	Journal of Pain and Symptom Management	3.2	+	THC:CBD extract showed potential for pain relief and slight appetite improvement, while the THC-only group showed minimal effect. Quality of life was not significantly improved.
Brisbois et al. (2011)	Annals of Oncology	56.7	+	Improved appetite (64% vs 50%) and chemosensory perception (36% vs 15%). No significant improvement in quality of life.
Portenoy et al. (2012)	The Journal of Pain	4.0	+	Significant reduction in pain observed in low and medium-dose groups compared to placebo. High-dose group had more adverse effects without additional pain relief benefits.
Johnson et al. (2013)	Journal of Pain and Symptom Management	3.2	+	Long-term use was generally well tolerated with no evidence of loss of analgesic effect. Sustained benefit without tolerance development.
Singh & Bali (2013)	Case Reports in Oncology	0.7	+	Symptomatic improvement. No adverse effects documented.
Lynch et al. (2014)	Journal of Pain and Symptom Management	3.2	+	3 patients reported a clinically significant reduction in pain (≥ 2 points on a numeric pain scale). nabiximols may reduce chemotherapy-induced neuropathic pain.
Côté et al. (2015)	Annals of Otology, Rhinology & Laryngology	1.3		No significant improvement in quality of life, pain, appetite, or nausea compared to placebo.
Elder & Knoderer (2015)	Journal of Pediatric Pharmacology and Therapeutics	1.3	+	Dronabinol provided symptomatic relief, but some patients reported mild adverse effects like dizziness.
Fallon et al. (2017)	British Journal of Pain	1.8	+	No significant improvement in primary endpoints for pain reduction in the full sample; however, post hoc analysis showed favourable effects in patients under 65.
Warren et al. (2017)	Neurocase	0.7	+	Reported improvement in seizure control, with no significant adverse effects reported.
Dorris et al. (2018)	Neuro-Oncology	16.4	+	Assessed quality of life impacts using the PedsQL 4.0 module. Reported benefits but did not specify adverse events.
Kasvis et al. (2018)	Annals of Palliative Medicine	1.9	+	Significant improvement in appetite scores (baseline: 5.07; follow-up: 3.56; $P = 0.0026$). No significant changes in weight.
Lichtman et al. (2018)	Journal of Pain and Symptom Management	3.2	+	Modest improvement in pain scores versus placebo in the per-protocol analysis but not the intention-to-treat population. Significant improvements were seen in quality-of-life measures.

Authors	Journal	IF	Res	Outcomes
Turcott et al. (2018)	Supportive Care in Cancer	2.8	+	Improved appetite and reduced pain and insomnia. Adverse events included drowsiness and dry mouth.
Anderson et al. (2019)	JCO Oncology Practice (Journal of Oncology Practice)	4.7	+	High patient-reported efficacy for anxiety and pain, with mild adverse effects including fatigue.
Kasvis et al. (2019)	Supportive Care in Cancer	2.8	+	Improvement in appetite across visits, though weight remained stable. 80% of patients reporting anorexia noted improvements.
Bar-Sela et al. (2019)	Integrative Cancer Therapies	3.1	+	≥10% weight gain. Others maintained stable weight. Improved appetite, mood. Reduction in fatigue and pain.
Doherty et al. (2020)	Palliative Medicine	3.6	+	Observed benefits for pain, nausea, vomiting, anorexia, and insomnia. Limited adverse effects
Zylla et al. (2021)	Supportive Care in Cancer	2.8	+	Improved pain control and reduced opioid requirements in the early cannabis group compared to the delayed group. However, some patients faced challenges with self-administering and maintaining documentation for dosing and effects.
Clarke et al. (2022)	PLOS ONE	2.9	+	Improvements in pain and quality of life metrics (EORTC-QLQ-30 scores). Noted rapid absorption and clearance of THC and CBD, indicating a well-tolerated profile at administered doses.
Sharon et al. (2024)	BMJ Supportive & Palliative Care	2.0	+	70% of patients reported improvement in pain and other symptoms. 40% reported improvement in coping with illness.

Table 3.41. *Studies evaluating use of medicinal cannabis in cancer patients.*

Outcome	Journals (Total)	Impact Factor (Median)	Proportion of High-Impact Journals	Impact Factor (Weighted Average)
Positive	23	2.85	8.7%	5.66
Neutral / Non-Positive	3	42.1	66.7%	28.50

Table 3.42. *Cancer: journal considerations grouped by impact factor values.*

Authors	Journal	IF	Res	Outcomes
Hemming & Yellowlees (1993)	Journal of Psychopharmacology	4.5	+	Complete resolution of tics with daily cannabis use. Improved quality of life reported.
Muller-Vahl et al. (1998)	Acta Psychiatrica Scandinavica	5.3	+	14 out of 17 users with prior cannabis use reported improvement in motor and vocal tics and associated symptoms, including obsessive-compulsive behaviours.
Muller-Vahl et al. (1999)	American Journal of Psychiatry	15.1	+	A reduction in both motor and vocal tics, with improvement lasting about 7 hours. 70% improvement in tic severity and improved attention and impulse control.
Muller-Vahl et al. (2001)	Pharmacopsychiatry	3.6	+	Significant reduction in TS tic severity and obsessive-compulsive symptoms with THC compared to placebo. No significant adverse effects.
Muller-Vahl et al. (2003)	The Journal of Clinical Psychiatry	5.3	+	Significant reduction in TS tic severity as measured by TS-CGI, STSSS and YGTSS compared to placebo.
Schindler et al. (2008)	American Journal of Psychiatry	15.1	+	Reduced OCD symptoms, particularly in compulsive behaviours. dronabinol was effective as an augmentation therapy in treatment-resistant OCD.
Hasan et al. (2010)	Journal of Clinical Psychopharmacology	2.9	+	Reduced tics and improved quality of life. Increased intracortical inhibition observed through transcranial magnetic stimulation, suggesting THC as an effective alternative for refractory TS, allowing concurrent ADHD treatment with methylphenidate.
Brunnauer et al. (2011)	Psychiatry Research	4.2	+	TS tic reduction. 75% decrease in YGTSS scores. Improved psychomotor functions, particularly in driving ability, without affecting neuropsychological performance.
Trainor et al. (2016)	Australasian Psychiatry	1.2	+	Substantial reduction in both motor and vocal tics, with a reported 85% reduction in motor tics and 90% reduction in vocal tics. No adverse effects were noted.
Abi-Jaoude et al. (2017)	The Journal of Neuropsychiatry and Clinical Neurosciences	2.4	+	60% reduction in TS tic scores, with 18 of 19 patients reporting significant improvement. Side effects noted, but well tolerated.
Cooper et al. (2017)	The Journal of Neuropsychiatry and Clinical Neurosciences	2.4	+	Reduction in OCD symptoms with a Y-BOCS score drop from 39 to 10, allowing tolerance to cognitive-behavioural therapy.
Jakubovski & Müller-Vahl (2017)	International Journal of Molecular Sciences	4.9	+	Significant improvement in tic reduction (up to 70%) and improvement in quality of life, with no adverse effects reported.
Kanaan et al. (2017)	Brain Sciences	2.7	+	Tic severity was reduced. Improvement in premonitory urges, global impairment, and quality of life. No significant adverse effects were reported.
Pichler et al. (2018)	The International Journal of Psychiatry in Medicine	1.1	+	Marked improvement in tic severity and frequency. YGTSS score from 73 to 44. Enhanced quality of life and no significant side effects.
Szejko et al. (2018)	European Journal of Medical Case Reports	-	+	Significant improvement in tics, ADHD symptoms, and quality of life. Reduced tic severity, depression, and anxiety.
Thaler et al. (2018)	Parkinsonism and Related Disorders	3.1	+	Majority reported improvement in tic severity, sleep, and mood. 10 patients discontinued due to side effects. 3.85/5 mean efficacy score.

Authors	Journal	IF	Res	Outcomes
Milosev et al. (2019)	Cannabis and Cannabinoid Research	3.1	+	Improvement in TS tic severity (average 60% reduction) and psychiatric comorbidities, especially OCD symptoms. Patients generally preferred THC-rich cannabis strains over other formulations, reporting fewer adverse effects and improved quality of life.
Szejko et al. (2019)	Medical Cannabis and Cannabinoids	1.03	+	Marked reduction in tic severity and premonitory urges observed within 30 minutes of vaporization. The combination of vaporized cannabis and oral THC was well-tolerated.
Jakubovski et al. (2020)	Frontiers in Psychiatry	3.2	+	≥30% reduction in Tourette Syndrome tic severity on the Yale Global Tic Severity Scale (YGTSS) after 13 weeks.
Kayser et al. (2020a)	Depression and Anxiety	4.9		No significant acute effect on OCD symptoms between placebo, THC, and CBD. However, anxiety was lower in the placebo condition immediately after administration.
Kayser et al. (2020b)	Journal of Clinical Psychopharmacology	2.9		Nabilone combined with exposure and response prevention (EX/RP) showed a larger reduction in OCD symptoms compared to nabilone alone. Improvements were maintained at the 1-month follow-up. Significant mean change in YBOCS scores.
Kayser et al. (2021)	Journal of Obsessive-Compulsive and Related Disorders	1.9	+	Most respondents reported cannabis improved OCD symptoms, particularly anxiety and compulsive behaviours. High-frequency users reported mixed effects.

Table 3.43. *Studies evaluating use of medicinal cannabis to address Obsessive-Compulsive Disorder and Tourette Syndrome.*

Outcome	Journals (Total)	Impact Factor (Median)	Proportion of High-Impact Journals	Impact Factor (Weighted Average)
Positive	20	3.1	10.5%	4.8
Neutral / Non-Positive	2	3.9	0%	3.9

Table 3.44. *Obsessive-Compulsive Disorder and Tourette Syndrome: journal considerations grouped by impact factor values.*

Authors	Journal	IF	Res	Outcomes
Devinsky et al. (2016)	The Lancet Neurology	46.5	+	Median reduction in monthly motor seizures by 36.5%. Common adverse events included somnolence (25%), decreased appetite (19%), diarrhoea (19%), and fatigue (13%).
Gofshteyn et al. (2016)	Journal of Child Neurology	2.0	+	6 out of 7 patients showed significant seizure reduction. 1 patient died due to multiorgan failure related to prolonged anaesthetic use.
Hess et al. (2016)	Epilepsia	6.6	+	Median seizure reduction of 48.8% at 3 months.
Devinsky et al. (2017)	The New England Journal of Medicine	96.2	+	Median reduction in convulsive seizure frequency (38.9%) compared to placebo (13.3%).
Rosenberg et al. (2017)	Epilepsia	6.6	+	Improvement in quality of life across various domains, including energy, memory, social interaction, and overall quality of life. Not directly correlated with changes in seizure frequency.
Devinsky et al. (2018b)	The New England Journal of Medicine	96.2	+	Significant reduction in drop seizure frequency (41.9% in 20mg group, 37.2% in 10mg group) compared to placebo (17.2%).
Devinsky et al. (2018c)	Epilepsy & Behavior	2.3	+	Median reduction in convulsive seizure frequency at 12 weeks was 51.4% and at 48 weeks was 59.1%. 50% of patients achieved at least a 50% reduction in seizure frequency by 12 weeks, with 57% achieving this threshold by 48 weeks.
McCoy et al. (2018)	Annals of Clinical and Translational Neurology	4.4	+	70.6% median reduction in motor seizures, with a 50% responder rate of 63%. Improved quality of life. Adverse events: somnolence (89.5%), anorexia (52.6%), and diarrhoea (31.6%).
Szaflarski et al. (2018a)	Epilepsia	6.6	+	Median reduction in monthly convulsive seizures by 51% and total seizures by 48% at 12 weeks, with sustained reductions through 96 weeks.
Szaflarski et al. (2018b)	Epilepsy & Behavior	2.3	+	Significant reductions in seizure frequency and severity at 12 weeks, sustained through 48 weeks. Improvements in adverse event profile and seizure severity score were also observed.
Thiele et al. (2018)	The Lancet	98.4	+	Median reduction in monthly drop seizure frequency by 43.9% in the cannabidiol group vs 21.8% in the placebo group.
Devinsky et al. (2019)	Epilepsia	6.6	+	Median reduction in monthly convulsive seizures by 38-44% and total seizures by 39-51%. Adverse events included diarrhoea, pyrexia, decreased appetite, and somnolence. 85% of patients/caregivers reported improvement on the Subject/Caregiver Global Impression of Change scale.
Klotz et al. (2019)	Frontiers in Neurology	3.5	+	Median reduction in motor seizure frequency by 40% at 3 months, increasing to 49% at 6 months.
Knupp et al. (2019)	Seizure: European Journal of Epilepsy	2.7	+	24% response rate ($\geq 50\%$ reduction in seizures). 14% discontinued CBD + THC due to an increase in seizures.
Laux et al. (2019)	Epilepsy Research	2.0	+	Significant reductions in monthly convulsive and total seizures. At 12 weeks, convulsive seizure reduction was 50%, and total seizures were reduced by 44%. Improvements up to 96 weeks.
Mitelpunkt et al. (2019)	Epilepsy & Behavior	2.3	+	56% reduction in seizure frequency. Improvements reported by caregivers in seizure severity and condition.
Miller et al. (2020)	JAMA Neurology	20.9	+	Reduction in convulsive seizure frequency by 48.7% for 10 mg/kg/day and 45.7% for 20 mg/kg/day groups, compared to 26.9% in the placebo group.

Authors	Journal	IF	Res	Outcomes
Thiele et al. (2021)	JAMA Neurology	20.9	+	Reduction in Tuberous sclerosis complex-associated seizures by 48.6% for 25 mg/kg/day and 47.5% for 50 mg/kg/day groups, compared to 26.5% for placebo.
Navarro (2023)	Neurological Sciences	2.7	+	At 12 weeks, 79.5% of patients achieved >50% reduction in seizure frequency, with a median reduction in seizure frequency of 84.1%. 27.3% of patients were seizure-free at 12 weeks.
Berg et al. (2024)	Epilepsy Research	2.0	+	85% of caregivers reported an improvement in seizure frequency. Nonseizure-related improvements in alertness, cognition, emotional functioning, and sleep. Caregivers also noted improvements in physical function and daily activities.

Table 3.45. *Studies evaluating use of medicinal cannabis to address epilepsy.*

Outcome	Journals (Total)	Impact Factor (Median)	Proportion of High-Impact Journals	Impact Factor (Weighted Average)
Positive	20	3.95	30%	21.81
Neutral / Non-Positive	0	0	0%	0

Table 3.46. *Epilepsy: journal considerations grouped by impact factor values.*

Authors	Journal	IF	Res	Outcomes
Kotin et al. (1973)	JAMA Psychiatry (Archives of General Psychiatry)	22.5		No significant antidepressant effects. Some patients experienced severe anxiety and depersonalization.
Ablon & Goodwin et al. (1974)	The American Journal of Psychiatry	19.2		High incidence of dysphoric reactions. THC did not produce significant euphoria or antidepressant effects.
Fabre & McLendon et al. (1981)	Journal of Clinical Pharmacology	2.4	+	Significant reduction in anxiety as measured by the Hamilton Anxiety Rating Scale.
Glass et al. (1981)	Journal of Clinical Pharmacology	2.4	+	Higher doses led to sedation, increased heart rate, and orthostatic hypotension. Low doses showed mild antianxiety effects in some subjects.
Blaas (2008)	Cannabinoids	-	+	Notable improvement in mood and reduced depressive symptoms. When not responding adequately to dronabinol alone included SSRIs or SNRIs, proving effective.
Zuardi et al. (2010)	Journal of Psychopharmacology	4.5		No additional improvement with CBD monotherapy. CBD may not be effective for treating manic episodes in bipolar disorder.
Bergamaschi et al. (2011)	Neuropsychopharmacology	6.6	+	Reduced anxiety levels during a public speaking test, measured by Visual Analogue Mood Scale (VAMS) and Self-Statements during Public Speaking Scale (SSPS-N).
Crippa et al. (2011)	Journal of Psychopharmacology	4.5	+	Reduced anxiety and brain activity changes in regions associated with anxiety, observed via SPECT imaging.
Portenoy et al. (2012)	The Journal of Pain	4.0		Nabiximols did not significantly impact depression or mood disorders as measured by MADRS. Higher doses were linked to cognitive side effects.
Shannon & Opila-Lehman (2016)	The Permanente Journal	0.4	+	Significant reduction in anxiety and improvement in sleep quality and duration. The child was able to sleep alone most nights and had decreased anxiety levels.
Masataka et al. (2019)	Frontiers in Psychiatry	3.2	+	Significant reduction in anxiety symptoms measured by FNE and LSAS scores in the CBD group compared to placebo.
Ergisi et al. (2022)	Expert Review of Clinical Pharmacology	3.6	+	Statistically significant reductions in anxiety (GAD-7), improvements in sleep quality (SQS), and general health-related quality of life (EQ-5D-5L). Mild-to-moderate adverse events were reported in 39.1% of patients, commonly dry mouth and somnolence.
Rifkin-Zybutz et al. (2023)	Psychopharmacology	3.5	+	Clinically significant improvements in anxiety (GAD-7 score), sleep quality, and quality of life. Adverse events reported in 12.9% of participants, most commonly dry mouth and fatigue.
Stack et al. (2023)	Journal of Pharmaceutical Technology	-	+	Improvement in anxiety, depression, fatigue, and social functioning. Common adverse events included dry mouth (32.6%) and somnolence (31.3%).
Li et al. (2024)	International Clinical Psychopharmacology	2.1	+	Significant improvements in anxiety severity (GAD-7) and quality of life (EQ-5D-5L) across all time points. 20% reported adverse events, with most being mild-to-moderate.

Table 3.47. *Studies evaluating use of medicinal cannabis to address mood disorders.*

Outcome	Journals (Total)	Impact Factor (Median)	Proportion of High-Impact Journals	Impact Factor (Weighted Average)
Positive	11	3.2	0%	3.19
Neutral / Non-Positive	4	11.85	50%	12.55

Table 3.48. *Mood disorders: journal considerations grouped by impact factor values.*

Authors	Journal	IF	Res	Outcomes
Budney et al. (1998)	Addiction	5.2		No significant adverse effect of concurrent marijuana use on opioid treatment outcome. No improvement in treatment retention or opioid abstinence.
Epstein & Preston (2003)	Addiction	5.2		Cannabis use did not predict poor outcomes in retention or other psychosocial functioning during methadone maintenance treatment.
Weizman et al. (2004)	Australian and New Zealand Journal of Psychiatry	4.0		Cannabis abuse did not significantly affect treatment outcomes, retention rates, or health risks in the methadone maintenance treatment setting.
Raby et al. (2009)	The American Journal on Addictions	2.5	+	Intermittent cannabis users showed improved retention in naltrexone treatment compared to abstinent or consistent cannabis users (days: 133 $\bar{x}$ vs 35 $\bar{x}$).
Hill et al. (2013)	Drug and Alcohol Dependence	3.9		Cannabis use did not significantly impact opioid treatment outcomes, including opioid abstinence.
Morgan et al. (2013)	Addictive Behaviors	3.7	+	CBD reduced cigarette consumption by approximately 40% compared to placebo.
Bisaga et al. (2015)	Drug and Alcohol Dependence	3.9		Reduced severity of opioid withdrawal during detoxification but no significant effect on treatment retention for naltrexone induction. Only 35% trial completion noted.
Mayet et al. (2015)	Journal of Substance Abuse Treatment	3.9		Cannabis use did not significantly impact treatment outcomes. Cannabis use patterns were consistent and associated with underlying health issues rather than methadone treatment itself.
Lofwall et al. (2016)	Drug and Alcohol Dependence	3.9		Modest withdrawal suppression but also induced side effects like tachycardia at higher doses, suggesting limited efficacy as a standalone treatment for withdrawal.
Socias et al. (2017)	Addictive Behaviors	3.7	+	Reduced frequency of crack use in subsequent periods after intentional cannabis use to control crack use.
Hurd et al. (2019)	American Journal of Psychiatry	15.1	+	CBD significantly reduced cue-induced craving and anxiety acutely and had protracted effects up to 7 days post-administration.

Authors	Journal	IF	Res	Outcomes
Rosic et al. (2021)	Harm Reduction Journal	4.0		Cannabis use, versus no use, was not significantly associated with differences in opioid use during treatment. Among cannabis users, daily use was linked to lower odds of opioid use compared to occasional use.
Naji et al. (2022)	Frontiers in Psychiatry	3.2		Cannabis use was not protective against opioid relapse, with a hazard ratio close to 1, indicating no significant effect on relapse prevention.
Elkrief et al. (2023)	Journal of Substance Use and Addiction Treatment	3.9		No statistically significant effect of cannabis use on opioid use, craving, or withdrawal symptoms in individuals on opioid agonist therapy.
Lake et al. (2023)	Cannabis and Cannabinoid Research	3.1	+	Daily cannabis use was associated with a reduced likelihood of illicit opioid use among those on lower methadone doses (30% vs 86%), suggesting cannabis might mitigate withdrawal symptoms at subtherapeutic methadone maintenance treatment levels.
Reddon et al. (2023)	International Journal of Drug Policy	4.4	+	Significant association between cannabis use to manage opioid cravings and self-reported reduction in opioid use (aOR: 2.13), mostly in moderate to severe pain (aOR: 4.44) and females (aOR: 8.19).
Bekier et al. (2024)	European Archives of Psychiatry and Clinical Neuroscience	3.5	+	60% reported using cannabis as a substitute for opioids, with self-reported reduction in opioid cravings and perceived effectiveness of cannabis for withdrawal management.
Reddon et al. (2024)	Addictive Behaviors	3.7	+	Self-reported reductions in stimulant use, with significant association between cannabis use for craving management and decreased stimulant use (77.6%; aOR: 0.24), particularly among crystal methamphetamine users (aOR: 0.08).

Table 3.49. *Studies evaluating use of medicinal cannabis for drug addiction management.*

Outcome	Journals (Total)	Impact Factor (Median)	Proportion of High-Impact Journals	Impact Factor (Weighted Average)
Positive	8	3.7	12.5%	4.96
Neutral / Non-Positive	10	3.9	0%	3.91

Table 3.50. *Drug addiction management: journal considerations grouped by impact factor values.*

Authors	Journal	IF	Res	Outcomes
Bonn-Miller et al. (2007)	Journal of Traumatic Stress	2.4		Severity of PTSD symptoms was significantly related to the use of marijuana for coping.
Fraser (2009)	CNS Neuroscience & Therapeutics	4.8	+	72% experienced either cessation or significant reduction in nightmare intensity.
Klumpers et al. (2012)	Journal of Psychopharmacology	4.5		Reduced conditioned skin conductance responses but demonstrated no effect two days later.
Mashiah et al. (2012)	-	-	+	Reported improvement in PTSD symptoms, especially sleep disturbances and anxiety reduction.
Reznik et al. (2012)	European Neuropsychopharmacology	6.1	+	Improvement in quality of life and reduction in PTSD symptoms, particularly in those with comorbid pain or depression.
Das et al. (2013)	Psychopharmacology	3.5	+	Enhanced consolidation of fear extinction when CBD was administered.
Rabinak et al. (2013)	Neuropharmacology	4.6	+	Participants registered lower skin conductance responses to a previously extinguished conditioned stimulus, suggesting improved extinction recall.
Bonn-Miller et al. (2014a)	Drug and Alcohol Dependence	3.9	+	Higher PTSD scores were linked to increased cannabis use for sleep improvement and coping.
Bonn-Miller et al. (2014b)	American Journal of Drug and Alcohol Abuse	2.7	+	Cannabis was perceived as helpful for alleviating symptoms such as anxiety, chronic pain, and sleep disturbances.
Cameron et al. (2014)	Journal of Clinical Psychopharmacology	2.9	+	Significant improvement in PTSD-related insomnia, nightmares, and overall functioning.
Earleywine & Bolles (2014)	Journal of Psychoactive Drugs	2.1	+	Significant correlations between PTSD symptom severity, marijuana use, and expectancies of symptom relief.
Greer et al. (2014)	Journal of Psychoactive Drugs	2.1	+	Greater than 75% reduction in PTSD symptom scores was reported during cannabis use compared to non-use.
Roitman et al. (2014)	Clinical Drug Investigation	2.9	+	Improvement in PTSD symptom severity, sleep quality, and reduction in nightmares.
Jetly et al. (2015)	Psychoneuroendocrinology	3.4	+	Significant reduction in nightmare frequency and intensity compared to placebo.
Wilkinson et al. (2015)	The Journal of Clinical Psychiatry	5.3		Cannabis use was associated with worse PTSD symptoms and increased violent behaviour.
Johnson et al. (2016)	Journal of Affective Disorders	4.9		No significant difference in PTSD severity between cannabis users and non-users.
Shannon & Opila-Lehman (2016)	Permanente Journal	1.2	+	Significant reduction in anxiety and improvement in sleep quality.
Tull et al. (2016)	Drug and Alcohol Dependence	3.9		Marijuana dependence moderated emotional reactivity in response to trauma cues, reducing arousal.
Loflin et al. (2017)	Addictive Behaviors	3.7		Medicinal cannabis users reported more PTSD symptoms and higher cannabis use than recreational users.

Authors	Journal	IF	Res	Outcomes
Elms et al. (2019)	The Journal of Alternative and Complementary Medicine	2.4	+	91% of patients experienced a reduction in PTSD symptoms, including decreased nightmares.
LaFrance et al. (2020)	Journal of Affective Disorders	4.9	+	Significant short-term reductions in symptoms though long-term symptom severity remained constant, indicating potential development of tolerance.
Bonn-Miller et al. (2021)	PLOS ONE	2.9		No significant difference in symptom reduction between active cannabis and placebo, but all groups showed symptom improvement.
Bonn-Miller et al. (2022)	Cannabis and Cannabinoid Research	3.1	+	Users showed greater reductions in PTSD symptom severity over time compared to controls.
Nacasch et al. (2023)	Frontiers in Psychiatry	3.2	+	Significant improvements in sleep quality and PTSD symptom scores, except for nightmares.
Lynskey et al. (2024)	British Journal of Psychiatry Open	3.9	+	Significant reduction in PTSD symptoms, with greater improvements in individuals with comorbid depression.

Table 3.51. *Studies evaluating use of medicinal cannabis to address post-traumatic stress disorder.*

Outcome	Journals (Total)	Impact Factor (Median)	Proportion of High-Impact Journals	Impact Factor (Weighted Average)
Positive	17	3.4	0%	3.39
Neutral / Non-Positive	7	3.9	0%	3.94

Table 3.52. *Post-traumatic stress disorder: journal considerations grouped by impact factor values.*

Authors	Journal	IF	Res	Outcomes
Naftali et al. (2011)	The Israel Medical Association Journal	1.8	+	Improved disease activity with reduced Harvey-Bradshaw index, fewer surgeries, and reduced use of other medications.
Lahat et al. (2012)	Digestion	3.0	+	Improved quality of life, disease activity, weight gain, and BMI increase. Reduction in Harvey-Bradshaw index (CD patients) and partial Mayo score (UC patients).
Naftali et al. (2013)	Clinical Gastroenterology and Hepatology	11.6	+	Reduction in Crohn's Disease Activity Index (CDAI) scores. Improved appetite, sleep, and steroid-sparing effect. Provided clinical benefits compared to placebo.
Naftali et al. (2017a)	Digestive Diseases and Sciences	2.5		No significant beneficial effects on CDAI or laboratory markers, possibly due to low dosage.
Naftali et al. (2017b)	-	-		Quality of life scores higher in the cannabis oil group (96.3 vs 79.9). However, GRADE analysis indicated low overall certainty of evidence due to significant imprecision. Mean CDAI scores were lower in cannabis group (118.6 vs 212.6).
Irving et al. (2018)	Inflammatory Bowel Diseases	4.5		No remissions yet improvements in Mayo scores, global illness severity, and quality of life were observed.
Kerlin et al. (2018)	Digestive Diseases and Sciences	2.5		Benefits in pain, appetite, anxiety, and fatigue but also more IBD symptoms, depression, and lower social satisfaction.
Naftali et al. (2018)	Gastroenterology	26.3	+	Significant clinical and endoscopic improvements in UC activity, including decreases in DAI and Mayo endoscopic score. Quality of life improved.
Mbachii et al. (2019)	Digestive Diseases and Sciences	2.5	+	Lower rates of complications such as fistulizing disease, need for parenteral nutrition, blood transfusion, and colectomy.
Benson et al. (2020)	Crohn's & Colitis 360	1.8	+	Improvements in abdominal pain, stress, sleep, cramping, and anxiety. The quality of life was reportedly better for cannabis users with ulcerative colitis.
Naftali et al. (2021a)	PLOS ONE	2.9		Clinical improvement with reduced Lichtiger DAI and enhanced quality of life, but without significant changes in endoscopic or inflammatory markers.
Naftali et al. (2021b)	Journal of Crohn's and Colitis	8.3		Improved CDAI and quality of life, but no significant changes in endoscopic scores or inflammatory markers.
Coates et al. (2022)	Cannabis and Cannabinoid Research	3.1		Cannabis users reported more symptoms like abdominal pain, gas, tenesmus, and arthralgias but no increased disease severity or complications.

Table 3.53. *Studies evaluating use of medicinal cannabis to address inflammatory bowel disease.*

Outcome	Journals (Total)	Impact Factor (Median)	Proportion of High-Impact Journals	Impact Factor (Weighted Average)
Positive	6	2.75	33.3%	7.83
Neutral / Non-Positive	6	3.0	0%	3.97

Table 3.54. *Inflammatory bowel disease: journal considerations grouped by impact factor values.*

Authors	Journal	IF	Res	Outcomes
Noyes et al. (1975)	Journal of Clinical Pharmacology	2.4	+	Pain relief was dose-dependent. 15-20 mg doses provided significant analgesia but were highly sedative.
Maurer et al. (1990)	European Archives of Psychiatry and Clinical Neuroscience	3.5	+	Significant reduction in spasticity and pain compared to placebo, without altered consciousness.
Ware et al. (2002)	Pain Research & Management	2.5	+	Improvement in pain, mood, and sleep for most patients. No tolerance was observed. Psychoactive effects were mild.
Karst et al. (2003)	JAMA	63.5	+	Statistically significant reductions in pain intensity, measured on the VAS scale, during intervention periods compared to placebo.
Lynch et al. (2003)	Journal of Pain and Symptom Management	3.2	+	Significant reductions in opioid usage (up to 100% in one case), improved pain control, spasticity, and sleep.
Wade et al. (2003)	Clinical Rehabilitation	2.6	+	Improvements in pain, spasticity, and muscle spasms compared to placebo.
Berman et al. (2004)	Pain	5.9	+	Both active treatments (THC + CBD or THC alone) showed statistically significant but not clinically meaningful pain reduction compared to placebo.
Notcutt et al. (2004)	Anaesthesia	7.5	+	THC-containing sprays were most effective in symptom control, particularly pain and spasticity. Side effects were common but manageable.
Svensen et al. (2004)	The British Medical Journal	93.7	+	Reduced median spontaneous pain intensity. Increased adverse events in the first treatment week.
Rog et al. (2005)	Neurology	8.3	+	Significant reductions in pain and sleep disturbance compared to placebo.
Beaulieu et al. (2006)	Canadian Journal of Anesthesia	3.4		No significant benefit of nabilone over placebo for pain management, but comparable to ketoprofen.
Blake et al. (2006)	Rheumatology	4.7	+	Significant improvements in pain on movement, pain at rest, and quality of sleep. Side effects were generally mild or moderate.

Authors	Journal	IF	Res	Outcomes
Gofeld et al. (2006)	Acute Pain	4.1	+	Improved pain control, reduced anxiety, and decreased morphine consumption when nabilone was included.
Holdcroft et al. (2006)	Anesthesiology	9.1	+	Dose-dependent pain relief, increasing as the dose increased.
Lynch et al. (2006)	Journal of Pain and Symptom Management	3.2	+	93% reported moderate to complete pain relief, with 70% reducing other medication usage.
Pinsger et al. (2006)	Wiener Klinische Wochenschrift	1.9	+	Nabilone provided superior pain relief, increased quality of life, and reduced headache intensity compared to placebo.
Wissel et al. (2006)	Journal of Neurology	4.8	+	Significant reduction in spasticity-related pain. No changes in motor function or daily living activities.
Abrams et al. (2007)	Neurology	8.3	+	Significant reduction in chronic pain. Median pain reduction of 72% in cannabis group compared to 15% in placebo group).
Nurmikko et al. (2007)	Pain	5.9	+	Significant reduction in pain intensity and improvement in secondary measures, such as sleep quality.
Wallace et al. (2007)	Anesthesiology	9.1		Medium doses reduced pain. High doses increased pain. Highlighted a narrow therapeutic window for analgesia.
Frank et al. (2008)	The British Medical Journal	93.7		Dihydrocodeine was more effective for pain relief than nabilone and had fewer side effects.
Haroutiunian et al. (2008)	Journal of Pain & Palliative Care Pharmacotherapy	0.9		7 patients discontinued due to lack of efficacy or adverse events. Others reported better pain scores and quality of life.
Narang et al. (2008)	The Journal of Pain	4.0	+	Additional analgesia with dronabinol; reduced pain inconvenience and increased treatment satisfaction.
Skrabek et al. (2008)	The Journal of Pain	4.0	+	Significant decreases in pain, improved quality of life, and anxiety reduction.
Wilsey et al. (2008)	The Journal of Pain	4.0	+	Significant analgesic response, dose-dependent reduction in pain intensity. High doses caused mild cognitive impairment.
Ellis et al. (2009)	Neuropsychopharmacology	6.6	+	Median reduction in pain recorded at 34% when compared to placebo. Improved quality of life.
Hornby et al. (2009)	(Cases Journal)	0.4	+	Effective pain management and improvement in quality of life with resistant chronic pain.
Bestard et al. (2010)	Pain Practice	2.5	+	Both nabilone and gabapentin significantly reduced pain scores, with similar efficacy.
Johnson et al. (2010)	Journal of Pain and Symptom Management	3.2	+	Significant pain reduction when compared to placebo. No significant benefit with THC-only spray.
Rintala et al. (2010)	American Journal of Physical Medicine & Rehabilitation	2.2		No significant difference in pain relief between dronabinol and diphenhydramine.

Authors	Journal	IF	Res	Outcomes
Selvarajah et al. (2010)	Diabetes Care	14.8		No significant difference in pain relief between Sativex® and placebo. Depression was a major confounder, influencing higher baseline pain scores and improved outcomes.
Ware et al. (2010)	Canadian Medical Association Journal	12.3	+	Significant pain relief with 9.4% THC. Lower doses showed non-significant effects. Improved sleep quality was observed.
Haroutiunian et al. (2012)	(European Journal of Pain Supplements)	0.1	+	Pain severity and interference improved by 14.5% and 24% respectively. High patient satisfaction reported.
Portenoy et al. (2012)	The Journal of Pain	4.0	+	Low- and medium-dose groups showed significant pain relief and sleep improvement compared to placebo. High-dose group had more adverse events.
Toth et al. (2012)	Pain	5.9	+	Pain relief, improved sleep, better quality of life. Minimal adverse effects.
Johnson et al. (2013)	Journal of Pain and Symptom Management	3.2	+	Sustained pain relief. Improved quality of life for patients. No evidence of dose escalation over time.
Langford et al. (2013)	Journal of Neurology	4.8		Modest improvements in pain and sleep quality. No statistically significant differences in mean pain scores between test and control groups.
Wilsey et al. (2013)	The Journal of Pain	4.0	+	Significant analgesic response to low and medium doses. Psychoactive effects minimal and cognitive effects short-lived.
Eisenberg et al. (2014)	Journal of Pain & Palliative Care Pharmacotherapy	0.9	+	Noted pain reduction at significant levels when compared to placebo.
Lynch et al. (2014)	Journal of Pain and Symptom Management	3.2	+	31.5% showed clinically meaningful pain reduction. ≥2-point drop on pain scale.
Serpell et al. (2014)	European Journal of Pain	3.5	+	Clinically significant improvements in pain and sleep quality. Adverse events were common but manageable.
Degenhardt et al. (2015)	Drug and Alcohol Dependence	3.9		No evidence of pain reduction or opioid-sparing effects with cannabis use.
Hoggart et al. (2015)	Journal of Neurology	4.8	+	Pain reduced from 6.9 (baseline NRS) to 4.2 (end of study). 30% or more pain relief reported in half of patients.
Turcotte et al. (2015)	Pain Medicine	2.9	+	Significant reduction in pain intensity and impact on daily activities.
Ware et al. (2015)	The Journal of Pain	4.0	+	Pain reduction and improved quality of life reported. No significant differences in serious adverse events
Boehnke et al. (2016)	The Journal of Pain	4.0	+	Reduction in opioid use, improvement in pain scores, and better quality of life reported by cannabis users.
Haroutounian et al. (2016)	The Clinical Journal of Pain	2.9	+	Improved pain scores and quality of life for patients.
Wilsey et al. (2016)	The Journal of Pain	4.0	+	Dose-dependent pain relief, with lower doses offering a better risk-benefit profile. Dose-dependent, mild psychoactive effects.

Authors	Journal	IF	Res	Outcomes
de Vries et al. (2017)	Clinical Gastroenterology and Hepatology	11.6	+	Statistically significant reduction in visual analog scale (VAS) pain scores for THC compared to placebo.
Fallon et al. (2017)	British Journal of Pain	1.8	+	Modest but significant improvements in pain scores. Better sleep quality.
Fanelli et al. (2017)	Journal of Pain Research	2.5	+	Effective in managing pain in 76% of patients. Mild side effects with <15% discontinuing due to adverse effects.
Lucas et al. (2017)	International Journal of Drug Policy	4.4	+	High substitution rates for prescription medications, particularly opioids. Improvement in pain and mental health symptoms.
Malik et al. (2017)	Diseases of the Esophagus	2.4	+	Increased pain thresholds, reduced pain intensity, and odynophagia frequency. No significant adverse effects noted.
Piper et al. (2017)	Journal of Psychopharmacology	4.5	+	76.7% reduced opioid use for pain management, 65.2% reduced sleep medications, and 71.8% reduced anti-anxiety medications.
Reiman et al. (2017)	Cannabis and Cannabinoid Research	3.1	+	97% reported reducing opioid use with cannabis. 92% preferred cannabis for fewer side effects.
Schimrigk et al. (2017)	European Neurology	2.1	+	No significant pain intensity reduction in blinded phase. Clinically relevant reductions during long-term follow-up.
Shah et al. (2017)	Journal of Substance Abuse Treatment	3.9		Both groups improved pain, depression and quality of life. Cannabis use was not associated with reduced opioid usage but linked to higher substance-use risk.
Vigil et al. (2017)	PLOS ONE	2.9	+	Higher opioid cessation rates and dose reductions. Reported improvements in pain, quality of life, and activity levels.
Bellnier et al. (2018)	Mental Health Clinician	1.2	+	Quality of life improved. Reduced pain intensity and opioid consumption (decreased from 79.94 to 19.65 morphine equivalents / day).
Campbell et al. (2018)	The Lancet Public Health	25.4		No evidence of pain reduction or opioid-sparing effects in cannabis users compared to non-users.
Liu et al. (2018)	Anesthesia & Analgesia	4.6		Cannabinoid users reported higher pain scores at rest and during movement, increased sleep disturbance and higher opioid requirements.
Lichtman et al. (2018)	Journal of Pain and Symptom Management	3.2		Modest improvements in pain management. No significant changes in opioid usage. Reduced sleep disruption.
Poli et al. (2018)	Clinical Therapeutics	3.2	+	Significant reductions in pain intensity, anxiety, depression, and pain disability.
Barlowe et. al (2019)	Clinical Gastroenterology and Hepatology	11.6	+	Lower mean morphine equivalent dose and fewer hospitalizations among cannabis users.
Capano et. al (2019)	Postgraduate Medicine	2.6	+	Significant reduction in anxiety and pain scores. Improved sleep quality.
Lavie & Ajayi (2019)	Pain Medicine	2.9	+	Significant improvements in pain management, reduced reliance on conventional pain medications, and enhanced QoL.

Authors	Journal	IF	Res	Outcomes
Lucas et al. (2019)	Harm Reduction Journal	4.0	+	Significant substitution effect for opioids (35.3% reported opioid cessation), antidepressants, and alcohol.
O'Connell et al. (2019)	Annals of Pharmacotherapy	2.3	+	Reduction in opioid use. Median decrease of 39.1mg morphine equivalents/day. No significant change in benzodiazepine use.
Rod et al. (2019)	American Journal of Psychiatry and Neuroscience	-	+	26% ceased opioids, 55% reduced use by 30%. Improved pain control, sleep, and quality of life.
Ueberall et al. (2019)	Journal of Pain Research	2.5	+	Improved pain-related disability, sleep, and quality of life. Neuropathic pain subgroup experienced better outcomes.
van de Donk et al. (2019)	Pain	5.9		THC-containing cannabis varieties increased pressure pain thresholds. Bediol provided a 30% pain reduction in more patients compared to placebo.
Yassin et al. (2019)	Clinical and Experimental Rheumatology	3.4	+	Improved pain scores, functional outcomes, and range of motion after 3-6 months. Better than standard therapy.
Almog et al. (2020)	European Journal of Pain	3.5	+	Dose-dependent pain reduction with minimal side effects. High dose, 1mg THC, showed greater efficacy than lower doses.
Eibach et al. (2020)	Clinical Pharmacology & Therapeutics	6.3	+	Significant 20% reduction in pain scores compared to placebo, with additional subgroup analyses.
Pawasarat et al. (2020)	Journal of Palliative Medicine	2.2	+	Improved physical and emotional symptoms with stable or reduced opioid consumption, up to a 33% decrease.
Pritchard et al. (2020)	Journal of the American Pharmacists Association	2.5		28.8mg vs 10.8mg morphine equivalent daily dose increase between control and test groups, with opioid-sparing effects.
Takakuwa et al. (2020)	Cannabis and Cannabinoid Research	3.1	+	50.8% stopped opioids completely. High-dose cannabis users had better opioid cessation rates.
Wallace et al. (2020)	The Journal of Pain	4.0	+	A U-shaped dose-response relationship was observed. Pain relief was most effective with plasma THC levels between 16 and 31 ng/mL. High doses impaired cognitive function.
Xu et al. (2020)	Current Pharmaceutical Biotechnology	2.2	+	Statistically significant reduction in pain intensity and associated sensations. No adverse events reported.
Aviram et al. (2021)	European Journal of Pain	3.5	+	20% reduction in average weekly pain intensity and decreased analgesic consumption. 43% stopped all analgesics, 24% stopped weak opioids, and 20% stopped strong opioids.
De Vita et al. (2021)	Experimental and Clinical Psychopharmacology	3.4	+	Pain unpleasantness was significantly reduced in drug, expectancy, and expectancy + drug conditions. Effects varied across pain outcomes.
Schubert et al. (2023)	British Journal of Pain	1.8	+	Significant improvements in pain intensity, pain interference, and quality of life for balanced products.

Table 3.55. *Studies evaluating use of medicinal cannabis to address pain.*

Outcome	Journals (Total)	Impact Factor (Median)	Proportion of High-Impact Journals	Impact Factor (Weighted Average)
Positive	67	3.3	7.2%	4.45
Neutral / Non-Positive	14	4.7	21.4%	13.45

Table 3.56. *Pain: journal considerations grouped by impact factor values.*

Authors	Journal	IF	Res	Outcomes
Gross et al. (1983)	Journal of Clinical Psychopharmacology	2.9		No significant effect on weight gain. Higher doses associated with adverse events that potentially counteracted weight-gaining effects.
Karayilan & Erol (2013)	Klinik Psikofarmakoloji Bülteni	0.6		Despite the appetite-increasing effects of cannabis, the patient used self-induced vomiting and excessive exercise to achieve weight loss.
Andries et al. (2014a)	Eating and Weight Disorders	2.9		Dronabinol modestly increased physical activity intensity but not duration, with no significant impact on eating disorder-related behaviours.
Andries et al. (2014b)	International Journal of Eating Disorders	4.7	+	Dronabinol induced a small but significant weight gain (0.73 kg $\bar{x}$) compared to placebo, without significant psychotropic side effects.
Andries et al. (2015)	Growth Hormone & IGF Research	1.6	+	Dronabinol modestly increased BMI, decreased urinary cortisol, and had no significant effect on IGF-1 or adipokine levels.
Avraham et al. (2017)	Israel Journal of Psychiatry	0.2		Significant improvements in psychological symptoms, including body care, sense of ineffectiveness, asceticism, and depression, though no significant change in BMI was observed. No adverse effects were reported at the low doses used.
Graap et al. (2017)	International Journal of Eating Disorders	4.7	+	Significant reduction in urge to be physically active and improved control over eating disorder-specific cognitions and compulsive behaviours.

Table 3.57. *Studies evaluating use of medicinal cannabis to address eating disorders.*

Outcome	Journals (Total)	Impact Factor (Median)	Proportion of High-Impact Journals	Impact Factor (Weighted Average)
Positive	3	4.7	0%	3.67
Neutral / Non-Positive	4	1.75	0%	1.65

Table 3.58. *Eating disorders: journal considerations grouped by impact factor values.*

Authors	Journal	IF	Res	Outcomes
Jatoi et al. (2002)	Journal of Clinical Oncology	42.1		Megestrol acetate was superior for improving appetite and weight gain. Combination therapy did not outperform megestrol acetate alone.
Strasser et al. (2006)	Journal of Clinical Oncology	42.1		No significant difference in appetite or quality of life between treatment arms. Well-tolerated.
Zutt et al. (2006)	Die Dermatologie (Hautarzt)	0.8	+	Significant improvements in appetite and nausea reported. Effects diminished with disease progression. Mild to moderate dizziness was the only notable side effect.
Johnson et al. (2010)	Journal of Pain and Symptom Management	3.2	+	Nabiximols was superior to placebo in pain reduction (mean pain score reduction: -1.37 vs. -0.69). THC alone showed no significant benefit.
Brisbois et al. (2011)	Annals of Oncology	56.7	+	Improved chemosensory perception, appetite, and food enjoyment, compared to placebo. Quality of life improvements.
Portenoy et al. (2012)	The Journal of Pain	4.0	+	Low and medium doses showed greater analgesia compared to placebo. High doses had adverse effects and no additional efficacy.
Johnson et al. (2013)	Journal of Pain and Symptom Management	3.2	+	Nabiximols spray was well tolerated long-term, with no evidence of dose escalation or loss of efficacy for pain relief.
Cote et al. (2016)	Annals of Otolaryngology, Rhinology & Laryngology	1.3		No significant improvement in quality of life, pain, nausea, or appetite compared to placebo.
Fallon et al. (2017)	British Journal of Pain	1.8		No significant difference in pain reduction compared to placebo, but improvements noted in quality of life measures for patients <65 years.
Lichtman et al. (2018)	Journal of Pain and Symptom Management	3.2		No significant difference in the primary endpoint, pain reduction. Patients showed improved secondary outcomes, including quality of life.
Casarett et al. (2019)	Journal of Palliative Medicine	2.2	+	THC-dominant cannabis improved neuropathic pain, insomnia, and depressive symptoms. No significant results for anxiety, PTSD, or anorexia.
Wilson et al. (2019)	Journal of Palliative Medicine	2.2	+	27% used cannabis, reporting benefits for pain and other symptoms, with some overlap in opioid usage.

Authors	Journal	IF	Res	Outcomes
Zarrabi et al. (2019)	Journal of Palliative Medicine	2.2	+	Reported symptom improvement, including pain and appetite, with minimal side effects.
Good et al. (2020)	Journal of Palliative Medicine	2.2	+	43% achieved a significant reduction in symptom burden. Emotional symptoms (anxiety, depression) improved significantly, but no overall reduction in physical symptoms.
Highet et al. (2020)	American Journal of Hospice & Palliative Medicine	1.5	+	Patients reported symptom improvement, including pain and appetite, with minimal side effects.
Hardy et al. (2022)	Journal of Clinical Oncology	42.1		CBD did not significantly outperform placebo for symptom relief.
Buchwald et al. (2023)	Palliative Medicine Reports	1.1	+	Significant improvement in cognitive function and reduction in pain, fatigue, and depressive symptoms.
Nathan et al. (2023)	American Journal of Hospice & Palliative Medicine	1.5		No statistically significant change in symptoms, though 37% reported a 30% pain reduction.

Table 3.59. *Studies evaluating use of medicinal cannabis to address palliative care.*

Outcome	Journals (Total)	Impact Factor (Median)	Proportion of High-Impact Journals	Impact Factor (Weighted Average)
Positive	11	2.2	9.1%	7.21
Neutral / Non-Positive	7	3.2	42.9%	19.16

Table 3.60. *Palliative care: journal considerations grouped by impact factor values.*

3.5. Phase 5: Clinical Trial Framework

Clinical research, a fundamental component of advancing medical knowledge and treatment, encompasses a broad spectrum of methodologies aimed at improving human health. Two primary types of clinical research are clinical trials and clinical studies, each with distinct characteristics and regulatory frameworks. Understanding these differences is essential for researchers, healthcare professionals, and policymakers involved in the design, execution, and regulation of clinical research.

A clinical study is an umbrella term that refers to any research involving human participants that aims to improve medical knowledge. This broad category includes both interventional and observational studies. The primary objective of clinical studies can range from understanding disease mechanisms, epidemiology, and health services to evaluating medical interventions and treatments. Clinical studies can be classified into interventional studies, where researchers actively intervene to test the effects of treatments, drugs, or procedures on participants, and observational studies, where researchers observe the participants without altering their medical care.

A clinical trial, a subset of clinical studies, is a rigorously controlled and systematic study designed to test the safety, efficacy, and optimal use of medical interventions. These trials are crucial for the development of new therapies and are essential for the regulatory approval of new drugs and treatments. Clinical trials involve specific interventions based on a research protocol created by the investigators. These interventions can include drugs, medical devices, procedures, or changes to participants' behaviour. To eliminate bias and ensure the reliability of results, participants are often randomly assigned to different intervention groups, a process known as randomization. Clinical trials may also be single-blind, where participants do

not know which intervention they receive, or double-blind, where both participants and researchers are unaware of the intervention assignments. Control groups are frequently used in clinical trials to provide a comparison against the experimental intervention, often receiving standard treatment or placebos. Additionally, clinical trials are subject to stringent regulatory requirements to protect participants' rights, safety, dignity, and well-being.

The distinction between clinical studies and clinical trials lies primarily in the scope and nature of the research. Clinical studies encompass a wide range of research goals, from understanding disease mechanisms to improving healthcare delivery, including both interventional and non-interventional (observational) studies. In contrast, clinical trials focus specifically on testing the efficacy and safety of interventions. They are a type of interventional study where participants receive treatments according to a predefined protocol. While observational studies do not involve active intervention but rather data collection through observation, surveys, or existing records, clinical trials are exclusively interventional, involving randomization, blinding, and the use of control groups to ensure the validity and reliability of results.

The regulatory framework for clinical trials is designed to ensure the protection of participants and the reliability of data. According to the European Union's Directive 2001/20/EC and subsequent regulations, clinical trials must adhere to specific criteria, including prior authorization from relevant regulatory authorities before commencing, rigorous protocol review, and adherence to Good Clinical Practice (GCP) guidelines. Clinical trial data should be recorded in publicly accessible databases to promote transparency and public trust. These regulations build on the dichotomy between clinical trials and non-interventional studies, recognizing the need for different levels of oversight based on the type and risk associated with the study.

3.5.1. Medicinal cannabis clinical framework overview

Ethical Planning

Ethical considerations are crucial when conducting clinical trials involving medicinal cannabis. Recruitment strategies must ensure transparency and fairness, often starting with advertisements that detail the trial's purpose, risks, and eligibility criteria. Informed consent is a fundamental aspect, requiring that participants or their legal representatives fully understand the study's nature, procedures, and potential risks. For medicinal cannabis trials, this is especially important due to the drug's psychoactive effects and legal status in different regions. Vulnerable populations, such as individuals with a history of substance use disorders or psychiatric conditions, may present special ethical challenges, requiring detailed protocols to protect their well-being. Ethical committees play a vital role in reviewing consent procedures and ensuring that potential participants are not subjected to undue risk. Researchers must also ensure the impartiality and qualifications of investigators, as their expertise in both cannabis pharmacology and clinical trial conduct is essential for maintaining ethical standards.

Facility Preparation

Facilities used for medicinal cannabis trials must meet stringent regulatory requirements to ensure safety and compliance. This includes having the necessary infrastructure to store and handle cannabis securely, adhering to GCP and Good Laboratory Practice (GLP) standards. Facilities must also be licensed for handling

controlled substances like cannabis, with protocols for restricted access to prevent misuse. The facility should have specialized equipment, such as medical-grade vaporizers or devices for accurate dose measurement, if inhalation methods are used. Given the trial's nature, emergency medical care must be readily available to handle any adverse reactions to cannabis. Additionally, data management systems should be in place to securely store participant information and trial data, complying with regulations like the GDPR. Proper documentation, facility inspections, and ongoing staff training are crucial to maintaining compliance throughout the trial.

Protocol Development

The clinical trial protocol for medicinal cannabis must comprehensively outline the trial's scientific, ethical, and operational aspects. The objectives should clearly state the purpose, such as evaluating the efficacy of cannabis for a specific condition, such as would be chronic pain or epilepsy. Methodology should include detailed descriptions of cannabis formulations, delivery methods like oral or vaporized for example, dosing schedules, and any dose titration plans. Ethical considerations must address how informed consent will be obtained, especially considering the psychoactive nature of cannabis. Participant safety measures, such as regular monitoring for adverse effects and procedures for dose adjustments, should also be included. The protocol should clearly state primary and secondary endpoints, such as symptom reduction or quality-of-life improvements. Additionally, statistical methods for analyzing the data must be specified, including sample size calculations, power analysis, and handling of missing data. Regular protocol reviews are necessary to ensure ongoing compliance with ethical and regulatory standards.

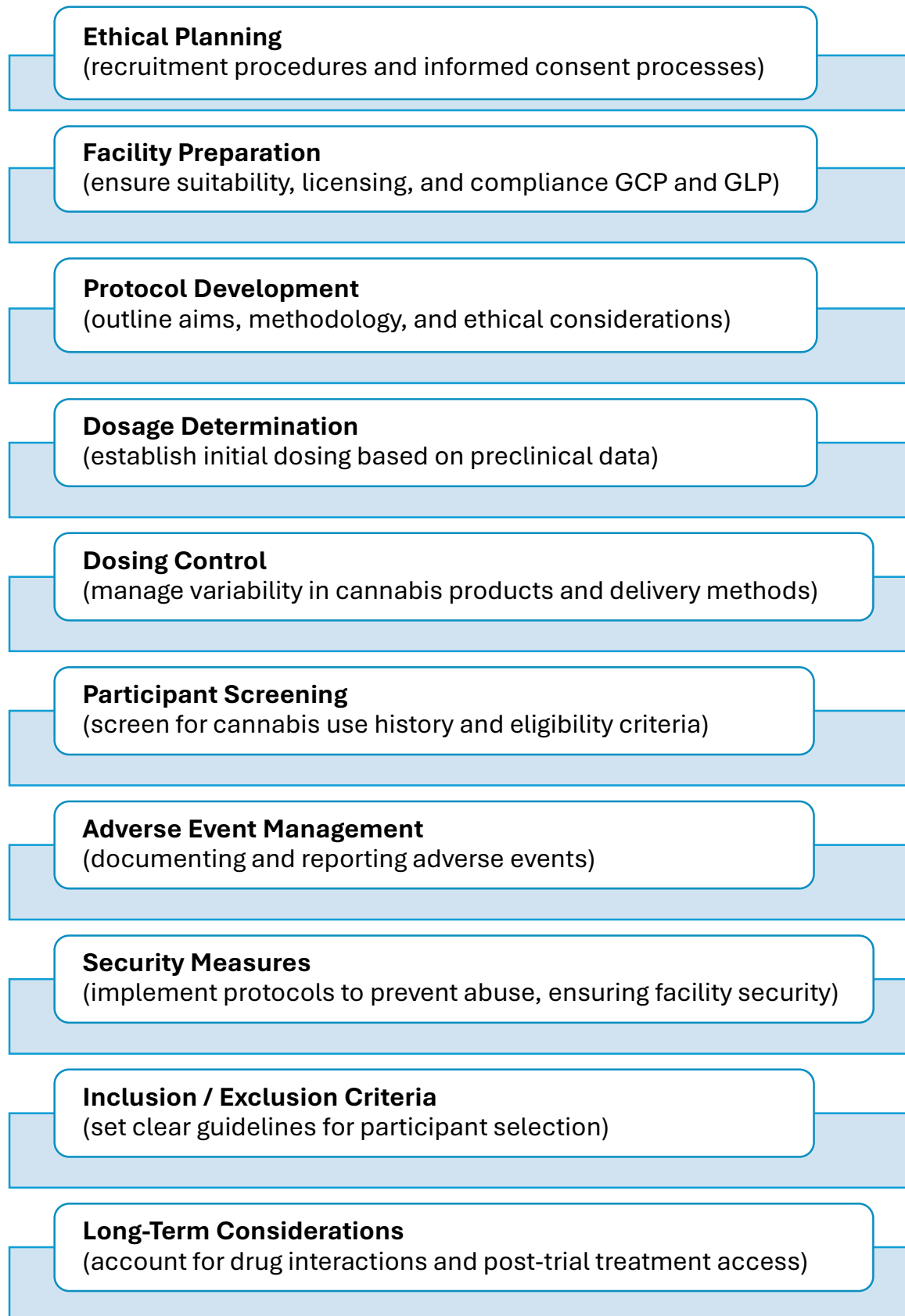


Figure 3.43. *Clinical trial framework for medicinal cannabis: flowchart depiction*

Dosage Determination

Determining appropriate dosages is critical in medicinal cannabis trials due to the variability in individual responses and the drug's biphasic effects. Preclinical studies and existing clinical data guide the initial dose selection, with considerations for safety and therapeutic efficacy. The pharmacokinetics and pharmacodynamics of cannabis, including how it is metabolized and the duration of its effects, are taken into account when establishing dosing. For trials involving chronic conditions, dose escalation schedules may be used to identify the optimal therapeutic dose while minimizing adverse effects. Careful documentation of dose levels, delivery methods, and participant responses is required to adjust dosages accurately. Different cannabis strains or products may have varying concentrations of active cannabinoids, requiring precise formulation selection and quality control.

Dosing Control

Ensuring consistency in dosing is vital in cannabis trials, given the variability in cannabis products and individual responses. Standardized cannabis formulations should be used, and their cannabinoid concentrations verified through rigorous quality control testing. If vaporization is the chosen method, medical-grade devices must be employed to control variables such as temperature and inhalation time. For oral products, standardized preparations like capsules or oils with known cannabinoid content are preferred. The dosing schedule must be strictly followed, and any deviations should be documented with justifications. Participants' adherence to the dosing protocol should be monitored through regular check-ins, and adjustments made as necessary to account for tolerance development or changes in symptoms.

Accurate and consistent dosing helps ensure the reliability and reproducibility of trial outcomes.

Participant Screening

Effective participant screening is essential to ensure the safety and validity of the medicinal cannabis trial. Screening should include a detailed assessment of participants' medical history, cannabis use history, and current medication use. Given cannabis's potential interactions with other drugs metabolized by the liver's cytochrome P450 system, participants with certain medical conditions or those taking contraindicated medications may need to be excluded. Additionally, individuals with a history of substance abuse or certain psychiatric conditions, such as psychosis, may be at higher risk of adverse effects from cannabis and should be carefully considered during the eligibility process. The screening process should include baseline assessments to establish participants' health status and severity of the condition being treated, providing a reference for evaluating treatment effects.

Adverse Event Management

Managing and documenting adverse events is a key component of medicinal cannabis trials. Given the psychoactive nature of cannabis, participants may experience side effects such as dizziness, anxiety, or cognitive impairment. Protocols should be in place to handle these events promptly and safely. Serious adverse events, including any that may require hospitalization, must be reported to regulatory authorities within specified timelines. The trial should include safety monitoring procedures, such as

regular medical check-ups or phone assessments, to identify adverse effects early. In cases where side effects become severe or persistent, dose adjustments or discontinuation of treatment may be necessary. Clear documentation of adverse events, along with the actions taken, is crucial for maintaining transparency and meeting regulatory requirements.

Security Measures

Stringent security measures are required in clinical trials involving medicinal cannabis to prevent misuse and ensure compliance with legal regulations. Facilities must implement protocols for restricted access to cannabis storage areas, with only authorized personnel allowed entry. Security measures should include video surveillance, alarm systems, and secure storage containers. Visitors to the facility should be accompanied at all times, and all cannabis handling activities must be logged. These precautions help prevent diversion or theft of the investigational product, protecting both the integrity of the trial and the safety of participants. Regular audits of security practices should be conducted to ensure compliance with national and international guidelines for handling controlled substances.

Inclusion/Exclusion Criteria

Setting appropriate inclusion and exclusion criteria is essential to ensure participant safety and the scientific validity of the trial. For medicinal cannabis trials, inclusion criteria may focus on specific medical conditions known to benefit from cannabis treatment, such as chronic pain, epilepsy, or multiple sclerosis. Exclusion criteria

should consider the potential risks associated with cannabis use, such as history of psychosis, severe cardiovascular disease, or concurrent use of substances that may interact with cannabinoids. This step ensures that the participant pool is well-defined and minimizes variability in trial outcomes. Criteria should also account for previous cannabis exposure, as tolerance may affect dosing and efficacy.

Long-Term Considerations

Long-term considerations for medicinal cannabis trials include managing potential drug-drug interactions. Concomitant medications should be documented and monitored throughout the trial. Post-trial access to effective treatments is an ethical consideration, particularly if participants benefit from the investigational product. Researchers should establish plans for ongoing prescription and supply of medicinal cannabis, if appropriate. Additionally, follow-up assessments to monitor for any long-term effects or delayed adverse events are necessary. Ensuring participants continue to receive medical support after the trial contributes to ethical responsibility and enhances the trial's overall quality.

3.5.2. Ethical considerations

The ethical planning and execution of clinical trials are paramount to safeguarding the rights, safety, and well-being of participants while ensuring the integrity and reliability of data. Ethical considerations in clinical trials encompass a range of elements, from recruitment and informed consent to investigator qualifications and facility suitability.

These considerations are guided by international guidelines, European Union regulations, and national laws.

One of the foundational ethical aspects of clinical trials is the recruitment of participants. Recruitment arrangements must be carefully designed to ensure transparency and fairness. A separate document should detail the procedures for subject inclusion and clearly indicate the first act of recruitment. If recruitment is conducted through advertisements, all materials, including printed and audiovisual content, must be submitted for review, and procedures for handling responses should be outlined. This ensures that potential participants receive clear and accurate information about the trial and that those who are not suitable for inclusion are handled appropriately.

Informed consent is one of the cornerstones of ethical clinical trial conduct. It involves providing potential participants or their legally designated representatives with all the necessary information to make an informed decision about their participation. This process ensures that participation is voluntary and based on a clear understanding of the trial's purpose, procedures, risks, benefits, and their rights. To achieve truly informed consent, the information provided must be comprehensive, clear, and understandable. This includes detailing the nature of the study, the interventions involved, potential risks and benefits, alternative treatments, and the rights of the participants, including the right to withdraw from the study at any time without penalty. The language used should be free of technical jargon, tailored to the participant's comprehension level, and available in the participant's native language if necessary.

The procedures for obtaining informed consent must be meticulously planned and executed, especially for vulnerable populations such as minors, incapacitated

individuals, and those in emergency situations. For each group, specific ethical and procedural considerations are paramount. In the case of minors, obtaining informed consent involves a two-step process. First, consent must be obtained from the minor's legally designated representative, usually a parent or guardian. This process includes providing detailed information about the trial's purpose, procedures, risks, and benefits. Second, depending on the minor's age and maturity, their assent should also be sought. Assent means that the minor should be given information about the trial in a way that is understandable to them and be asked to agree to participate. This dual consent process respects the autonomy of the minor while ensuring parental oversight. For incapacitated subjects who cannot provide informed consent due to mental or physical conditions, the process involves obtaining consent from their legally designated representatives. The representatives must be fully informed about the trial and should make decisions in the best interest of the incapacitated person. The involvement of an impartial witness can add an additional layer of protection, ensuring that the consent process is free from coercion and undue influence. In emergency situations where immediate medical intervention is required, obtaining informed consent can be challenging. These situations often involve life-threatening conditions such as severe trauma, stroke, or heart attack, where there may not be enough time to obtain consent before starting the intervention. In such cases, ethical guidelines and regulations allow for a deferred consent process, where consent is sought as soon as reasonably possible after the intervention. Documentation of the urgency and the steps taken to minimize risks and ensure participant safety is crucial.

Some clinical trials involve methodologies where groups of subjects are assigned to receive different interventions, rather than individual subjects making decisions independently. In these cases, simplified means of obtaining informed consent may

be used. Simplified consent procedures still require thorough information delivery, but the process is streamlined to accommodate the group-based nature of the trial. For example, information sessions or community meetings might be used to inform groups of participants simultaneously, followed by opportunities for individual questions and clarifications. Regardless of the population or setting, the informed consent process must ensure that participants or their representatives fully comprehend the information provided. This may involve multiple sessions, use of visual aids, or other methods to enhance understanding. Participants should be encouraged to ask questions and should be given sufficient time to consider their participation without feeling rushed or pressured.

Voluntariness is a key aspect of informed consent. Participants must feel free to decline participation or withdraw from the study at any time without fearing negative consequences. This principle protects participants from coercion, whether overt or subtle, and ensures that their participation is genuinely voluntary. All steps of the informed consent process must be thoroughly documented. This includes the information provided, the questions asked by participants, their responses, and the final consent given. Documentation ensures transparency and accountability, allowing for review and oversight by ethical committees and regulatory bodies. Ethical oversight plays a critical role in the informed consent process. Institutional Review Boards (IRBs) or Ethics Committees review and approve the informed consent documents and procedures before the trial begins. They ensure that the information is accurate, complete, and presented in a way that is understandable to participants. They also monitor the consent process during the trial to ensure ongoing compliance with ethical standards.

The qualifications and impartiality of investigators are essential to the ethical conduct of clinical trials. Investigators must provide current curriculum vitae detailing their qualifications, training in GCP, and experience in clinical trials and patient care. Any conditions that might influence their impartiality, such as economic interests or institutional affiliations, must be disclosed. This transparency ensures that investigators are competent and unbiased, thus upholding the integrity of the trial.

The suitability of the facilities where the trial is conducted also requires careful consideration. A written statement must justify the suitability of the clinical trial sites, adapted to the nature and use of the investigational medicinal product. This includes descriptions of facilities, equipment, human resources, and expertise, validated by the head of the clinic or another responsible authority. Ensuring that the facilities are appropriate for the trial's requirements is crucial for the safety and efficacy of the interventions being tested.

Proof of insurance or indemnification is mandatory to protect participants in the event of harm resulting from the trial. Sponsors must provide documentation of insurance cover or a similar arrangement, ensuring that participants are compensated for any adverse outcomes. Financial arrangements, including the financing of the trial, compensation to subjects and investigators, and any agreements between the sponsor and the trial site, must also be transparently documented. This financial transparency helps prevent conflicts of interest and ensures that all parties are fairly compensated.

The processing of personal data in compliance with the General Data Protection Regulation (GDPR) is another crucial ethical consideration. Sponsors must submit a statement ensuring that data will be collected and processed in accordance with EU

data protection laws. This commitment to data privacy protects the personal information of participants, maintaining their confidentiality and trust.

Additionally, ethical considerations extend to the sustainability of investigators, the suitability of facilities, and the overall design and implementation of the trial. Investigators must be qualified and free from conflicts of interest, facilities must be equipped and staffed appropriately for the trial, and the trial design must prioritize participant safety and data integrity. Ensuring compliance with these ethical standards requires coordination between sponsors, investigators, regulatory bodies, and ethical committees, each playing a vital role in maintaining the high standards expected in clinical research.

3.5.3. Facilities and settings

The selection and preparation of suitable facilities are paramount in ensuring the successful planning and execution of clinical trials. These facilities must meet rigorous standards to maintain the integrity of the data collected and to protect the safety and rights of the participants. Several factors play a critical role in determining the appropriateness of a facility for clinical trials, including its suitability, licensing, compliance with GCP and GLP, and specific requirements for handling certain types of investigational products.

The suitability of a facility for a specific clinical trial is determined by its ability to meet the unique requirements of the investigational medicinal product and the trial protocol. A duly justified written statement must be provided, detailing the facility's suitability, including the available equipment, human resources, and expertise. This statement is

typically issued by the head of the clinic or another responsible authority within the institution. The facility must have the necessary infrastructure to support the trial, such as specialized medical equipment, adequate space for patient interactions, and systems for data management and storage. For instance, a trial involving advanced imaging techniques requires access to high-quality imaging devices and trained personnel to operate them.

Clinical trials often involve follow-up periods to monitor participants over time, which can range from a few months to several years. The suitability of a facility for follow-up depends on its ability to maintain consistent participant contact, provide ongoing medical care, and manage continuous data collection. This is especially critical in long-term studies where participant retention and data integrity are vital. Facilities must have robust systems to support regular follow-ups, including scheduling, record-keeping, and the ability to perform necessary medical evaluations. The logistical capacity to handle follow-ups efficiently ensures that data is consistently collected and that participants remain engaged throughout the study period.

Facilities used for clinical trials must be appropriately licensed and comply with national and international regulations. Licensing ensures that the facility meets basic standards for safety, hygiene, and operational competency. Regulatory bodies may conduct inspections to verify compliance and ensure the facility's readiness to conduct clinical trials. Compliance with these regulations is crucial to maintaining the ethical and scientific integrity of the trial. Adherence to GCP and GLP standards is essential for facilities involved in clinical trials. GCP guidelines ensure that trials are conducted ethically, with the safety and rights of participants protected, and that the data collected is reliable and accurate. This involves comprehensive documentation, regular audits,

and continuous training of staff. For laboratory-based aspects of clinical trials, adherence to GLP standards is equally important. GLP ensures that laboratories maintain high-quality scientific integrity and reliability in non-clinical safety tests, supporting the development and approval of new medicinal products. Clinical trials involving drugs of addiction or substances that can be abused, such as cannabis, require additional security measures. Facilities must have suitable security systems, including restricted access areas, secure storage for these substances, and protocols to ensure that only authorized personnel can access them. Visitors should be accompanied at all times to prevent unauthorized access. These security measures are critical to prevent misuse and ensure the safety of both the participants and the investigational products. In addition to the above points, other considerations include the adequacy of the facility's support services, such as emergency medical care, which must be readily available in case of adverse events. The facility must also have mechanisms for maintaining participant confidentiality and data protection, in compliance with regulations such as the GDPR. This includes secure data storage solutions and protocols for data access and sharing. Moreover, financial arrangements and proof of insurance coverage are essential aspects of the preparation for clinical trials. The facility must have clear financial agreements in place, including funding sources, compensation for participants, and coverage for potential trial-related injuries. Documentation proving insurance or indemnification arrangements provides an additional layer of protection for participants and investigators.

3.5.4. Protocol

The development and implementation of protocols in clinical trials are critical steps that define the scientific, ethical, and operational aspects of the study. A well-crafted protocol ensures the reliability of results, the safety of participants, and compliance with regulatory standards. The protocol must encompass various elements, including the study's objective, design, methodology, statistical considerations, and organizational structure, to provide a clear roadmap for the trial.

The protocol begins with an identification section, detailing the title of the clinical trial, the EU trial number, the sponsor's protocol code number, the version number, and the date. This section also includes the name and address of the sponsor and the authorized representatives. Clear identification ensures traceability and proper documentation throughout the trial. Central to the protocol is a statement of compliance, affirming that the trial will be conducted according to the protocol, relevant regulations, and Good Clinical Practice (GCP) guidelines. This commitment to compliance underscores the trial's adherence to ethical standards and regulatory requirements. The protocol must list all investigational and auxiliary medicinal products involved, accompanied by summaries of non-clinical and clinical findings relevant to the trial. This includes an evaluation of known and potential risks and benefits, providing a foundation for ethical assessment and informed consent processes.

Participant involvement is another critical element. The protocol must describe the groups and subgroups of participants, including those with specific needs such as different age groups, genders, or those with rare diseases. It should outline the involvement of patients in the trial design, justifying dosages, administration routes, and treatment periods for all medicinal products used. This participant-focused

approach ensures the study addresses relevant clinical questions while safeguarding participant welfare. The trial's design must be clearly articulated, including a discussion of its relevance and the scientific rationale. This section includes a schematic diagram of the trial design, detailing procedures, stages, and endpoints. It must specify primary and secondary endpoints, measures to minimize bias (e.g., randomization and blinding), and the expected duration of participant involvement. This comprehensive design framework ensures the trial's scientific rigor and operational clarity. Statistical methods are integral to the protocol, encompassing sample size calculations, power analysis, significance levels, and interim analysis plans. The protocol should describe criteria for trial termination, handling of missing or spurious data, and subject selection for analyses. This statistical rigor ensures the trial's results are scientifically valid and interpretable.

Ethical considerations are woven throughout the protocol, including procedures for obtaining informed consent, especially from vulnerable populations such as minors or incapacitated individuals. The protocol must justify the inclusion or exclusion of specific demographic groups and detail the recruitment and consent processes. Additionally, it outlines treatments permitted before and during the trial, procedures for monitoring compliance, and post-trial care arrangements for participants. Safety monitoring is another critical component, with the protocol detailing adverse event reporting procedures, including definitions of critical safety evaluations and serious adverse events. It must describe the processes for recording, reporting, and following up on adverse reactions, ensuring robust pharmacovigilance throughout the trial. If a single safety report is planned for all investigational products, the protocol must justify this approach.

Data management is also addressed, with the protocol describing the collection, storage, and future use of biological samples, compliance with data protection laws, and measures to ensure confidentiality and security of participant data. This includes organizational and technical arrangements to prevent unauthorized access and mitigate the impact of data breaches. Finally, the protocol should include a synopsis, providing a concise summary of the trial's objectives, design, methodology, and key considerations. This overview facilitates understanding and communication among stakeholders, including regulatory bodies, ethics committees, and trial personnel.

3.5.5. Quality

Ensuring quality in the planning and execution of clinical trials is paramount to obtaining reliable and valid results, protecting participant safety, and maintaining compliance with regulatory standards. Various components, such as the Investigator's Brochure (IB), compliance with Good Manufacturing Practice (GMP), and the meticulous preparation of the Investigational Medicinal Product Dossier (IMPD), play critical roles in maintaining the integrity and quality of clinical trials.

The Investigator's Brochure is a key document that provides essential information to investigators and others involved in the clinical trial. Prepared in accordance with the latest scientific knowledge and international guidelines, the Investigator's Brochure facilitates an understanding of the trial's rationale, dosing regimens, methods of administration, and safety monitoring procedures. The information within the Investigator's Brochure must be concise, objective, balanced, and presented in a non-promotional manner. This format ensures that clinicians and investigators can make unbiased risk-benefit assessments regarding the trial's appropriateness. If the

investigational medicinal product is already authorized and used according to its marketing authorization, the approved Summary of Product Characteristics (SmPC) can serve as the Investigator's Brochure. In cases where the product is used differently in the trial, the SmPC must be supplemented with relevant non-clinical and clinical data to support its use. This approach ensures that all safety information is consolidated and accessible, providing a robust basis for understanding and monitoring the investigational product's effects. Adherence to GMP is crucial for the quality assurance of investigational medicinal products. Documentation relating to GMP compliance must be provided unless the product is authorized and unmodified, irrespective of whether it is manufactured within the Union. For products not authorized or lacking a marketing authorization from an ICH country, additional documentation, including certification by a qualified person in the Union, is required to confirm that manufacturing practices are equivalent to those in the Union. Ensuring GMP compliance involves rigorous control over the manufacturing process, including the maintenance of detailed records, regular inspections, and validation of manufacturing methods. This compliance guarantees that investigational products are produced consistently and meet predefined quality standards, thereby safeguarding participant safety and ensuring the reliability of trial results. The IMPD is another critical document that provides comprehensive information on the quality, manufacture, and control of the investigational product. It includes data from non-clinical studies and prior clinical use, presented in a logical and concise manner. The IMPD should be structured according to the ICH Common Technical Document format, facilitating a thorough evaluation of the product's safety and efficacy. The IMPD must include summaries of non-clinical pharmacology and toxicology data, highlighting key findings and providing an assessment of the study's adequacy. These summaries allow reviewers to evaluate

whether the studies were conducted according to acceptable protocols and if the data supports the safe use of the investigational product. Additionally, the dossier should include a critical analysis of the data, justifying any omissions and assessing the product's safety in the context of the proposed trial.

Ensuring comprehensive documentation and compliance with regulatory standards is fundamental to maintaining the quality of clinical trials. This includes the preparation of the Auxiliary Medicinal Product Dossier (AMPD) for any auxiliary medicinal products used in the trial. The AMPD should comply with the same documentation requirements as the IMPD, ensuring that all products used in the trial meet stringent quality standards. Moreover, scientific advice and paediatric investigation plans (PIP) should be documented and submitted if available. This ensures that the trial design incorporates expert recommendations and complies with regulatory expectations, particularly for trials involving paediatric populations. Labeling of investigational medicinal products must also comply with regulatory standards, providing clear and accurate information to trial participants and investigators. Proper labeling ensures correct product identification, usage, and tracking throughout the trial, which is essential for maintaining participant safety and data integrity.

3.5.6. Special considerations for cannabis trials

The increasing interest in cannabis for medicinal purposes has led to a growing number of clinical trials to evaluate its efficacy and safety. However, planning and executing these trials come with unique challenges that need careful consideration. These challenges span from determining appropriate dosages to ensuring the security of the trial facilities, given the nature of the substance.

One of the initial steps in planning a clinical trial involving cannabis is to determine the appropriate starting dosage. This determination is often based on pre-clinical studies, which provide crucial data on the pharmacokinetics and pharmacodynamics of cannabis. These studies help establish baseline safety profiles and effective dose ranges, which are critical in setting initial dosages for human trials. Such pre-clinical data can guide the initial dose selection and titration schedules, ensuring that human subjects receive a dose that is both effective and safe. Accurate dosing is paramount in clinical trials involving cannabis. Variability in cannabis products, such as differences in cannabinoid concentrations and formulations, necessitates precise dosing to achieve reliable results. Trials must ensure that dosing is consistent across all participants, which involves careful selection of cannabis products and rigorous control of dosing protocols. This precision helps mitigate variability and enhances the reproducibility of trial outcomes.

The method of cannabis delivery significantly impacts its effectiveness and safety profile. For example, vaporization, a common delivery method, involves variables such as the length of inhalation, the temperature of the vaporizer, and the type of vaporizer used. Medical-grade vaporizers are preferred over those designed for recreational vaping to ensure consistent dosing and reduce the risk of contamination. In contrast, oral delivery methods involve fewer variables, making them simpler and often more reliable. Regardless of the method, an accurate and detailed description of the delivery methodology is essential for replicability and reliability in clinical settings. Cannabis is known for its potential to develop tolerance, which can affect the outcomes of clinical trials. Participants with previous exposure to cannabis may have different tolerance levels compared to those who are cannabis-naïve. This variance can influence the starting dose and the drug's effects, necessitating tailored dosing strategies. Thorough

screening of participants' cannabis use history is crucial to adjust dosages appropriately and ensure the validity of the trial results.

Given the complex pharmacology of cannabis, managing and reporting adverse events is a critical component of clinical trials. Adverse events must be meticulously documented and reported in compliance with regulatory standards such as those outlined in the Clinical Trials Regulation 536/2014. Sponsors are required to report serious unexpected suspected adverse reactions (SUSARs) to the EudraVigilance database within specified timelines, ensuring transparency and regulatory compliance. Effective management of adverse events involves not only prompt reporting but also having robust mechanisms in place to address these events and protect participant safety.

The potential for cannabis to be abused or diverted necessitates stringent security measures at trial facilities. Facilities must implement security protocols to prevent theft and unauthorized access, especially when handling drugs of addiction like cannabis. This includes restricted access areas, secure storage solutions, and ensuring that visitors are always accompanied. These measures are vital to maintaining the integrity of the trial and safeguarding the investigational product. Setting appropriate inclusion and exclusion criteria is crucial to ensure the safety of participants and the validity of the trial results. For instance, individuals with a history of psychosis should be excluded from trials involving cannabis due to the potential exacerbation of their condition by THC. Similarly, other vulnerable populations, such as those with severe cardiovascular conditions, may need to be excluded to avoid undue risks. Clear criteria help in selecting a suitable participant pool and maintaining the trial's ethical standards.

In addition to the points discussed, researchers must consider the long-term implications of cannabis use in their trials. This includes potential drug-drug interactions, given that cannabinoids are metabolized by the cytochrome P450 system, which is a common site for interactions with other medications. Thorough monitoring and documentation of any concomitant medication use are essential to understanding these interactions. The potential for post-trial access to cannabis treatments should also be considered. Ensuring that participants have continued access to effective treatments post-trial is an ethical obligation that must be addressed during trial planning. This may involve setting up mechanisms for ongoing prescription and supply of the investigational product if it proves beneficial.

3.5.7. Expert panel feedback

An expert panel, comprising individuals with extensive experience in the field of medicinal cannabis, was presented with a detailed proposal outlining a clinical trial framework. The panel was composed of a consultant psychiatrist, and two regulatory pharmacists with involvement in research and the regulation of medicinal use. The framework was designed to systematically evaluate the therapeutic potential of medicinal cannabis through ten distinct stages, each representing a critical component of the trial design. The proposal was submitted to leverage the panel's specialized knowledge and to obtain recommendations that could refine and enhance the structure and feasibility of the proposed clinical trial. The expert input was deemed crucial to ensure that the framework was both methodologically sound and clinically relevant.

To facilitate a comprehensive evaluation of the clinical trial framework, the panel members were requested to express their level of agreement or disagreement with

each of the seven stages using a four-point Likert scale. This instrument was selected to capture nuanced opinions regarding each aspect of the framework, allowing for a gradation of responses from disagreement to agreement. In addition to the quantitative ratings, panelists were encouraged to provide free-form comments on each stage, thereby offering qualitative insights that could illuminate specific strengths and potential areas for improvement. An additional question solicited an overall assessment of the complete clinical trial framework, ensuring that both detailed and holistic perspectives were incorporated into the final recommendations.

Overall, the feedback received from the expert panel was predominantly positive. Each expert provided varying levels of agreement with the different stages of the proposed clinical trial framework, as well as with the overall design and structure of the framework. This range of responses not only underscored the multi-dimensional nature of the evaluation process but also highlighted the areas where consensus was reached, thereby affirming the robustness of the proposed framework. A significant proportion of the expert responses indicated full agreement, reflecting a strong endorsement of the clinical trial framework's methodology and structure. This predominant level of full agreement suggests that the framework, as originally proposed, was well-aligned with current scientific standards and clinical expectations in the field of medicinal cannabis research. Such a consensus among experts reinforces the credibility and potential impact of the trial design.

For instances where the level of agreement was marked as 'somewhat agree,' the qualitative comments provided by the panel were carefully analyzed. These insights were instrumental in identifying specific aspects of the framework that required refinement or further clarification. In response to this constructive feedback, revisions

and upgrades were systematically implemented, leading to a revised and finalized version of the clinical trial framework. This iterative process ensured that the final design was both comprehensive and optimized to address any identified limitations, thereby enhancing its overall scientific rigor and practical applicability.

Chapter 4 - Discussion

4. Discussion

4.1. Prologue

In November 2018, the World Health Organization Expert Committee on Drug Dependence (ECDD) during its introductory meeting, acknowledged that robust scientific evidence on the use of cannabis for medicinal purposes is very limited (World Health Organisation, 2019)². Further research is required to support the development of policies, guidelines and best practice attributed to the process of medicinal cannabis production and use (Bonn-Miller et al, 2019; Freeman et al, 2019). The perception and attitude of healthcare professionals towards the clinical applications of medicinal cannabis need to be addressed. Studies indicate that there is a knowledge gap amongst healthcare professionals on the use of medicinal cannabis (Hwang et al, 2016; Carlini et al, 2017; Karanges et al, 2018; Zolotov et al, 2018; Gardiner et al, 2019; Philipot et al, 2019). This research attempts to address these issues within the national setting and sharing the recommendations obtained at international fora. The outcomes of the research on the clinical use of medicinal cannabis are to address a lacuna in the knowledge of medicinal cannabis prescribing information, educational initiatives for healthcare professionals and encourage further studies on medicinal cannabis.

² World Health Organization. Annex 1: Extract from the Report of the 41st Expert Committee on Drug Dependence: Cannabis and cannabis-related substances Geneva: WHO; 2019: 1-8. Available from: https://www.who.int/medicines/access/controlled-substances/Annex_1_41_ECDD_recommendations_cannabis_22Jan19.pdf?ua=.

4.2. Demographic distribution

Responses registered came from a fairly well-balanced population in terms of sex and profession as representation on the former category was distributed along percentages that read 54.5% - 45.5%, and for the profession category pharmacists totalled 44% with the rest being medical practitioners. In terms of participant age, a median of 45.5 demonstrated good distribution and representation of the population. The area within which the healthcare professionals practiced were relatively varied in both major categories: medical practitioners and pharmacists. Considering also that the total number of respondents amounted to 200 individuals, the study should have generated a particularly representative set of data with regards to attitudes and beliefs of healthcare professionals in the local context, with regards to use of medicinal cannabis.

The Pearson correlation analysis in Table 3.7, comparing data collected for doctors indicates a statistically significant, albeit weak, positive relationship ($r = 0.20$, $p = 0.040$) between age and Prescription Attitude in relation to the clinical use of medicinal cannabis. Table 3.8, which sought to bring to light gender differences in the same categories among doctors who responded to the questionnaire, noted that for female physicians there was no significant correlation between age and Prescription Attitude but that for male doctors there was a significantly positive correlation ($r=0.34$, $p<0.009$). This suggests that with older doctors, there is a slight trend towards a less favourable attitude regarding the use of medicinal cannabis in clinical practice. This finding may reflect generational differences in perspectives or comfort levels with newer treatment modalities. Older practitioners may have more established clinical routines and might be less inclined to adopt newer treatment modalities, particularly

those that have only recently entered the mainstream of clinical practice. In addition, generational differences in education and exposure to alternative therapies may contribute to a more cautious stance among older doctors. Such findings underscore the importance of targeted educational initiatives and continuous professional development, which could help bridge the gap between traditional practices and emerging therapeutic options like medicinal cannabis. Table 3.9, a hierarchical regression analysis was conducted to identify predictors of Prescription Attitude among doctors regarding the clinical use of medicinal cannabis, provided ulterior confirmation. The initial model accounted for 4% of the variance in Prescription Attitude, with $F(2, 105) = 2.345$, $p = 0.101$, indicating that the model was not statistically significant at this stage. Even here, age emerged as a weak predictor of Prescription Attitude ($\beta = 0.22$, $p = 0.033$, $t = 2.17$), suggesting that older doctors tend to hold less favourable attitudes toward prescribing medicinal cannabis. In general, however, age did not emerge as an influential factor.

Gender did not significantly predict Prescription Attitude in this model, and in any other analysis conducted no significant gender differences in attitudes or knowledge were noted. This confirms that attitudes, beliefs and knowledge related to medicinal cannabis among our sample is largely independent of demographics. Other recent studies largely concur, finding that factors like gender and age are at most minor influences compared to the dominant effects of education and legal context. A systematic review of European healthcare workers did not identify any consistent gender-based attitude gaps in the included surveys (Hordowicz et al., 2021b).

4.3. Benefits to patients and hesitancy in discussing medicinal cannabis

When the healthcare professionals were asked about whether they think that some patients could derive benefit from a cannabis-based therapy 65% claimed that they did. It has to be noted that the majority of them, 72 respondents of these 130 in agreement, stood on a tepid position of agreement. That represents 36% of the total sample. A further 7% expressed 'no opinion' on the matter.

Legislative framework in the Maltese islands with regards to use of medicinal cannabis has changed relatively recently, and matters are developing slowly towards more commonplace use of this form of therapy. The questionnaire results reported here are intimately linked to this current legal status. Regulations in place influence attitudes and behaviours of healthcare professionals. Whereas prior to the introduction of governance and supervisory mechanisms medical practitioners and pharmacists are likely to approach the idea of recommending or prescribing medicinal cannabis with caution, consequent legislation embraced by local authority would tend to encourage alternative perceptions given the legal protection afforded as well as the belief that legalization is the result of informed research. Many medical professionals may be hesitant to prescribe a medication that has not been thoroughly studied and tested, and which may have potential side effects or risks for patients. Governing bodies are assumed to have consulted an extensive and recent body of research ahead of embracing a new form of therapy. This could explain why 65% of healthcare professionals consulted seem keen on accepting use of medicinal cannabis for some patients that could benefit from it. 36% still stand on a cautious acceptance, however. Possibly due to the relatively recent introduction of legal guidelines as well as the

gradual progression and controlled pace in the introduction of a new pharmaceutical therapy that effectively delays transition.

Information disseminated locally and changing regulations are not taken in isolation clearly, as more Western countries have been taking steps in allowing for supervised use of medicinal cannabis. More studies keep being published about the efficacy or otherwise of medicinal cannabis in alleviating symptoms for a number of ailments. A growing body of evidence suggests that cannabis and its derivatives may have therapeutic potential for certain medical conditions. This may lead some doctors and pharmacists to view medicinal cannabis as a potentially useful option for treating specific patients, particularly those who have not responded to more conventional treatments.

Discussing the therapeutic alternative with patients seemed to find a majority of respondents in agreement. The question directed at the healthcare professionals was not one whereby they suggested medicinal cannabis to patients but whether they would feel comfortable discussing it with patients. This could entail the patient raising the matter with the healthcare professional and initiating discussion. 127 respondents stated they would feel comfortable discussing medicinal cannabis. A total of 26.5% mostly agreed they would feel comfortable and 22.5% somewhat agreed. 57 (28.5%) of the total respondents claimed they would not feel comfortable discussing the subject with patients. The level of confidence, although shifting towards agreement, was therefore not convincingly high, and fell lower when enquiring about confidence levels in dealing with questions coming from patients about the use of medicinal cannabis. The least selected option for this particular question was 'strongly agree' with 6%. This supposedly stemmed from a desire by many to welcome cannabis-based therapy, yet

in attendance of being better prepared in dealing with all aspects connected to discussing and potentially dispensing treatment, as well as perhaps a more deeply engrained and structured cultural shift.

The slight differences in mean scores between doctors and pharmacists recorded in Table 3.1 suggest that, while both groups share some common ground in their attitude to the clinical use of medicinal cannabis, doctors tend to be more cautious or reserved in their approach ($M=6.20$, $SD=2.88$ vs $M=5.19$, $SD=2.26$, $t(195.78) = -2.71$, $p = 0.006$, Cohen's $d = -0.4$). This may be influenced by their clinical responsibilities, such as the need to weigh potential risks and benefits more rigorously before prescribing, or their exposure to patients with complex medical conditions where evidence for medicinal cannabis use may be limited. Pharmacists, on the other hand, may have a more favourable approach due to their expertise in drug mechanisms, interactions, and dosing, which could make them more comfortable with integrating medicinal cannabis into treatment plans.

Similar results were reported in a recent Croatian study by Batinic et al. (2023), where pharmacists demonstrated significantly more favourable attitudes towards CBD compared to physicians. Pharmacists (63.8%) and pharmacy students (72.2%) were more optimistic regarding CBD's therapeutic potential and particularly its ability to reduce the use of opioids prescribed for chronic pain. Pharmacists in this study were significantly more likely to have engaged with scientific literature on CBD, which correlated with their more favourable attitudes and confidence in recommending it therapeutically. Findings from Szaflarski et al. (2020) in the United States similarly indicated that pharmacists generally displayed higher knowledge and more positive attitudes towards cannabis-based therapies compared to neurologists and nurses.

This study highlighted pharmacists' greater familiarity with the pharmacology and clinical applications of cannabinoid therapies, contributing to their more supportive stance towards medicinal cannabis use. Neurologists, while recognizing cannabis-based treatments' efficacy in conditions such as epilepsy, demonstrated greater caution and hesitancy, primarily attributed to concerns over inadequate formal clinical guidelines and uncertainty regarding legal implications.

The findings highlight the importance of interdisciplinary collaboration and communication between pharmacists and doctors to bridge the gap in attitudes. While the differences are slight, they underscore the need for shared decision-making frameworks and standardized guidelines to ensure that patients receive consistent and evidence-based recommendations regarding medicinal cannabis. Additionally, these results suggest that targeted educational interventions tailored to the specific concerns of doctors, such as addressing evidence gaps and risk management, could help align their approach more closely with that of pharmacists. It is important to note that the differences noted in Table 3.1, while statistically significant, are slight, indicating that the practical implications of these findings may be modest. Further qualitative research could provide deeper insights into the underlying reasons for these differences and inform strategies to address them.

Australian surveys carried out by Bawa and colleagues among doctors and pharmacists recorded very similar results for both categories of professionals. The study with general practitioners showed that a majority of them were cautiously supportive of medicinal cannabis, particularly for specific conditions such as palliative care, cancer pain, and epilepsy. While their support had increased since an earlier survey, many GPs still reported feeling uncomfortable discussing cannabis with

patients due to insufficient knowledge and training. The study highlighted a clear need for further education among doctors, indicating moderate acceptance combined with caution and knowledge gaps (Bawa et al., 2022). Similarly, Bawa et al. (2023) explored the attitudes of Australian pharmacists and found parallel results. Pharmacists expressed general support for the accessibility and dispensing of medicinal cannabis, with more than half having already dispensed cannabis prescriptions. Despite their support, pharmacists acknowledged significant gaps in their knowledge and confidence regarding medicinal cannabis products. Like doctors, pharmacists emphasized the need for additional training to confidently manage patient inquiries and adequately counsel patients, especially considering recent regulatory shifts allowing over-the-counter CBD product sales in pharmacies. The international survey by Russo et al. (2024) further reinforces this cross-professional alignment among pharmacists and doctors. The healthcare professional sample included neurologists, psychiatrists, general practitioners, pharmacists, and nurses from 16 different countries. They shared favourable attitudes towards cannabis-based products, with few significant differences noted between professions or regions. Professionals across these disciplines demonstrated high levels of interest and generally felt knowledgeable and confident when discussing cannabis-based products. Nonetheless, they collectively acknowledged a strong need for further education, particularly robust clinical trial evidence to enhance patient safety and professional confidence.

Results in Table 3.3 revealed that male pharmacists ($M = 4.42$, $SD = 2.15$), compared to their female ($M = 5.63$, $SD = 2.21$) counterparts, had a slightly more favourable stance to the clinical use of medicinal cannabis, indicating a potential increased openness exploring alternative treatments, while female pharmacists may adopt a

more cautious stance due to concerns about safety or regulatory complexities. Table 3.4, assessing the same metrics for doctors, revealed no such relationship.

In Table 3.7 a robust positive relationship was found between Approach and Prescription Attitude ($r = 0.68$, $p < 0.001$), indicating that doctors who maintain a positive perspective on medicinal cannabis are considerably more likely to hold favourable views about prescribing it. This strong correlation suggests that a doctor's overall attitude and approach toward medicinal cannabis play a pivotal role in shaping their willingness to integrate it into clinical practice. Specifically, doctors who view medicinal cannabis as a viable and beneficial treatment option are more inclined to support its use and consider it a legitimate therapeutic tool for patients. This relationship highlights the interconnectedness of attitudes and clinical decision-making, emphasizing that a positive mindset toward medicinal cannabis is closely tied to practical prescribing behaviours. It also underscores the importance of addressing potential biases or reservations that doctors may have, as these could hinder the adoption of medicinal cannabis in clinical settings. Efforts to foster a more favourable approach, such as providing evidence-based education, sharing success stories, and addressing misconceptions, could significantly enhance doctors' willingness to prescribe medicinal cannabis. Furthermore, the strength of this correlation suggests that interventions aimed at improving doctors' attitudes toward medicinal cannabis could have a cascading effect, not only increasing their openness to its use but also potentially improving patient access to this treatment option. This finding reinforces the need for targeted strategies to cultivate positive perspectives among healthcare professionals, as their attitudes are a critical determinant of the integration of medicinal cannabis into mainstream medical practice.

A strong positive correlation was found between Approach and Knowledge for both male ($r = 0.66$, $p < 0.001$) and female doctors ($r = 0.48$, $p < 0.001$), as evidenced in Table 3.8. This finding indicates that irrespective of a doctor's gender, a higher level of knowledge about medicinal cannabis is associated with a more positive approach toward its clinical use. In other words, doctors who are well-informed about the pharmacological properties, therapeutic potential, and associated risks of medicinal cannabis tend to have a more favourable perspective on incorporating it into clinical practice. The stronger correlation among male doctors ($r = 0.66$ vs $r = 0.48$) suggests that for this group, knowledge may play a slightly more influential role in shaping their clinical attitudes, potentially highlighting a greater reliance on factual information when forming opinions about new treatment modalities. In Table 3.8 as well, it was noted that among female doctors, a significant positive correlation was observed between Approach and Education ($r = 0.42$, $p < 0.003$). This suggests that female practitioners who report more favourable educational experiences or possess a positive educational outlook regarding medicinal cannabis are more likely to maintain an open and positive approach toward its use in clinical settings. The absence of a significant correlation between Education and Approach among male doctors implies that while both knowledge and education are important, formal educational experiences may have a more pronounced impact on shaping the attitudes of female doctors.

A robust positive relationship was observed between Approach and Prescription Attitude in Table 3.8 for both male ($r = 0.67$, $p < 0.001$) and female doctors ($r = 0.71$, $p < 0.001$). This finding emphasizes that a positive approach toward medicinal cannabis is a key determinant in shaping a doctor's willingness to prescribe it, irrespective of gender. In essence, doctors who view medicinal cannabis favourably are much more likely to consider it a viable treatment option in their practice. Moreover,

the slightly stronger correlation among female doctors indicates that their prescribing behaviours are even more closely aligned with their overall attitudes. This suggests that for female practitioners, a positive outlook on medicinal cannabis might translate more directly into clinical practice, highlighting the potential impact of targeted educational and policy interventions that nurture a positive approach to emerging therapies.

The hierarchical regression analysis evidenced in Table 3.9, conducted to identify predictors of Prescription Attitude among doctors regarding the clinical use of medicinal cannabis, had Approach toward the clinical use of medicinal cannabis, Knowledge of medicinal cannabis, and Education added to the model in the second step. This significantly improved the explanatory power of the model, which now accounted for 46% of the variance in Prescription Attitude, with $F(5, 102) = 20.66$, $p < 0.001$. This substantial increase in variance highlights the critical role of attitudinal and educational factors in shaping doctors' prescribing behaviours. Approach toward the clinical use of medicinal cannabis was found to be the strongest predictor of Prescription Attitude ($\beta = 0.71$, $p < 0.001$, $t = 6.84$). This indicates that doctors who maintain a positive perspective on medicinal cannabis, with affirmative views on benefits that may be derived by patients and comfort in discussing therapy with patients, are significantly more likely to support its clinical use. The strength of this relationship underscores the importance of fostering favourable attitudes among healthcare professionals to promote the integration of medicinal cannabis into clinical practice. While Knowledge and Education were included in the model, their individual contributions were not statistically significant in this analysis. This suggests that, although knowledge and education are important, their influence on Prescription Attitude may be mediated or overshadowed by the dominant role of Approach.

However, their inclusion in the model still adds value, as they collectively contribute to the overall understanding of the factors influencing Prescription Attitude.

The final model, combining demographic, attitudinal, and educational variables, accounted for 50% of the variance in Prescription Attitude. This robust explanatory power demonstrates the multifaceted nature of doctors' attitudes toward medicinal cannabis, with Approach emerging as the most influential factor. The results, as detailed in Table 3.9, provide a comprehensive overview of the predictors and their relative contributions. These findings highlight the importance of addressing doctors' attitudes and perceptions as a primary strategy for increasing acceptance and support for the clinical use of medicinal cannabis. Educational initiatives aimed at enhancing knowledge and fostering positive attitudes could play a pivotal role in overcoming reservations and promoting evidence-based prescribing practices.

The study by Adler et al. (2022) reveals a split in the perceptions of Israeli primary care physicians regarding the benefits of medicinal cannabis. Only 51% of the 201 respondents believed that medicinal cannabis is an effective treatment. Meanwhile, 11% of the physicians thought that medicinal cannabis was ineffective, and 38% remained unsure. These mixed views highlight the uncertainty and cautiousness among primary care physicians when it comes to recommending medicinal cannabis to patients. The willingness to discuss and prescribe medicinal cannabis is influenced by these perceptions, as physicians who believe in its effectiveness are significantly more likely to be willing to prescribe it. The study found that willingness to prescribe medicinal cannabis increased dramatically among those who agreed with its efficacy, with an odds ratio of 14.8 for those who somewhat agreed and 21.9 for those who

strongly agreed. This indicates that the belief in the therapeutic potential of cannabis is a critical factor in whether doctors are open to discussing its use with patients.

Similarly, Rosenbæk et al. (2023) investigated attitudes among Danish general practitioners, finding a parallel trend. Their nationwide survey showed that a positive attitude toward medicinal cannabis was strongly associated with increased prescription behaviour (OR = 5.2). Importantly, this attitude was closely correlated with perceived knowledge levels, indicating that attitudes and perceived competence reinforce each other in influencing prescribing practices. However, even among physicians with prescribing experience, nearly half maintained a negative or uncertain stance toward medicinal cannabis, underscoring the critical role of attitudes in clinical decision-making.

Alsolamy et al. (2023) demonstrate that Saudi physicians, particularly those specializing in paediatrics and neurology, exhibit a cautious attitude toward the use of CBD for treating paediatric epilepsy. The findings show that only 38.3% of physicians agreed or strongly agreed that there is a stigma associated with recommending CBD for epilepsy, suggesting that while stigma exists, a significant portion of physicians may be neutral or undecided about its implications. When it comes to the perceived effectiveness of CBD, a mere 8.5% of respondents strongly agreed that CBD is effective for epilepsy, and only 13.8% favoured its use as a treatment option. These low percentages indicate that most physicians are either uncertain or unconvinced about the benefits of CBD, reflecting a general hesitancy to actively discuss or recommend it to patients. This hesitancy could stem from the limited exposure to CBD in their medical training or the novelty of CBD as a therapeutic agent in epilepsy management.

A significant portion of Croatian physicians, pharmacists, and students hold positive attitudes towards CBD, with approximately 60% of the total respondents believing that CBD treatment is generally efficacious (Batinic et al., 2023). This positive attitude was particularly prominent among pharmacists and pharmacy students, as noted earlier. More convinced than doctors that CBD could help reduce the use of opioids prescribed for chronic pain ($p < 0.05$), indicating a belief in its potential as an alternative pain management tool. Despite the positive perceptions, only a small percentage of participants had directly engaged with CBD in a clinical or personal context, highlighting a gap between theoretical support and practical application. Moreover, most respondents agreed that they lacked sufficient knowledge to recommend CBD confidently, with 94% of physicians and 88.7% of pharmacists expressing this sentiment. This suggests that while there is a recognition of CBD's potential benefits, there is hesitancy in its clinical use due to a lack of comprehensive understanding and training.

This hesitancy is clear in the results obtained in the present study as well and confirms the sentiment expressed in previous international research with acknowledgment of medicinal cannabis benefits being counterbalanced by timidity in recommending it to patients. Australian GPs, as studied by Bawa et al. (2022), also demonstrated a multifaceted stance. The survey found that 85.3% of GPs had received patient inquiries about medicinal cannabis in the preceding three months, indicating a high level of patient interest. However, only 52.3% of GPs felt comfortable discussing medicinal cannabis with their patients, reflecting ongoing hesitancy and uncertainty. Despite this discomfort, there is strong support for the use of medicinal cannabis in specific contexts, particularly for palliative care (92.7%), chronic cancer pain (91.9%), and chemotherapy-induced nausea and vomiting (86.7%). This represents an

increase in support compared to a 2017 survey, suggesting that GPs are becoming more open to the potential benefits of medicinal cannabis in certain severe and refractory conditions. However, there remains less enthusiasm for prescribing medicinal cannabis for mental health conditions such as depression (37.2%) and anxiety (49.3%), which might be due to concerns about the evidence base for these uses or the potential risks associated with medicinal cannabis. In a subsequent study by Bawa et al. (2023), a substantial proportion of Australian pharmacists (60%) had experienced dispensing at least one medicinal cannabis prescription during their careers, and 58.5% had received at least one inquiry about medicinal cannabis in the preceding two weeks. This suggests a growing engagement with medicinal cannabis among pharmacists, reflecting an increasing demand from patients. Despite this engagement, only 53.9% of pharmacists felt comfortable supplying medicinal cannabis products, and even fewer (39.3%) were confident discussing cannabis-related inquiries. This discomfort might stem from a combination of factors, including the relatively recent legalization of medicinal cannabis and ongoing societal stigma associated with cannabis use. However, more than half of the respondents (58.7%) supported the provision of low-dose CBD products through pharmacies, indicating a cautious but positive attitude towards expanding access to medicinal cannabis. These findings suggest that while pharmacists acknowledge the potential benefits of medicinal cannabis, there is still significant hesitation in fully embracing its use, particularly in patient discussions.

A survey in Washington State, which included 494 healthcare providers, found that while there is a general recognition of the potential benefits of medicinal cannabis, this recognition is often accompanied by a lack of confidence in discussing or recommending it to patients (Carlini et al., 2017). Approximately 73.7% of respondents

agreed that medicinal cannabis can help people with chronic debilitating conditions, reflecting a broad acknowledgment of its therapeutic potential. However, only 27% of those legally permitted to authorize medicinal cannabis had done so, indicating a significant gap between perceived benefits and actual clinical practice. This gap suggests that despite understanding the potential benefits, many providers are hesitant to discuss or prescribe medicinal cannabis, possibly due to concerns about legal ramifications, lack of standardized guidelines, or personal discomfort with the topic. Ebert et al. (2015) findings suggest that while there is a significant level of support for medicinal cannabis among Israeli physicians, there are also concerns and variations in acceptance depending on the medical specialty. Specifically, 79.2% of the participating physicians agreed that medicinal cannabis could be beneficial for chronic patients and those who are terminally ill. This indicates a broad recognition of its potential therapeutic benefits, especially in managing pain and symptoms associated with serious, long-term conditions. However, the study also revealed that oncologists and pain specialists were more likely to acknowledge the benefits of medicinal cannabis compared to other specialties. This divergence suggests that while the perceived benefits of medicinal cannabis are acknowledged, they are not uniformly accepted across all fields of medicine.

The study by Boyd et al. (2023) explores the perceptions and understanding of medical students and orthopaedic residents regarding the use of CBD in medicine, particularly in pain management. The study reveals that while there is some recognition of the potential benefits of CBD, many trainees are still hesitant to fully embrace its use, largely due to the stigma associated with cannabis. Specifically, the study found that most trainees, regardless of whether they were in states where CBD is legal or not, believed that there is a stigma attached to CBD use. This perception likely affects their

willingness to discuss or recommend CBD to patients. Despite this, a considerable portion of the respondents recognized the potential of CBD in pain control, with some trainees acknowledging its benefits in improving physical function, sleep quality, and quality of life. However, the study indicates that this recognition is not yet strong enough to overcome the stigma and the associated hesitancy, suggesting that while there is an awareness of the potential benefits, it is not fully integrated into clinical practice discussions.

The study by Chin et al. (2021) sheds light on the perspectives of orthopaedic traumatologists regarding the benefits of medicinal cannabis, particularly in managing postoperative pain. According to the survey, 73% of the respondents believe that cannabis or CBD products play a role in managing postoperative pain, indicating a generally favourable sentiment towards the potential therapeutic benefits of these substances. However, despite this belief, only 29% of the respondents had suggested cannabis, and 38% had suggested CBD to their patients. This discrepancy suggests that while orthopaedic traumatologists recognize the potential benefits of medicinal cannabis, there is a hesitancy to recommend its use. This hesitancy could be attributed to various factors, including a lack of comprehensive knowledge, legal concerns, or the perceived stigma associated with cannabis use. Notably, 67% of respondents did not believe they would be stigmatized for suggesting cannabis to patients, and 83% felt the same about CBD, indicating that stigma might not be the primary barrier to its recommendation. Healthcare professionals working in a cancer hospital in Australia generally acknowledge the potential benefits of medicinal cannabis, particularly for patients with advanced cancer, according to a study by Grant et al. (2023). About 50.9% of respondents believed that medicinal cannabis could be beneficial for patients with advanced disease receiving supportive care or end-of-life care, and 49.1%

thought it could help those receiving active disease-modifying treatment for advanced or metastatic cancer with refractory symptoms. However, there was less agreement on the benefits for cancer survivors with persisting refractory symptoms (43.9%) or early-stage patients with treatment-related refractory side effects (38.7%). This indicates a recognition of the role of medicinal cannabis in more severe and palliative cases, but uncertainty remains regarding its broader applications across different stages of cancer treatment. Despite recognizing potential benefits, only 10.3% of healthcare professionals felt they had sufficient knowledge to discuss medicinal cannabis with their patients confidently. Similarly, in an Italian-based study, oncologists and palliative care physicians demonstrated awareness of the potential benefits of medicinal cannabis in cancer care (Filetti et al., 2021). Among the respondents, 90% reported being familiar with medicinal cannabis, and 79% had been asked about it by patients, indicating that there is a substantial patient-driven demand for information on this topic. However, despite this familiarity, only 29% of the respondents had actually prescribed medicinal cannabis to their patients.

The study by Patell et al. (2022) highlights a significant gap between patient inquiries about medicinal cannabis and the ability of oncology fellows to provide informed recommendations. The majority (57%) of oncology fellows reported having discussed medicinal cannabis with more than five patients in the previous year, underscoring the growing interest among cancer patients in cannabis as part of their symptom management. However, despite these frequent discussions, only 13% of the fellows felt sufficiently informed to make cannabis-related clinical recommendations. This discrepancy between patient interest and provider knowledge reflects an unmet need in clinical practice. Most oncology fellows viewed medicinal cannabis as a useful adjunctive therapy, particularly for managing cancer-related symptoms such as

anorexia/cachexia (72%), nausea/vomiting (45%), and pain (41%). However, the study also revealed that discussions about cannabis were primarily patient-initiated, with 80.4% of fellows indicating that it was the patients or their families who brought up the topic. This indicates a reluctance among oncology trainees to proactively discuss medicinal cannabis, likely due to a lack of formal education and confidence in its use. The study by Philpot et al. (2019) shows that primary care providers in a Minnesota-based healthcare system largely recognize medicinal cannabis as a legitimate therapeutic option. Approximately 58.1% of respondents either "strongly" or "somewhat" agreed that medicinal cannabis could serve as a valid medical treatment. However, only 38.7% believed that physicians should actively offer medicinal cannabis to patients for managing medical conditions. Providers predominantly viewed medicinal cannabis as effective in treating specific state-designated qualifying conditions, such as cancer, terminal illness, and intractable pain, where the therapeutic benefits were most recognized. These conditions reflect areas where cannabis is often recommended for its potential to alleviate chronic pain, nausea, and muscle spasms. Despite this recognition of cannabis's benefits in certain areas, a notable challenge exists in how comfortable providers feel when discussing cannabis with their patients. More than half of the surveyed providers did not feel prepared to engage in discussions about medicinal cannabis with patients, which indicates a critical gap in knowledge and confidence. This hesitancy to discuss cannabis may stem from broader concerns about its efficacy in treating conditions outside of the more widely accepted uses such as cancer-related pain and palliative care.

The majority of Colombian psychiatrists engaged by Orjuela-Rojas et al. (2021) support the availability of medicinal cannabis for various medical conditions, with 82% agreeing that it should be accessible for a range of uses. However, their approval is

much stronger for non-psychiatric conditions than for psychiatric ones. For example, 87.6% of the surveyed psychiatrists supported medicinal cannabis for cancer-related chronic pain, and 78.6% approved its use for chemotherapy-related nausea and vomiting. On the other hand, the use of cannabis for psychiatric conditions garnered less enthusiasm. Insomnia received the highest approval at 35.2%, while anxiety disorders were approved by 29% of respondents. While a large portion of psychiatrists indicated a willingness to prescribe medicinal cannabis (73.1%), many acknowledged that they were reluctant to recommend it for mental health conditions due to a lack of strong evidence supporting its efficacy in those areas. This cautious stance is compounded by concerns over cannabis potentially worsening psychiatric symptoms, particularly in vulnerable populations such as individuals with schizophrenia, where 66.9% of respondents disapproved of its use. Despite these concerns, most psychiatrists (72.4%) felt comfortable discussing medicinal cannabis with their patients, indicating a generally open attitude toward engaging in conversations about its potential benefits and risks. However, the overall limited approval for psychiatric applications suggests that psychiatrists are more likely to view cannabis as a viable option for non-psychiatric conditions rather than mental health disorders. Most French psychiatrists that participated (84.4%) in a 2024 study by Leclerc et al. are in favour of the medical use of cannabis, indicating a general acceptance of its potential therapeutic benefits. Psychiatrists particularly highlighted the potential of cannabis derivatives, like CBD, in managing psychiatric disorders, such as anxiety and PTSD. However, the study also found a more cautious attitude towards recommending cannabis for psychiatric conditions, reflecting concerns about the lack of robust evidence for its efficacy in mental health care. Interestingly, despite the high level of support for medicinal cannabis, only 61.3% of psychiatrists favoured the legalization

of recreational cannabis. This distinction suggests that while psychiatrists recognize the potential medical benefits of cannabis, they remain wary of broader legalization, particularly due to concerns about the potential for misuse and the impact on mental health.

Strube et al. (2023) offer valuable insights into the perceptions of Swiss psychiatrists regarding the benefits of medicinal cannabis, particularly in the treatment of mental disorders. The survey reveals that 49% of participating psychiatrists believe that medicinal cannabis might have a therapeutic effect on mental disorders. However, despite this belief, 50% of respondents expressed concerns that there is insufficient scientific evidence to support such use. A considerable number of psychiatrists felt insecure about providing counseling on cannabis use. Specifically, about one-third of the respondents expressed a lack of confidence in their ability to counsel patients about medicinal cannabis, which highlights a critical gap in their professional training. This indicates a cautious optimism among Swiss psychiatrists about the potential benefits of medicinal cannabis, tempered by a significant demand for more rigorous clinical research. Interestingly, psychiatrists working in an outpatient setting or those with more experience tended to be more skeptical about the therapeutic potential of cannabis for mental health issues. This skepticism reflects a broader uncertainty within the psychiatric community about the appropriateness of integrating cannabis into psychiatric care without stronger evidence of its efficacy.

It emerged in Patel et al. (2021) that there exist significant gaps in the knowledge and confidence of community pharmacists in discussing the benefits of non-prescription CBD products with their patients. Over 50% of pharmacists in the survey had received questions from patients about non-prescription CBD products, indicating considerable

patient interest in these products. However, only 20.4% of the surveyed pharmacists had recommended such products in the last 12 months, despite the demand for information from patients. One of the main reasons for this hesitancy is the limited evidence available to support the use of non-prescription CBD products, particularly in community pharmacies. The legal grey areas and lack of standardization in product quality create further challenges for pharmacists, making it difficult for them to provide clear and reliable guidance. Although CBD is often marketed for conditions like chronic pain and anxiety, the study notes that the clinical evidence supporting these claims remains insufficient. As a result, many pharmacists do not feel comfortable discussing the potential benefits of CBD with their patients, let alone recommending it. Additionally, even though the pharmacists understood that patients seek these products for therapeutic purposes, such as pain management and anxiety relief, there is still a strong need for formalized education and better research to guide these discussions effectively. This highlights the importance of enhancing the clinical knowledge base around CBD to meet patient expectations while ensuring evidence-based recommendations.

Ross et al. (2023) offers valuable insights into the perceptions and practices of sports medicine physicians regarding medicinal cannabis, particularly CBD. Among the 333 respondents, 40.8% reported recommending CBD for therapeutic purposes, while 24.8% had recommended cannabis products. These findings suggest a relatively high level of acceptance of CBD and cannabis among sports medicine providers, especially for conditions like chronic musculoskeletal and neuropathic pain. The study also highlights that community and private practice physicians were more likely to recommend CBD and cannabis compared to their academic counterparts, possibly reflecting differing levels of exposure to patient demands or varying institutional

policies. Interestingly, the study found that despite these recommendations, the physicians' confidence in discussing and endorsing cannabis use for therapeutic purposes varied significantly based on demographic factors like age, gender, and practice setting. Older physicians, female physicians, and those practicing in rural areas were generally less supportive of cannabis use, reflecting a more conservative approach to its integration into sports medicine.

Nussbaum et al. (2022) surveyed members of the National Psoriasis Foundation Medical Advisory Board to explore their views on the benefits of medicinal cannabis. One of the central findings is that, while most dermatologists and rheumatologists surveyed support the use of medicinal cannabis, their practical experience with recommending it to patients remains limited. A significant 83.3% of respondents indicated their support for medicinal cannabis use, yet only 21.7% had actually recommended it to their patients. This discrepancy suggests that while physicians recognize the potential benefits, their reluctance to recommend medicinal cannabis stems from a combination of factors, including limited education and clinical experience. Interestingly, the study reveals that 54.2% of respondents encountered 10 or more patients asking about medicinal cannabis in the past year, a sharp rise compared to a 2018 survey in which only 9.1% of dermatologists reported this frequency. This increase reflects growing patient interest in cannabis as a therapeutic option, potentially driven by greater public acceptance and expanding legal access. Despite this patient demand, most healthcare professionals are still hesitant to discuss cannabis openly. The study highlights that dermatologists and rheumatologists need more robust evidence to confidently incorporate medicinal cannabis into treatment plans for conditions such as psoriasis and psoriatic arthritis. In the field of paediatric dermatology the findings by Shah et al., (2021) reveal that a significant majority (87%)

of respondents were aware of cannabis use in dermatology, and a notable portion (62%) expressed comfort in proposing an FDA-approved cannabinoid-based drug to paediatric patients. This suggests that while there is a considerable level of awareness about the potential benefits of medicinal cannabis, its integration into patient care is approached with caution. Interestingly, although 71% of the respondents had been approached by at least one patient regarding cannabinoids, only a small percentage had actually recommended (13%) or educated their patients about cannabinoid-based products (17%). Yeroushalmi et al. (2020) conducted a pilot survey among US dermatologists, focusing on their perceptions and recommendation behaviours concerning medicinal cannabis. The survey revealed that a significant majority of dermatologists (91%) supported the use of medicinal cannabis, indicating a broad recognition of its potential benefits. However, only 13.8% of respondents had actually recommended medicinal cannabis for a dermatologic condition. Among those who did recommend it, the most common conditions were atopic dermatitis (45%) and psoriasis (40%). The primary form of administration recommended was topical, chosen by 75% of those who suggested medicinal cannabis, likely due to its safety profile and lack of systemic effects. This suggests that while there is a theoretical acceptance of medicinal cannabis within dermatology, its practical application remains limited, possibly due to concerns about the lack of robust clinical evidence and the need for more experience with its use.

As evidenced by the international studies cited throughout this review, there is a notable alignment between global trends and the findings of the current study involving Maltesen healthcare professionals. Across diverse jurisdictions, doctors and pharmacists consistently express a robust acknowledgment of the therapeutic benefits that medicinal cannabis may offer for specific conditions and patient populations. This

recognition is mirrored in our results, where Maltese healthcare providers showed generally favourable attitudes toward the clinical potential of cannabis-based treatments. However, this theoretical support is often accompanied by a clear hesitancy to engage in actual clinical application. Similar to their international counterparts, Maltese professionals appear restrained in their willingness to recommend or prescribe medicinal cannabis. This reluctance can be attributed to several interrelated factors, most prominently the lack of well-established, evidence-based clinical guidelines that could support decision-making. In addition, insufficient access to targeted training and continuing education on cannabis therapeutics, along with a perceived deficiency in knowledge, further limits clinicians' confidence. These barriers appear to transcend national borders, highlighting a shared need for systemic changes that equip healthcare professionals with the tools, knowledge, and regulatory clarity required to confidently incorporate medicinal cannabis into routine clinical practice.

4.4. The absence of evidence-based clinical guidelines

The absence of evidence-based guidelines for the prescription of medicinal cannabis is also a recurring theme in similar studies carried out with healthcare professionals in other countries. Canadian pain management physicians were hesitant to recommend medicinal cannabis as a first-line therapy for chronic pain management, primarily due to the limited availability of clinical practice guidelines (Ng et al., 2022). The authors noted physicians expressing uncertainty regarding proper dosing, administration, and frequency, stemming from insufficient evidence and clear professional protocols. This uncertainty significantly reduced their comfort in prescribing cannabis, despite

recognizing its potential therapeutic benefits. Similarly, many paediatric oncology physicians from Illinois, Massachusetts and Washington cited the absence of standards around formulations, potency, and dosing as the primary barrier to recommending medicinal cannabis in the survey by Ananth et al. (2018). This uncertainty likely contributes to the cautious approach many providers take when considering medicinal cannabis as a treatment option. Although there is some recognition of medicinal cannabis's potential benefits, such as its use for managing nausea, vomiting, and anorexia in paediatric cancer patients, the limited knowledge about its full range of therapeutic effects and side effects hampers its broader adoption in clinical practice. This suggests a critical need for more robust education and clear guidelines to help healthcare professionals navigate the complexities of medicinal cannabis use.

An Italian national survey involving medical oncologists and palliative care physicians, identified a critical discrepancy between the clinicians' generally favourable attitudes toward medicinal cannabis and their actual prescribing behaviours (Filetti et al., 2021). The researchers noted that this reluctance primarily resulted from inadequate knowledge and the absence of clear national guidelines. Most surveyed physicians lacked comprehensive awareness of legislative frameworks, further underscoring the necessity for standardized, evidence-based clinical guidelines to guide safe and informed prescribing practices.

Norwegian physicians, while generally recognizing the legitimacy of medicinal cannabis as a therapeutic option, overwhelmingly reported very limited knowledge about the drug, particularly in areas such as dosing, legislation, and the prescribing process (Arnfinnsen and Kisa, 2021). The majority of participants were unfamiliar with

the Norwegian Medical Agency guidelines that allow certain specialists to apply for prescribing authorization. This lack of awareness stems from a broader systemic issue concerning guidelines. While technically in place, they are not widely disseminated or understood. Physicians cited the absence of information on appropriate dosing and uncertainty surrounding drug interactions as significant barriers to clinical engagement with medicinal cannabis. California pharmacists also expressed hesitation, indicating that they would be considerably more comfortable discussing and recommending medical cannabis if it had clear FDA approval and standardized dosing guidelines (Szyliowicz & Hilsenrath, 2019). Pharmacists explicitly mentioned a significant gap between federal and state regulations, leading to discomfort and uncertainty, thereby limiting their proactive involvement in patient counseling regarding medical cannabis use.

A survey of licensed and unlicensed healthcare providers across the United States revealed a significant deficiency in structured clinical guidance and training related to cannabis-based therapeutics (Corroon et al., 2019). Despite increasing patient demand and the gradual legalization of medicinal cannabis in many jurisdictions, healthcare professionals reported navigating clinical decisions in a regulatory vacuum. The authors observed that a substantial proportion of providers were recommending cannabis in the absence of formal, evidence-based dosing protocols, interaction data, and contraindication guidelines. This lack of standardized clinical practice recommendations has led to the emergence of a 'community standard of practice', where clinicians rely heavily on peer experiences, anecdotal evidence, and personal judgment to guide therapy. The study's authors conclude that reducing barriers to clinical cannabis research and developing robust clinical guidelines are essential steps in closing the gap between theory and practice. In the absence of such frameworks,

even well-intentioned clinicians are left to practice in uncertainty, perpetuating a cautious stance toward cannabis integration in conventional care.

Analysis of European healthcare professionals' attitudes, knowledge, and prescribing patterns presented a recurring finding that medicine and pharmacy students alike supported the idea of incorporating cannabinoids into clinical practice (Hordowicz et al., 2021b). However, their willingness to do so was significantly hampered by uncertainty surrounding legal and clinical guidance. Across the reviewed studies, healthcare professionals frequently reported a lack of knowledge about local legal regulations, approved indications, and proper dosing of cannabis-based treatments. A common barrier identified was the absence of standardized, evidence-based prescribing protocols, which left even well-disposed clinicians unsure of how to proceed with cannabis therapeutics in a practical setting. The follow-up national survey by Hordowicz et al. (2022) reinforced this conclusion, this time with data from Polish physicians. Although most participants supported the legalization and recognized potential benefits of medicinal cannabis, only a small minority had actually prescribed it. The principal reasons for this gap between theory and practice included insufficient training, lack of clinical experience, and most importantly, the absence of national treatment guidelines. Doctors indicated that without official recommendations on indications, dosing, and contraindications, they felt ill-equipped to prescribe confidently or safely. This limitation persisted even in the presence of favourable attitudes or patient interest.

Cheng et al. (2022) conducted a comprehensive systematic review examining healthcare professionals' attitudes, beliefs, and perceived barriers related to the clinical use of medicinal cannabis across several countries, including the United

States, Israel, Canada, Australia, Ireland, and Norway. Across all the contexts surveyed, the review revealed a recurring theme of clinician hesitancy in prescribing medicinal cannabis. Although many healthcare professionals acknowledged potential therapeutic benefits, particularly in managing chronic pain, they expressed considerable reluctance to incorporate cannabis into routine practice. A central finding of the review was that this reluctance was not due to moral or ideological opposition, but rather stemmed from the absence of robust, universally endorsed clinical guidelines. Clinicians cited a lack of clarity regarding the efficacy and safety of different cannabis preparations, along with inadequate dosing recommendations and insufficient training in navigating existing legal and regulatory frameworks. The review emphasized that this absence of standardized, evidence-based protocols left many physicians and pharmacists uncertain about how to responsibly and effectively recommend or prescribe cannabis products. This was particularly pronounced in the context of chronic pain management, where clinicians often must weigh multiple treatment options and monitor for long-term outcomes. Cheng and colleagues also noted that the variability in national policies compounded the confusion. In jurisdictions where medicinal cannabis had been legalized, the rollout of training and clinical support tools often lagged behind, leaving healthcare professionals to operate in an environment where patient expectations and legal allowances outpaced the available clinical infrastructure. The authors concluded that addressing these deficits, through the development and dissemination of clear, research-based clinical guidelines and structured professional education, would be essential to increase provider confidence and promote responsible integration of medicinal cannabis into mainstream care.

4.5. Awareness of clinical use and knowledge gaps

One of the biggest challenges that arises with the introduction of medicinal cannabis is the need for doctors and pharmacists to become more educated about the potential benefits and risks associated with its use. When consulted about their knowledge of therapeutic and side effects of medicinal cannabis the most popular reply by healthcare professionals was 'somewhat agree', at 40.5% and 31.5% of the respondents for the two statements respectively. 26.5% disagreed to some extent that they were knowledgeable of therapeutic effects and 28.5% disagreed with respect to side effects knowledge. A sentiment of indecisiveness evidently prevailed among the majority of participants. One which intensified when the enquiry concerned the confidence levels in dealing with a patient exhibiting side effects after use of medicinal cannabis. The total number of those expressing negative confidence levels in such situations was 96, amounting to 48% of respondents. 51 (25.5%) others expressing mild conviction by selecting 'somewhat agree'.

Results clearly suggest that there is need for vigorous interventions in order to prepare a workforce of healthcare professionals in dealing effectively with discussing and dispensing medicinal cannabis to eligible patients. Requirements will include a significant investment of time and resources, as well as a willingness on the part of healthcare professionals to engage with the latest research and to learn about the various ways in which cannabis can be used as a therapeutic alternative in some clinical contexts. The absolute majority of healthcare professionals surveyed expressed an eagerness to know more about the subject, even in cases where there was scepticism on the clinical use of medicinal cannabis. The more unyielding

obstacle to tangible cultural reform lies in the ability to derive resources for dissemination of sound and reliable knowledge.

The absence of significant differences in knowledge about the medicinal cannabis between pharmacists and doctors reflected in Table 3.2 suggests that they are equally informed about the clinical use of medicinal cannabis. This parity may reflect the growing availability of educational resources, guidelines, and professional development opportunities that have contributed to a shared understanding of medicinal cannabis among healthcare professionals. Both groups appear to have a foundational level of knowledge, which is essential for safe and effective clinical application. It indicates a common ground for collaboration and shared decision-making in clinical practice. This alignment in knowledge can facilitate interdisciplinary communication and ensure that patients receive consistent and evidence-based recommendations regarding medicinal cannabis. However, the results also highlight the need for continued education and training, as both groups identified gaps in their understanding during other sections of the questionnaire.

Table 3.3 showed male pharmacists ($M = 21.82$, $SD = 9.22$), claiming more knowledge of medicinal cannabis than female pharmacists ($M = 25.70$, $SD = 8.73$). This might stem from a greater exposure to or interest in emerging therapies, leading to more proactive engagement with educational resources or training programs. Differences in professional networks or mentorship opportunities may influence access to information about medicinal cannabis. The same analysis conducted for male and female doctors in Table 3.4 noted no significant differences in this category.

Jacobs et al. (2019) showed that while Australian psychiatrists and trainees were generally aware of the main clinical indications for medicinal cannabis, they struggled

to differentiate between the appropriate uses of CBD and THC. On average, participants correctly identified only 4.73 out of 11 indications for CBD and 5.64 out of 11 for THC. This indicates a need for more detailed education on the pharmacological differences between these compounds. Moreover, the respondents expressed substantial concern about the potential side effects of medicinal cannabis, particularly the risk of psychotic symptoms, addiction, apathy, and recreational misuse. These concerns were cited as significant barriers to prescribing, reflecting a cautious approach driven by the potential risks associated with cannabis use in vulnerable psychiatric populations. In Karanges et al. (2018), only 28.8% of Australian GPs felt comfortable discussing medicinal cannabis with their patients, and a large majority rated their knowledge of the topic as poor. For instance, 65.4% of respondents strongly disagreed that they knew how to access medicinal cannabis for their patients, and over half were unfamiliar with the available products or the regulatory framework. GPs generally perceived medicinal cannabis as less hazardous than opioids, benzodiazepines, and antipsychotics, indicating an advanced understanding of its risk profile.

While Malige et al. (2024) showed that most US surgeons involved in their nation-wide research agree on the efficacy of CBD for chronic pain management, there is less consensus regarding its application in other therapeutic areas. Chronic pain management was recognized by 91% of surgeons from legal states and 75% from non-legal states as a valid use for CBD. In contrast, the use of CBD for acute traumatic pain was less supported, with 41.8% of surgeons from legal states and 37.5% from non-legal states endorsing its use. There was similarly limited enthusiasm for using CBD to treat postoperative pain (58.2% vs. 50%). Regarding the side effects of medicinal cannabis, only a small proportion of surgeons believed that CBD has

negative consequences for patients. Less than 15% thought that it could adversely affect surgical outcomes, and only a minor fraction, under 10%, considered it harmful to bone healing, wound healing, or overall pain control. Furthermore, there is no consensus on the most effective forms of CBD. While 40.3% of surgeons from legal states and 37.5% from non-legal states thought certain forms of CBD were more effective than others, there was no agreement on which forms those might be. This lack of consensus reflects the need for more clinical evidence and education about different delivery methods of medicinal cannabis to maximize its therapeutic potential.

Results in the Thailand-based study by Mekrungrongwong et al. (2022) show that both groups, healthcare professionals and health volunteers, had relatively low self-perceived knowledge regarding medicinal cannabis. Among healthcare providers, 60-70% rated their self-perceived knowledge as low to very low, with health volunteers showing similar results (50-60%). The study also highlighted specific areas where health care providers felt less informed, including the appropriate use of cannabis, its adverse effects, warning signs, and legal issues surrounding its prescription. One key area of concern among healthcare providers was the potential for addiction, with 22.3% of them agreeing that the use of medicinal cannabis might lead to addiction to other drugs. This was echoed by health volunteers, although the concern was slightly lower (17.6%). Both groups also expressed caution about the potential for cannabis use to increase crime rates and cause hallucinations, reflecting a broader hesitancy about its safety. For instance, 21.6% of healthcare providers and 13.2% of health volunteers believed that patients using medicinal cannabis are at risk of experiencing hallucinations. These concerns emphasize the need for greater clarity on the pharmacological properties of cannabis and its effects. Interestingly, while there was limited confidence in the use of medicinal cannabis to treat chronic conditions, with

only 43.4% of healthcare providers agreeing that it could relieve chronic symptoms, 40.4% of health volunteers expressed this belief. This suggests that despite limited knowledge, there is a recognition of cannabis' therapeutic potential, particularly among volunteers who may be more exposed to traditional uses of cannabis in local communities. These findings highlight the importance of increasing awareness among both professionals and volunteers about the side effects and therapeutic benefits of medicinal cannabis to ensure safe and effective usage. Only 14% of respondents could correctly identify the exact legislative reference governing medicinal cannabis use in Italy, indicating a significant knowledge gap regarding its legal status (Filetti et al., 2021). Additionally, 31% of respondents could not clearly differentiate between the side effects of opioids and those of medicinal cannabis, and only 9 respondents reported any side effects such as anxiety, insomnia, or muscle spasms. This lack of detailed knowledge about the therapeutic and adverse effects likely contributes to the hesitancy observed in prescribing medicinal cannabis more widely.

Most orthopaedics sports medicine providers engaged in the study by Li et al. (2023) acknowledged CBD's potential in pain management, but a significant 89% admitted they were not knowledgeable about the mechanism of action of CBD. 73% were unfamiliar with its modes of administration, and 66% were unaware of their state's laws concerning CBD use. Only 25% of respondents believed that CBD has psychoactive properties, and 19% thought it had addictive potential. This lack of knowledge extends to the effects of CBD on healing, with 90% believing it had no impact on bony healing and 89% on soft tissue healing. This indicates that while there is some awareness of CBD's potential benefits, the understanding of its therapeutic effects and possible side effects is limited, which may hinder its integration into standard clinical practice. A striking 88% of respondents in a survey carried out among US-based orthopaedic

traumatologists admitted that they did not feel knowledgeable about the mechanism of action of cannabis or CBD, which likely contributes to their reluctance to recommend these substances more frequently (Chin et al., 2021). While most respondents correctly identified that THC, a component of cannabis, has psychoactive effects (88%) and that CBD does not (79%), there was a notable lack of familiarity with other aspects of cannabinoid use.

Only 36.9% of Illinois pharmacists involved in the observational cross-sectional study conducted by Link et al. (2020) felt competent in understanding the pharmacodynamics of over-the-counter CBD products, and a similar percentage (36.5%) felt competent in understanding pharmacokinetics. This lack of knowledge extended to safety concerns as well. 69.4% of respondents were moderately or highly concerned about the safety of over-the-counter CBD products, including potential drug interactions, contraindications, and adverse reactions. Additionally, 87.2% expressed concern about the consistency and quality of these products. This affects pharmacists' ability to counsel patients but may also lead to hesitation in recommending these products, despite potential benefits for some patients. The pharmacists' concerns are rooted in the limited regulatory oversight of over-the-counter CBD products, which can vary widely in terms of quality and content, further complicating their ability to make informed recommendations. In Grant et al. (2023) although a significant portion recognized potential benefits for symptom management, such as cancer-related nausea and vomiting (84.2% and 83.2% respectively), the general confidence in understanding and managing these therapies was low. Only 18% of participants were familiar with the endocannabinoid system, which is crucial for understanding how medicinal cannabis works. Moreover, 63.2% of respondents identified driving impairment, and 66.3% identified drowsiness as major side effects of medicinal

cannabis. This highlights a significant knowledge gap, particularly regarding the broader range of side effects and the pharmacology of cannabis.

In the pre-course survey utilized in Mendoza and McPherson (2018), US-based participants displayed limited understanding of cannabis pharmacology, formulations, dosing, side effects, and drug interactions. Only 25% of participants correctly identified that long-term cannabis use could cause cognitive impairment, and only 55% were able to recognize common side effects of cannabis. This lack of knowledge likely contributed to healthcare providers' hesitation in recommending medicinal cannabis, despite recognizing its potential benefits. However, after completing the online educational modules, the knowledge of side effects improved significantly, with more than 75% of participants answering correctly regarding cannabis' side effects and safety. The study noted that participants from states where cannabis was not legal showed statistically significant improvement in their knowledge about the side effects and drug interactions of medicinal cannabis, likely because they had less prior exposure to the topic. Despite these improvements, the study did find that knowledge gaps persisted in certain areas. For example, awareness of adverse effects was not significantly different after the course for some participants, particularly those in states where cannabis was illegal, suggesting that additional training might be needed in these areas. This data underscores the need for continued education, as it directly impacts how healthcare professionals approach discussions about the therapeutic use of medicinal cannabis. A deeper understanding of its potential benefits and risks can equip hospice providers to better guide their patients in making informed decisions, especially as cannabis becomes more commonly used for symptom management. Less than half of the Colombian psychiatrists (46%) in the study of Orjuela-Rojas et al. (2021) felt they were familiar with the therapeutic effects of cannabis, and only

17.2% had knowledge of the various forms in which cannabis-based products are available. In the study conducted by Patell et al. (2022) with US oncology trainees only 12.8% of trainees considering themselves adequately informed.

Only 16.7% of respondents in Nussbaum et al. (2022) reported having received prior education on the topic, and 79.2% felt they did not have sufficient knowledge to explain the risks and benefits of cannabis to their patients. This knowledge gap is reflected in the hesitation to recommend cannabis despite general support for its use. Respondents were also divided on key issues such as the potential worsening of psoriatic disease with cannabis use. While 54.2% of respondents believed that cannabis could safely be used for their patients, only 4% thought it could worsen psoriatic conditions. Among dermatologists questioned by Yeroushalmi et al., (2020) it also appears that lack of this knowledge appears to be a limiting factor in its broader recommendation. The study found that the main reasons for not recommending medicinal cannabis were limited knowledge (56%) and lack of experience (48%). These findings indicate that while dermatologists may be aware of the potential benefits, there is significant uncertainty regarding the broader therapeutic effects and potential side effects of medicinal cannabis, particularly in dermatology. The preference for topical administration suggests that dermatologists are more comfortable with methods that minimize systemic exposure and potential side effects, reflecting a cautious approach driven by the current gaps in knowledge.

The study conducted by Lee et al. (2023) sheds light on the inconsistent effects of cannabis reported by patients, which further complicates doctors' role in recommending and managing cannabis use. Physicians' limited knowledge may stem from the rapidly evolving landscape of cannabis products and the lack of

comprehensive, accessible information about these products, including their THC and CBD content and their potential interactions with other medications. Bottorff et al. (2013) provide a detailed exploration of how stigma affects individuals who use cannabis for therapeutic purposes. Although the study primarily focuses on the experiences of cannabis for therapeutic purposes users, it indirectly sheds light on the knowledge and perceptions of healthcare professionals regarding medicinal cannabis. The findings suggest that many healthcare professionals may not fully recognize or appreciate the benefits of medicinal cannabis, as evidenced by the stigmatization that cannabis for therapeutic purposes users face, even from within the medical community. Some participants reported that their healthcare providers dismissed their use of medicinal cannabis as merely an excuse to use drugs recreationally, rather than acknowledging its therapeutic benefits. This indicates a significant gap in understanding and acceptance among healthcare professionals regarding the legitimate medical uses of cannabis, which in turn impacts the willingness of patients to discuss their cannabis use openly with their doctors.

A study among sports medicine physicians in the United States noted that while there is a growing acceptance of the therapeutic potential of cannabinoids, particularly CBD, perceptions vary widely among respondents (Ross et al., 2023). Older physicians were more likely to view both CBD and cannabis as detrimental to athletic performance and the integrity of sports, with 39% considering cannabis harmful to sports performance compared to only 9.9% for CBD. This disparity suggests that while CBD is increasingly seen as a safer and more acceptable option, concerns about the psychoactive effects of THC and the potential for misuse still influence physician attitudes. Additionally, male physicians were less likely than their female counterparts to view cannabis as

performance-enhancing, indicating that gender may also play a role in how the risks and benefits of cannabis are perceived in the context of sports medicine.

Canadian doctors who were interviewed by Poisblaud et al. (2023) were particularly concerned about the lack of long-term data on the safety and efficacy of cannabis products. Although some physicians had authorized cannabis for patients, the general consensus was that more high-quality, randomized controlled trials are needed to establish a reliable evidence base. This lack of comprehensive studies led to a precautionary approach, with many physicians hesitant to authorize cannabis use due to uncertainties about its long-term consequences. In an earlier Canadian study among family physicians there was a clear significant concern expressed by the healthcare professionals regarding the potential harms associated with medicinal cannabis, particularly around neurocognitive development, exacerbation of mental health issues, and drug interactions in older adults (Ng et al., 2021). Doctors in the study expressed uncertainty about the safety of cannabis use, especially among adolescents and young adults, where concerns about the drug's impact on neurodevelopment were prevalent. Some physicians worried that legalization, especially with a legal age set at 18, could send a misleading message to younger populations that cannabis is entirely safe for therapeutic use. Another prominent concern involved older adults, a population typically dealing with polypharmacy. Physicians highlighted the potential for harmful drug interactions when cannabis is combined with other medications commonly prescribed to the elderly. These interactions, coupled with risks of side effects like dizziness and sedation, raised red flags about older patients' ability to manage daily activities safely, such as driving or maintaining their independence. Physicians also noted that cannabis could

exacerbate pre-existing mental health conditions, particularly in patients with depression, anxiety, or schizophrenia, further complicating their treatment.

Most providers responses in Phillips et al. (2020) confirmed perception of cannabis use as both physically and mentally harmful to patients. Specifically, 67% of paediatric transplant providers and 60% of adult congenital heart disease providers believed that cannabis is physically harmful, while 72% of paediatric providers and 70% of adult congenital heart disease providers believed it is mentally harmful. Just 19.3% of Danish GPs reported having quite some knowledge of medicinal cannabis with the majority, 80.6%, admitting to little or no knowledge about it (Rosenbaek et al., 2023). This knowledge gap likely contributes to the overall negative attitude towards prescribing it. Moreover, among those who had prescribed medicinal cannabis, 40.5% still had little knowledge of its effects, raising concerns about informed decision-making. GPs' hesitation to prescribe medicinal cannabis is closely tied to uncertainties about its safety profile. The study revealed that GPs feared potential side effects and lacked confidence in the existing evidence to support medicinal cannabis use, which aligns with broader concerns raised by medical communities globally. Physicians' perception of inadequate knowledge may hinder their ability to engage in informed discussions with patients, and this is reflected in the study's finding that those with greater knowledge had more favourable attitudes toward prescribing medicinal cannabis.

4.6. Positive correlation between higher cannabis knowledge and a positive attitude to clinical use

In the present study, on assessing the relationship between age, Approach, Knowledge and Education among pharmacists (Table 3.5) the only significant positive correlation noted was between Approach and Knowledge ($r=0.41$, $p<0.001$), indicating that pharmacists with greater knowledge about medicinal cannabis are more likely to hold a favourable attitude toward its clinical application. When separating the analysis by gender in Table 3.6 the same results were confirmed (males: $r=0.39$, $p<0.001$) (females: $r=0.38$, $p<0.001$). This finding underscores the importance of education and awareness in shaping pharmacists' perspectives on medicinal cannabis, suggesting that enhancing knowledge in this area may positively influence their acceptance and support for its use in clinical settings. The analysis, however, revealed no significant correlations between pharmacists' age, Approach, or Education and their attitudes toward the clinical use of medicinal cannabis. This implies that these factors do not play a substantial role in influencing pharmacists' attitudes in this context. The lack of correlation highlights that knowledge, rather than demographic or educational background, is the key driver of favourable attitudes toward medicinal cannabis among pharmacists. Findings were replicated for doctors (Table 3.7), noting a significantly positive correlation noted was between Approach and Knowledge ($r=0.57$, $p<0.001$).

Table 3.7, a Pearson product moment correlation analysis assessing the relationship between age, Approach, Knowledge, Education and Prescription Attitude among doctors, a significant positive correlation was observed between Knowledge of medicinal cannabis and Prescription Attitude ($r = 0.31$, $p < 0.001$). This finding reinforces the idea that doctors with a deeper understanding of medicinal cannabis

are more likely to hold favourable attitudes toward its clinical use. The relationship suggests that increased knowledge about the therapeutic potential, safety profile, and appropriate applications of medicinal cannabis contributes to greater acceptance and support for its integration into clinical practice. This correlation highlights the critical role of education in shaping doctors' perspectives and attitudes. When healthcare professionals are well-informed about the evidence-based benefits, risks, and guidelines surrounding medicinal cannabis, they are better equipped to make informed decisions and feel more confident in considering it as a treatment option. This highlights the significance of comprehensive educational initiatives, including training programs, workshops, and access to current research, to close knowledge gaps and resolve any misconceptions or uncertainties that doctors may harbour. The positive association between knowledge and prescription attitudes suggests that enhancing doctors' understanding of medicinal cannabis could lead to broader acceptance and utilization in clinical settings. By prioritizing education, healthcare systems can empower doctors to make patient-centred decisions, potentially improving access to medicinal cannabis for individuals who may benefit from its therapeutic effects.

Knowledge of medicinal cannabis demonstrated a significant positive correlation with Prescription Attitude for both male ($r = 0.32$, $p < 0.014$) and female doctors ($r = 0.30$, $p = 0.036$). This finding indicates that as doctors' understanding of medicinal cannabis increases, their attitudes towards prescribing it become more favourable. The similar trend observed across genders reinforces the critical role that comprehensive knowledge plays in shaping clinical perspectives on medicinal cannabis. These insights, as detailed in Table 3, underscore that by enhancing the depth and breadth of information available to practitioners, educational initiatives can help foster more

positive prescribing behaviours, thereby supporting the integration of medicinal cannabis into therapeutic practice.

Sabmeethavorn et al. (2022) analysed pharmacists' perceptions and experiences globally, including their knowledge and preparedness to counsel patients about medicinal cannabis. A key finding was that pharmacists with higher perceived knowledge of medicinal cannabis were more likely to hold favourable attitudes toward its clinical use. The study underscores the congruence between pharmacists' self-reported knowledge levels and their willingness or comfort in guiding patients, noting that the majority of pharmacists surveyed felt underprepared or lacked confidence when engaging with patients on this topic. This gap was largely attributed to a lack of formal education and accessible, high-quality training resources. The association between greater knowledge of medicinal cannabis and more favourable clinical attitudes is well supported also in other studies previously referred to. In their study of clinicians in Washington State, Carlini et al. (2015) observed that those who had authorized the use of medicinal cannabis rated their knowledge of the endocannabinoid system and cannabis-based therapies significantly higher than those who had not. Importantly, this enhanced knowledge corresponded with more positive attitudes toward the clinical utility of cannabis. Physicians with higher self-rated knowledge expressed greater comfort in discussing medicinal cannabis with patients and were more likely to endorse its use for chronic medical conditions. In contrast, clinicians with lower knowledge scores were more hesitant and often cited legal uncertainties or lack of efficacy as reasons for their reluctance. The authors emphasized that knowledge was not only correlated with attitude, but also with actual clinical behavior, as those who felt better informed were markedly more likely to have written medicinal cannabis authorizations. The study concluded that structured

education and training on cannabis pharmacology are essential to bridging the gap between legal frameworks and clinical implementation, reinforcing the notion that enhancing professional knowledge is key to fostering more open and confident attitudes toward medicinal cannabis use (Carlini et al., 2015). The study by Ebert et al. (2015) provides further evidence that increased knowledge of medicinal cannabis is closely linked to more favourable professional attitudes toward its use. In their survey of Israeli physicians, the authors found that clinicians who felt more knowledgeable about cannabis-based therapies were significantly more likely to express willingness to prescribe or recommend such treatments. This positive association between knowledge and attitude was particularly pronounced among those who had prior exposure to cannabis in medical contexts or had engaged with clinical literature on the subject. Physicians who reported limited or no formal education on medicinal cannabis, by contrast, exhibited markedly greater skepticism and reluctance to consider it as a legitimate therapeutic option. The study highlighted that even among physicians supportive of cannabis use for specific conditions, such as palliative care or oncology, hesitation remained strong in the absence of detailed pharmacological knowledge or regulatory clarity. As such, Ebert et al. underscored the importance of integrating cannabis-related education into medical curricula and continuing professional development programs to improve physician confidence and normalize evidence-based cannabis prescribing in clinical settings (Ebert et al., 2015).

The self-assessed knowledge level of the participants in a Saudi Arabian study was strikingly low, with a mean score of only 11.1 out of a possible 88, and 94.7% of the participants categorized as having a low level of perceived knowledge (Alsolamy et al. (2023). This lack of knowledge was also evident in the objective knowledge test, where the mean score was 1.59 out of 4, and only one participant answered all questions

correctly. The majority of physicians (58.5%) were not familiar with the mechanism of action of CBD, and 69.1% did not know the differences between various forms of cannabinoids. This lack of awareness extends to the potential side effects of CBD, with many participants showing uncertainty or neutrality in their responses regarding the efficacy and safety of CBD in reducing seizure frequency, severity, and duration. The data indicate that most physicians do not feel sufficiently informed to confidently discuss or prescribe CBD, which could explain the overall cautious attitude toward its use. Yet the Pearson correlation analysis conducted by the researchers evidenced that doctors who scored higher on knowledge tests also tended to show more favourable attitudes toward the clinical use of CBD in epilepsy. The study emphasized that all three domains, perceived knowledge, actual knowledge, and attitude, were interconnected and influenced one another, and should be addressed together when considering cannabis-based treatments. According to the findings by Bawa et al. (2022), only 22.6% of Australian GPs reported feeling that they had adequate knowledge about medicinal cannabis. However, those who had prescribed medicinal cannabis ("prescribers") demonstrated significantly higher levels of self-rated knowledge compared to non-prescribers ($p < 0.001$). These prescribers also reported more comfort discussing medicinal cannabis with patients and showed broader support for its use across a range of indications, such as chronic pain, palliative care, and chemotherapy-induced nausea and vomiting (Bawa et al., 2022). Importantly, the study identified that prescribers were more likely to endorse the therapeutic value of cannabis and feel confident in navigating the regulatory systems required for access. In contrast, the broader group of GPs frequently reported lacking both the knowledge and practical training necessary to feel comfortable discussing or recommending cannabis in clinical settings. In open-ended responses, a recurring theme was the

need for improved training and education, with nearly 80% of respondents endorsing the idea that GPs should receive specific training to prescribe medicinal cannabis.

The study by Mitchell et al. (2016) provides additional confirmation that higher levels of knowledge among healthcare professionals, in this case, Canadian hospital pharmacists, are associated with more favourable attitudes toward the clinical use of medicinal cannabis. Although nearly half of the 769 respondents agreed that cannabis was safe (44.6%) or effective (55.2%) for medical use, only a small fraction (17.2%) considered themselves knowledgeable on the topic. Importantly, the study identified a statistically significant association between prior education or self-directed learning about medicinal cannabis and more positive opinions regarding its safety and effectiveness. Pharmacists who had received any formal cannabis-related training, either during their undergraduate studies or through continuing education, were more likely to agree that cannabis was both safe and effective for medical use. Furthermore, self-directed learning emerged as a powerful determinant: those who pursued independent learning had significantly greater odds of agreeing that cannabis was safe (OR 1.13), effective (OR 1.11), and that they were knowledgeable about it (OR 1.12), compared to those with no such learning experience. Personal experience with cannabis, either through their own use or via someone they knew, also predicted higher knowledge self-assessments.

Conducted among US-based neurologists, nurses, and pharmacists, the national survey conducted by Szaflarski et al. (2020) found that both perceived and actual knowledge were significant predictors of more favourable attitudes toward cannabis-based therapies. Healthcare professionals who scored higher on objective knowledge tests or rated themselves as having greater familiarity with cannabinoid pharmacology

and clinical applications expressed more openness to recommending or supporting medicinal cannabis use (Szaflarski et al., 2020). Specifically, regression analyses showed that higher scores on both the knowledge test and perceived knowledge scale were independently associated with more favourable attitudes, even after adjusting for profession, workplace policies, and legal context. Importantly, the study highlighted that although pharmacists scored highest on factual knowledge, nurse practitioners and nurses showed the most favourable attitudes, suggesting that perceived competence can play a powerful role in shaping beliefs. Nevertheless, the findings underline the broader point that the more healthcare professionals know about cannabis, the more likely they are to view it positively in clinical settings. Conclusions of these studies strongly support ongoing educational interventions to enhance both factual and perceived knowledge among healthcare providers as a strategy for improving comfort and confidence in clinical cannabis use, with integration of medicinal cannabis education into pharmacy and medical student curricula to better equip future professionals with the confidence and competence needed to engage with patients about cannabis therapeutics.

4.7. Enhancing education on medicinal cannabis

A good number of healthcare professionals have sought to gain more knowledge about medicinal cannabis, as evidenced by this study. Most have referred to online resources, reputable journals and studies, and attended courses or webinars to inform themselves on the increasingly popular application of medicinal cannabis to treat specific conditions and patient symptoms. Admittedly, the majority confessed to having received little education on the subject during their formal academic education, with 80 respondents claiming strong disagreement with a statement reading 'I have

received satisfactory formal education about medicinal cannabis'. With a mean age of 45.5 for the participant population it is understandable that the subject was not addressed in curricula during formative years given that by then cannabis had long been classified as a harmful drug. Its therapeutic potential came to be revived relatively recently and gradually. Building on this, 120 healthcare professionals expressed strong agreement with introducing more advanced instruction on medicinal cannabis in the curricula of students of pharmacy and medicine. That made up 60% of participant responses with a further 33.5% expressing agreement on the matter (21.5% opted for 'mostly agree' and 12% chose 'somewhat agree').

It is not surprising that most healthcare professionals believed that within the general population there is little understanding of medicinal cannabis. 183 participants (91.5%) agreed to some extent that this was the case, with 39% declaring maximum agreement and 35% settling for a 'mostly agree' response. The context is one of slow progression towards a stable framework within medicine and law that legitimize cannabis-based therapy on far more than mere regularization. Culturally, medicinal cannabis is not yet a widely recognized therapeutic equivalent. The need and eagerness for more knowledge on the subject is also recognized for the healthcare professionals themselves, as 174 of participants (87%) expressed a degree of interest in themselves attending educational activities intended to teach about clinical uses of medicinal cannabis. When asked about their confidence levels in addressing patient questions about medicinal cannabis the most popular answers were 'somewhat agree' (27%) and 'somewhat disagree' (20.5%), demonstrating that preparation on the subject is not exceptional. This again settles into the climate of slow-paced progression towards adoption of medicinal cannabis as a therapeutic alternative available for discussion

with the patient, whether to recommend or dissuade from use in the specific clinical scenario.

No significant differences were observed between male and female pharmacists in the Education category, in Table 3.3. The same was true for doctors in Table 3.4. This indicates that both groups perceive their formal education and training on medicinal cannabis similarly, with comparable levels of satisfaction or dissatisfaction regarding its adequacy. The lack of gender differences in this category suggests that educational gaps are a universal concern among pharmacists, rather than being influenced by gender.

Table 3.7 reveals that doctors' approach to the clinical use of medicinal cannabis showed a significant positive correlation with both Knowledge ($r = 0.57$, $p < 0.001$) Education ($r = 0.33$, $p < 0.001$). This suggests that those with more extensive knowledge and more positive educational experiences regarding medicinal cannabis tend to adopt a more favourable stance toward its clinical application. These findings underscore the importance of robust education and training programs designed to enhance doctors' understanding and acceptance of medicinal cannabis. By integrating comprehensive curricula that cover the pharmacological properties, therapeutic benefits, and potential risks associated with medicinal cannabis, medical education can equip practitioners with the evidence-based knowledge necessary to make informed clinical decisions. Moreover, ongoing professional development through continuing medical education (CME) courses and targeted workshops can help bridge any gaps in current understanding, ensuring that practitioners remain up-to-date with evolving research and regulatory changes. Ultimately, fostering a well-informed medical community through such initiatives not only promotes greater acceptance of

medicinal cannabis as a viable treatment option but also supports the safe and effective integration of this therapy into clinical practice. Additionally, a significant positive correlation was found between Education and Prescription Attitude ($r = 0.30$, $p < 0.002$), indicating that doctors who have more favourable educational experiences or perspectives regarding medicinal cannabis are more likely to support its clinical use. This suggests that exposure to comprehensive, evidence-based education about medicinal cannabis, including its therapeutic benefits, potential risks, and appropriate clinical applications, plays a crucial role in shaping doctors' attitudes and willingness to prescribe it.

A significant positive correlation was observed in Table 3.8 between Education and Prescription Attitude for both male ($r = 0.29$, $p = 0.030$) and female doctors ($r = 0.32$, $p = 0.025$). This finding indicates that doctors who have more favourable educational experiences or perspectives regarding medicinal cannabis are more likely to support its clinical use, irrespective of gender. The correlation suggests that exposure to comprehensive, evidence-based education about medicinal cannabis, including its therapeutic benefits, potential risks, and appropriate clinical applications, plays a key role in shaping doctors' attitudes and their willingness to prescribe it. While the relationship holds true for both male and female doctors, the slightly stronger correlation among female doctors ($r = 0.32$) compared to their male counterparts ($r = 0.29$) suggests that education may have a marginally greater influence on female doctors' prescribing attitudes. This could imply that female doctors are more responsive to educational interventions or that their attitudes are more closely tied to their educational experiences. It may also reflect differences in how male and female doctors integrate knowledge into their clinical decision-making processes. These

findings further underscore the importance of prioritizing educational initiatives to enhance doctors' understanding of medicinal cannabis.

A significant 93.1% of physicians in the Polish study by Hordowicz et al. (2021a) expressed the need for clear guidelines on the use of cannabinoids in clinical practice, and 92.4% stated that they would like to expand their knowledge to better address patient inquiries. The study underscores the importance of educational interventions, noting that most physicians have not received formal training on the medical applications of cannabinoids. This lack of education is a critical barrier to the broader acceptance and use of medicinal cannabis in clinical settings. The respondents indicated that they would benefit from targeted educational programs, including independent courses, conferences, and possibly the integration of cannabinoid education into medical curricula. Such initiatives would not only improve the knowledge base of physicians but also their confidence in prescribing and discussing medicinal cannabis with patients. The study by Karanges et al. (2018) provides strong evidence of a clear demand among GPs for increased educational efforts aimed at building clinical knowledge about medicinal cannabis. Conducted across five major Australian cities with a sample of 640 GPs, the survey revealed that although over 60% of respondents had encountered patient inquiries about medicinal cannabis in the previous three months, the majority rated their own knowledge of the subject as poor. Specifically, more than two-thirds of GPs disagreed with statements indicating confidence in their knowledge of cannabis products, how to access them, or understanding the regulatory landscape, with 65.4% strongly disagreeing that they knew how to help patients obtain these treatments. This widespread self-acknowledged knowledge gap translated into significant discomfort in clinical settings, more than half of respondents reported not feeling comfortable discussing medicinal

cannabis with patients. Furthermore, 86% of the surveyed GPs were classified as having poor perceived knowledge according to the study's composite scoring method. GPs who rated themselves as more knowledgeable were significantly more supportive of prescribing cannabis for conditions such as chronic non-cancer pain and neuropathic pain compared to their less-informed peers, indicating a direct link between knowledge and willingness to prescribe. Importantly, this call for improved training was not only evident in quantitative findings but also echoed in the open-ended responses, where nearly half of the comments expressed a need for further education or acknowledged lack of knowledge. The authors concluded that the provision of structured, evidence-based education and regulatory guidance is essential to equip GPs with the tools needed to manage patient requests and engage in evidence-informed cannabis prescribing. This study aligns with a broader international pattern, where clinician hesitancy is often rooted not in opposition to cannabis itself, but in the lack of access to reliable educational resources and clear clinical guidelines. The low levels of knowledge registered in the Carlini et al. (2017) research explains the strong support among respondents for incorporating medicinal cannabis education into medical curricula and continuing medical education programs. Approximately 96% of respondents agreed that continuing medical education on medicinal cannabis should be available, and 87% believed that medicinal cannabis training should be included in both undergraduate and graduate medical education. This widespread support indicates a recognition of the need for structured educational opportunities to bridge the existing knowledge gap. Moreover, the study found that most healthcare providers currently rely on informal sources of information, such as news media, patients, and other clinicians, rather than peer-reviewed medical literature or formal training

programs. This reliance on potentially unreliable sources further emphasizes the need for credible, evidence-based educational resources on medicinal cannabis.

Despite the recognized need for knowledge in medicinal cannabis, only 42% of pharmacists in Link et al. (2020) had participated in any CBD-related continuing education in the two years preceding the survey. The pharmacists expressed a clear desire for more education, with a particular focus on topics like the safety and pharmacotherapy of OTC-CBD products. The preferred methods for receiving this education included online courses and emails, which reflect the need for accessible and flexible learning opportunities. This demand for education is driven by the pharmacists' awareness of their own knowledge gaps, with 63% reporting feeling incompetent in areas critical to understanding and advising on CBD products.

A large majority (76.7%) of pharmacists involved in the study by Patel et al. (2021) expressed a desire for more educational resources specifically focused on CBD formulations, safety, and efficacy. Similarly, 66% of participants indicated they needed more education on the legal status of these products, highlighting confusion over the complex and evolving legal framework for CBD sales. Formal education on medicinal cannabis was found to be rare among the participants. Only 14.5% had received formal training on non-prescription CBD products, and those who had such training were significantly more confident in answering patient questions and providing evidence-based recommendations. This suggests that targeted training can substantially improve pharmacists' ability to discuss these products with patients. Moreover, younger pharmacists and those with formal education on the topic were notably more confident in making treatment recommendations and providing safety advice. The study recommends introducing medicinal cannabis, particularly non-

prescription CBD products, into the pharmacy school curriculum as one way to address this knowledge gap. With the expanding market for CBD products and increasing patient interest, equipping pharmacists with the necessary knowledge and tools to confidently address patient queries and concerns about CBD is essential. Integrating educational resources, continuing education programs, and formal training could bridge the gap between patient demand and pharmacists' ability to provide expert guidance.

While nearly half of the 769 respondents in research conducted by Mitchell et al. (2016) with hospital pharmacists in Canada, agreed that medicinal cannabis is safe (44.6%) and effective (55.2%), only 17.2% considered themselves knowledgeable on the topic, and over 65% reported having received no formal training related to cannabis during their undergraduate or postgraduate education. The study found a strong association between knowledge and confidence: pharmacists who had received formal or self-directed education on medical cannabis were more likely to agree that it was safe and effective and more comfortable advising patients and healthcare colleagues. Conversely, a lack of formal education was identified as a major barrier to engagement, with many respondents citing insufficient evidence, uncertainty around regulations, and absence of institutional protocols as reasons for discomfort in advising on or handling medicinal cannabis. Moreover, over 70% of respondents had relied primarily on self-directed learning, such as reading articles or online sources, underscoring the absence of structured, evidence-based educational pathways in the pharmacy curriculum or continuing professional development programs. Mitchell and colleagues emphasized that professional responsibilities such as identifying indications, assessing drug interactions, and counselling patients on adverse effects cannot be effectively fulfilled without proper education. Their findings

strongly advocate for the integration of unbiased, scientifically grounded cannabis education into pharmacy curricula and clinical training programs

The review by Shulman et al. (2022) offers robust support for this argument. Synthesizing data from multiple countries, including Canada, Australia, the Netherlands, the United States, and across Europe, the authors found that while pharmacists generally support the dispensing of medical cannabis, they overwhelmingly report a lack of adequate knowledge to do so confidently and safely. This deficit extends across critical domains such as pharmacodynamics, drug interactions, adverse effects, dosing strategies, and regulatory frameworks. In jurisdictions like Australia and the United States, pharmacists have explicitly stated that they need formal training on topics ranging from therapeutic indications to legal compliance before feeling competent in advising patients. For instance, in Minnesota, only 29% of pharmacists reported being able to help patients select the appropriate strength and strain, and the majority expressed minimal confidence in their cannabis-related knowledge. Similar sentiments were echoed among pharmacy students in the United States and Serbia, where education about medical cannabis was either absent or limited, leaving students unprepared for patient counselling roles. In Canada, the review cited multiple surveys indicating that pharmacists desire structured educational resources, and the Canadian Pharmacist Association has responded by developing specific training modules. However, despite these resources, only 17.2% of hospital pharmacists felt knowledgeable about medical cannabis, underscoring that educational uptake remains insufficient relative to the pace of policy reform. The systematic review by Weisman and Rodríguez (2021) offers robust support for the theme that increased knowledge about medicinal cannabis among healthcare professionals is associated with more favourable attitudes toward its clinical use, while

also emphasizing the widespread demand for more education in this area. Across the 40 studies included in the review, involving 15,200 respondents from multiple countries, a consistent trend emerged: respondents who expressed greater self-reported knowledge about medicinal cannabis also tended to hold more positive views on its therapeutic utility. Although only 41% of all respondents expressed confidence in their knowledge of cannabis's health effects, a remarkable 86.2% indicated a desire for more education on medicinal cannabis, highlighting a critical educational gap in current healthcare training. The authors explicitly state that both medical professionals and students expressed a "consistent, strong desire for more educational material" about medicinal cannabis. This educational deficit was mirrored by the fact that only a minority of professionals reported feeling adequately informed about medicinal cannabis's clinical effects, a key barrier to prescribing behaviour. Importantly, this review also observed that medical professionals tended to support medicinal cannabis legalization at higher rates than students (52% vs. 42%), possibly due to their clinical exposure. Still, many professionals acknowledged the inadequacy of their formal education on medicinal cannabis, reinforcing the conclusion that educational interventions are essential to equip healthcare providers with the tools necessary for safe and effective use of medicinal cannabis.

The study conducted by Denneler et al. (2024) strongly indicated that, across all groups, students expressed a clear demand for more training, both in medical school and through continuing medical education. Those who were exposed to materials that positively framed medicinal cannabis were more likely to advocate for its inclusion in the medical curriculum, as well as in ongoing professional development. For instance, students in Group 3 (positive article) were more inclined to believe that medicinal cannabis should be a part of medical training ($p < 0.05$) compared to those in other

groups. The study concludes that current medical education does not sufficiently prepare students to handle medicinal cannabis therapy, leaving them feeling underprepared and lacking confidence. This gap in education is critical, as it affects how future physicians will approach medicinal cannabis in their practice. The findings suggest that integrating structured, evidence-based education on medicinal cannabis into the medical curriculum could significantly improve students' competence and confidence in this area, ultimately leading to better patient outcomes.

An overwhelming majority (86.9%) of the Russian students questioned by Gritsenko et al. (2020) indicated that there is a lack of education on medicinal cannabis within their current curriculum. Despite the recognition of this educational gap, the sources of information about medicinal cannabis reported by students were limited, with only 20.1% citing classroom lectures and 6.7% citing clinical practice settings as sources of their knowledge. This reliance on limited educational resources, coupled with the significant percentage of students who reported no knowledge of medicinal cannabis, suggests that formal education on this topic is severely lacking. The study recommends that additional evidence-based research and education be incorporated into medical curricula to better prepare future healthcare professionals to engage with medicinal cannabis as part of patient care, particularly in contexts where its use may become more prevalent. Conducted at the Belarusian State Medical University, where cannabis for any use is illegal, the study by Khamenka and Pikirenia (2021) surveyed 333 medical students to assess their knowledge, attitudes, and beliefs regarding medical cannabis. Despite the restrictive legal environment, the majority of students (61%) expressed willingness to recommend medical cannabis to patients and recognized its potential physical (69%) and mental (72.9%) health benefits. However, this generally favourable attitude was not matched by adequate educational

preparation. A striking 83.1% of students reported receiving no formal education about medical cannabis, and an even greater percentage (87.5%) believed that healthcare professionals should be formally trained before recommending cannabis to patients. This mismatch between willingness and preparedness underscores a serious educational gap. Furthermore, students primarily relied on informal sources such as the internet or peers for information, with only a small proportion citing medical literature or academic instruction, particularly among female students. The authors conclude that the inclusion of evidence-based cannabis content in medical curricula is essential. Not only to prepare future clinicians in Belarus should policy evolve, but also to ensure that even current debates are informed by accurate, scientific information. The findings strongly advocate for proactive educational reform, even in prohibitionist contexts, as students themselves recognize the therapeutic potential of medicinal cannabis and the necessity of being adequately trained to advise patients confidently and responsibly. This view was supported by another study conducted in the region in 2021. A substantial portion of the foreign medical students in Russia and Belarus (41.6%) in the study by Konstantinov et al. (2021) reported having received formal education about cannabis, which is significantly higher than their Russian and Belarusian peers (14.7%). Despite this, a large number of students still expressed the need for more comprehensive education on the topic. The study suggests that foreign students rely on both formal sources, such as medical literature and classroom lectures, and informal sources like the internet, to gather information on medicinal cannabis. This reliance on varied sources may contribute to the inconsistencies in knowledge about cannabis's therapeutic and adverse effects. The authors recommend that medical curricula in Russia and Belarus be updated to include evidence-based education on medicinal cannabis, which could help bridge the

knowledge gap and prepare future healthcare professionals to manage and discuss medicinal cannabis use more effectively.

More than half of the medical students questioned by Felinhofer et al. (2021) had been exposed to information about medicinal cannabis in their studies, but this exposure was insufficient to build comprehensive knowledge or confidence in the subject. The study concludes that a more coordinated approach is needed to integrate medicinal cannabis education into medical training to ensure that future healthcare professionals are adequately prepared to discuss and recommend its use. This is particularly important given the increasing popularity and legalization of cannabis-based therapies. The study's emphasis on the need for formal education aligns with the growing demand among students for more structured and evidence-based learning opportunities in this area. There was overwhelming support by medical students questioned by Likhitsathian et al. (2021) for integrating medicinal cannabis education into medical curricula. Nearly all students, regardless of nationality, believed that formal training on medicinal cannabis should be included in both academic curricula (90.7%) and clinical training (92.5%). This consensus underscores the recognized need for structured education on medicinal cannabis, which would help bridge the gap between students' awareness of the substance and their preparedness to discuss and recommend it in clinical settings. Interestingly, the study also highlighted the sources of information students rely on for knowledge about medicinal cannabis. Israeli students were more likely to use formal sources, such as medical literature and classroom lectures, but also significantly relied on informal sources, including information from family and friends who use cannabis. This reliance on informal sources can lead to misinformation and further emphasizes the importance of

incorporating accurate, evidence-based education on medicinal cannabis into medical training programs.

In the cross-sectional study conducted by Sokratous et al. (2023) in the Republic of Cyprus, participants who had received formal education on medicinal cannabis were significantly more likely to report feeling prepared to answer patient questions and to recommend its use for medical purposes. Specifically, those with formal MC training were more likely to express confidence in the therapeutic benefits of cannabis, particularly for conditions like mental health disorders and terminal illnesses. For example, 93.1% of postgraduate students, who were more likely to have had formal training, stated that they would recommend medicinal cannabis to patients, compared to 84.1% of undergraduates ($p = 0.042$). Moreover, the study demonstrated that education was a strong enabler of positive disposition: students with academic exposure to cannabis-related content showed higher agreement with statements on its clinical efficacy and were more supportive of its integration into standard healthcare curricula. Findley et al. (2021) strongly emphasize the need for enhanced education on medicinal cannabis in social work programs. A significant majority of students from both countries expressed the belief that training on medicinal cannabis should be incorporated into medical, health, and social work curricula. Specifically, 79.6% of Israeli students and 95.7% of U.S. students supported the inclusion of medicinal cannabis education in academic programs, and 96.2% of Israeli students and 92.2% of U.S. students believed it should be part of residency or field practice requirements. These findings indicate a clear recognition among students of the need for formal education to address the knowledge gaps identified. The study concludes that developing a dedicated curriculum on medicinal cannabis, tailored to the needs of

social workers, is essential for equipping them with the necessary skills and knowledge to address the complexities of cannabis use in their professional practice.

The study by Jankie et al. (2023) offers strong evidence that there is a widespread and urgent demand for increased educational initiatives on medicinal cannabis among prospective healthcare professionals. Conducted at the Faculty of Medical Sciences at the University of the West Indies in Trinidad and Tobago, this cross-sectional survey revealed that although a large majority of students (87.3%) believed they could identify therapeutic uses and adverse effects of cannabis, only 14.2% felt prepared to answer patient questions on the subject, highlighting a considerable gap between general awareness and clinical competence. Crucially, the main source of cannabis-related information among students was not formal education but rather the internet, media, and peers. Only 4.2% of respondents cited the medical school curriculum as a source of information, pointing to a significant shortfall in structured academic instruction. This gap was further emphasized by the fact that 94.6% of respondents expressed a desire for university-organized training seminars to improve their therapeutic knowledge, understanding of adverse effects, and clinical application of cannabis-based treatments. This overwhelming call for education underscores the students' recognition of their limitations and the necessity for formal inclusion of medicinal cannabis in the curriculum. Jankie et al. conclude that despite legislative advancements surrounding medical cannabis in Trinidad and Tobago, academic institutions have not kept pace in equipping future healthcare professionals with the necessary tools to manage, prescribe, or advise patients confidently.

In Sokratous et al. (2022) 60.5% of participants believe that formal training on medicinal cannabis should be integrated into academic programs, and 58% expressed

a strong need for additional research on its use. Moreover, 55.9% of participants felt that educational training programs about medicinal cannabis should be integrated into clinical practice. These findings suggest a significant demand for more comprehensive education and training to bridge the existing knowledge gaps. The study's results align with similar international studies, which have also pointed out the lack of formal education on medicinal cannabis among healthcare professionals. The participants' support for integrating medicinal cannabis education into both academic and clinical settings reflects a broader recognition of the importance of equipping healthcare professionals with the necessary knowledge to effectively manage and discuss medicinal cannabis with patients.

Nearly all respondents (99.1% of undergraduates and 92.1% of postgraduates) in the study by Giannakopoulou et al. (2021) agreed that they should receive formal education on medicinal cannabis, including theoretical knowledge, clinical application, and legal regulations. The study found that the limited exposure to medicinal cannabis in the current curriculum, such as a single 3-hour lecture offered as an elective in the 3rd year, was insufficient to provide students with the comprehensive knowledge they need. This lack of formal education likely contributes to the uncertainty and lack of confidence reported by students regarding medicinal cannabis. The study suggests that integrating a more robust educational framework on medicinal cannabis into the nursing curriculum is essential for preparing future healthcare professionals to meet the growing demand for cannabis-based therapies. By doing so, nursing students would be better prepared to provide evidence-based recommendations and support to patients considering medicinal cannabis as a treatment option.

One of the primary findings of the study by Meyers et al. (2024) is the profound impact that targeted education can have on healthcare providers' understanding of medicinal cannabis. Before the educational intervention, the knowledge of marijuana pharmacotherapy and drug interactions was notably deficient. For example, only 41% of healthcare providers answered knowledge-based questions correctly in the pre-education survey. However, after attending the educational session, there was a significant increase in knowledge across all healthcare provider categories, with correct responses rising to more than 75% overall. Physicians, nurses, pharmacists, and nurse technicians all demonstrated statistically significant improvements in their understanding of marijuana pharmacology, drug interactions, and legality after the educational intervention. These results highlight the need for ongoing educational programs, especially as medicinal cannabis becomes more widely legalized and used in clinical settings. The study suggests that many healthcare providers are not adequately trained to handle the complexities of medicinal cannabis, particularly when it comes to advising patients on safe use and avoiding drug interactions. The study also emphasizes the importance of expanding educational content in medical and pharmacy schools to include information about medicinal cannabis. In fact, only 9% of medical schools currently include marijuana-related content in their curricula. Furthermore, the study found that misconceptions about cannabis persisted even after the educational intervention, particularly among older providers. This highlights the need for not only increasing factual knowledge but also addressing the biases and attitudes that may hinder the adoption of medicinal cannabis in clinical practice. Given the increasing use of cannabis for therapeutic purposes, continued education is essential to ensure that healthcare providers can offer evidence-based guidance to their patients.

Conducted as part of the national “Ask Your Provider About Cannabis” (APAC) project, the study by Klein and Bindler (2022) evaluated the impact of a 2-hour accredited continuing education module on the knowledge, attitudes, and practices of nursing practitioner concerning cannabis use in clinical care. Prior to completing the module, 82.6% of participants acknowledged knowing less than half of the educational content, particularly in key pharmacological areas such as metabolism, pharmacokinetics, and drug–drug interactions. Following the training, there was a significant increase in knowledge, with an average improvement of 39.3% across all tested domains, and nearly 97% of participants agreed that the module had substantially strengthened their knowledge base. The training translated into greater willingness to engage patients in discussions about cannabis: 92.4% of NPs reported being likely or highly likely to inquire about cannabis use, and 81.5% were likely to counsel patients on the topic, despite only a modest proportion having applied the training directly in practice by the time of follow-up. The module also led to attitudinal shifts, with over half of participants reporting that their perspective on medical cannabis had changed after completion of the continuing education.

The significant improvements in knowledge and confidence among participants following the CPE program highlight the effectiveness of structured educational interventions. This emerged from the study by Farmer et al. (2023). Before the program, only a minority of pharmacists felt adequately prepared to counsel patients on CBD, with 20.7% feeling moderately or highly prepared. However, after the program, there was a marked increase in confidence levels, with participants reporting significant improvements in their ability to counsel patients, answer questions from other healthcare professionals, and ensure patient safety (average Likert scale increases of 1.75, 1.73, and 1.70, respectively; all $P < .001$). This suggests that such

educational programs are essential for filling knowledge gaps and empowering healthcare professionals to make informed recommendations about medicinal cannabis, ultimately improving patient care. The study concludes by advocating for more widespread and state-specific educational programs to address the varying legal landscapes and ensure that pharmacists across different regions are equally well-prepared.

These findings align with our own study, where knowledge gaps and limited educational exposure were key barriers cited by participants. It is evident that enhancing cannabis-related education, both in undergraduate curricula and through continuing professional development, could meaningfully shift provider attitudes and improve patient access to informed clinical guidance.

4.8. Outcomes and practice-based evidence for the clinical use of medicinal cannabis

The results of the statistical analyses carried out on journal metrics were evaluated to determine the extent to which the clinical use of medicinal cannabis can be justified based on practice-based evidence. The analysis involved assessment of the scholarly support for the therapeutic application of medicinal cannabis across various conditions. The categorized outcomes allowed for a systematic evaluation of the evidence and based on these findings, it was determined that for certain conditions, the clinical use of medicinal cannabis, particularly where extensive clinical experience and empirical observations have underscored its potential benefits, could be justified despite the absence of formal licensing.

Impact factor analyses summarized in Tables 3.28 to 3.60 reveal a compellingly positive view of medicinal cannabis for certain clinical applications. In particular, the data indicate a consistently favourable perspective on its use for chemotherapy-induced nausea and vomiting and epilepsy across several metrics: the number of journals reporting positive findings versus negative ones, the median impact factor of those journals, the proportion of high-impact journals with positive outcomes, and the weighted average impact factor favouring positive results.

The data reveal a consistently favourable view of medicinal cannabis for managing CINV (Table 3.28), a debilitating side effect of chemotherapy that significantly impacts patients' quality of life. The metrics indicate that a substantial majority of high-impact journals report positive findings regarding the efficacy of cannabis-based treatments for this condition. Notably, the median impact factor of journals publishing positive results is higher than those publishing negative findings, suggesting that the most influential and rigorous scientific outlets are more likely to endorse the use of medicinal cannabis for CINV. Additionally, the weighted average impact factor, which accounts for the relative influence of each journal, further supports the conclusion that the research community largely views medicinal cannabis as an effective intervention for CINV. This positive perspective is further reinforced by the fact that Marinol® (dronabinol), Syndros® (dronabinol) and Cesamet® (nabilone), synthetic cannabinoids, have already been approved by the FDA for the treatment of CINV. These approvals were based on robust clinical evidence demonstrating their ability to reduce nausea and vomiting in cancer patients undergoing chemotherapy. However, the EMA has yet to grant similar approval for cannabis-based products for this indication. This discrepancy highlights a potential gap in regulatory alignment between

the US and Europe, despite the strong practice-based evidence supporting the use of medicinal cannabis for CINV.

The favourable impact factor metrics and the existing FDA approvals create a strong argument for EMA jurisdictions to reconsider their stance on medicinal cannabis for CINV. The data suggest that the scientific community widely supports the efficacy of cannabis-based treatments for this condition, and the high-quality evidence from high-impact journals underscores the validity of these findings, supporting practice-based evidence use of medicinal cannabis for CINV. By endorsing this stance, the EMA could provide patients in Europe with access to a valuable therapeutic option that has already demonstrated success in other regions. The approval of cannabis-based treatments for CINV by the EMA would align with the growing body of evidence and the positive trends observed in the scientific literature. It would also address the unmet needs of cancer patients who continue to suffer from chemotherapy-induced nausea and vomiting despite the availability of conventional antiemetic therapies. Given the robust evidence base and the favourable impact factor metrics, there is a compelling case for the EMA to take a more proactive approach in evaluating and potentially approving medicinal cannabis for this indication.

The analysis of epilepsy-related research (Table 3.46) reveals an overwhelmingly positive trend in the scientific literature, further solidifying the therapeutic potential of medicinal cannabis for seizure disorders. This trend aligns with regulatory decisions from both the EMA and the FDA, which have approved Epidiolex® (cannabidiol, CBD) for the treatment of Lennox-Gastaut syndrome (LGS) and Dravet syndrome, two rare and severe forms of epilepsy. The consistency of favourable findings in high-impact publications not only underscores the efficacy of cannabis-based treatments for

epilepsy but also reinforces their credibility as a viable and scientifically validated option for managing seizure disorders.

The FDA granted approval for Epidiolex® in June 2018, followed by the EMA in September 2019, making it the first cannabis-derived medicine to receive such widespread regulatory endorsement. These approvals were based on robust clinical trial data showing significant improvements in seizure control and patient quality of life. The positive trend in epilepsy-related research is reflected in the impact factor analyses, which highlight the growing body of high-quality evidence supporting the use of medicinal cannabis for seizure disorders. Key metrics, such as the number of high-impact journals reporting positive findings, the median impact factor of these journals, and the weighted average impact factor favouring positive outcomes, all point to a strong consensus within the scientific community. This consistency across multiple metrics reinforces the credibility of cannabis-based treatments and suggests that the therapeutic benefits observed in clinical trials are supported by rigorous, peer-reviewed research.

The impact factor analyses for the use of medicinal cannabis in multiple sclerosis spasticity reveal a generally positive trend, though the level of support is not as strong as that observed for CINV or epilepsy. Despite this, the distribution of research findings suggests that medicinal cannabis holds therapeutic potential for managing multiple sclerosis-related spasticity, a common and often debilitating symptom of the disease. Among the studies analyzed, 22 research papers reported favourable findings, compared to only 4 with non-positive results, indicating a clear trend toward supporting its efficacy. However, the regulatory landscape for this indication remains inconsistent, with the EMA approving Sativex® (nabiximols) for multiple sclerosis spasticity, while

the FDA has yet to grant approval for a comparable product. The EMA has approved Sativex® for this indication, making it available to patients in many European countries. This approval was based on clinical trials demonstrating its efficacy in reducing spasticity and improving patient quality of life. However, the FDA has not yet approved a cannabis-based product for multiple sclerosis spasticity, creating a disparity in access to these treatments between the US and Europe. This discrepancy highlights the need for continued evaluation of the evidence to ensure that regulatory decisions are aligned with the latest clinical research.

4.9. Study limitations and recommendations

There was a substantial number of respondents but logically the higher the number of participants the better the representation of local healthcare professionals. Any future study follow-ups would ideally manage to gather more participation in order to improve results and provide a more widespread perspective about perceptions and attitudes on medicinal cannabis.

The measure of knowledge about medicinal cannabis relied on self-assessment. A common approach in similar research. It is important to recognize that self-assessed knowledge should not be conflated with actual competence. Previous research has demonstrated that healthcare professionals, including doctors, frequently underestimate or overestimate their true level of knowledge (Davis et al., 2006). Therefore, self-evaluation in our study should be regarded primarily as a reflection of confidence rather than an objective measure of factual knowledge.

A few questions that focused on the actual prescription of medicinal cannabis isolated responses to medical practitioners only, excluding pharmacist opinion and restricting the possibility of tapping into that subset's perceptions for those specific questions. This is a limitation if for those questions pharmacist input is sought, thus requiring reformulation of those few questions. In this study they were intended to elicit medical practitioners' responses with regards to the actual prescription process.

Literature suggests that physicians tend to adopt different attitudes with respect to the clinical use of medicinal cannabis depending on their specialization, and therefore due to the direct interaction they have with specific patients and medical conditions. Neurologists and pain management physicians are reported to get firsthand positive patient experiences while primary care providers have less opportunities for assessing such outcomes and are therefore more sceptical in comparison to the former. Future studies would do well to explore this aspect.

A useful recommendation would be a repetition of the study within a number of years to survey healthcare professionals' attitudes and contrast results with those presented in the current study. The study was carried out in one country and despite this might be considered a limitation in some instances, it could also be an opportunity to compare results to other countries or regions where either the situation in terms of legislation and its timing is similar, or else for comparison to other states where a legislative framework has been present for longer or still oversees banning of medicinal cannabis.

4.10. Conclusion

Questionnaire results demonstrate that for the most part there is an openness to, if not embrace, at least explore the potential of using medicinal cannabis in select clinical scenarios by local healthcare professionals. A majority tends to exhibit enthusiasm, although prevalently tepid, with regards to its therapeutic potential. The lukewarm nature of this approach is essentially attributable to a gradual cultural change in the profession and in society in general, as cannabis perception is reformulated into one that commends its beneficial therapeutic effects while cautious on the psychoactive potential that has rightly built consensus towards a demand for strict control over the substance across past decades.

The majority's hesitancy, which is not disapproval but merely timid and vigilant agreement with medicinal cannabis therapy, is intensified when questioned about the clinical application as well as assessing and dealing with side effects. Mostly, there is convinced awareness by many healthcare professionals that not enough knowledge is available about the subject and that more can be done for dissemination of better information. For many there is an acknowledgement that they should also be involved as the recipients of more instruction and understanding in order to gain better insight into a phenomenon that is relatively new given its return into the world of medicine, accompanied by more robust and comprehensive science this time round.

Different factions in most societies nowadays disagree on the place cannabis should hold from a legal and sociocultural perspective, with some regarding its recreational use and purposes in medicinal application as a potential disruptor of the social fabric while others consider its widespread use as a victory for civil rights movements. The debate is still ongoing as different nations start embracing less stringent regulations.

The majority might still disagree with use of cannabis for recreational purposes but an increasing number of people have started seeing benefit of a regulated market for medicinal cannabis targeting patients with a need to alleviate symptoms that are not addressed by the current pharmaceutical arsenal.

Caution is mandatory, and this derives more than anything from a continuously evolving scientific understanding of cannabis and its associated systems. Knowledge such as that in relation to the endocannabinoid system and its pervasive nature in the human body, with a wide central nervous system distribution. This quality presents pharmacological obstacles in drug development with regards to targeting specific outcomes. Rimonabant, an anti-obesity drug initially approved for clinical use in Europe and recalled two years later due to causation of depressive and other severe psychiatric symptoms, is a case in point. Increasingly safer methodologies in cannabis-based drug development have resulted in better medicinal products with less adverse effects and more acceptable safety profiles.

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6. Appendices

APPENDIX 1

Re: FRECMDS_2021_101 ID: 8166_25032021_David Zammit Dimech  

FACULTY RESEARCH ETHICS COMMITTEE <research-ethics.ms@um.edu.mt>

to me, Anthony, Louise ▾

Dear David Zammit Dimech,

Since your self-assessment resulted in no issues being identified, FREC will file your application for record and audit purposes but will not review it.

Any ethical and legal issues including data protection issues are your responsibility and that of your supervisor.

Kindly **confirm** that you sent all the documents which you attached to the UREC form and also other documents related to your study. These documents are also requested for audit purposes.

Regards,



Ruth Stivala | Secretary
B.A.(Hons)(Medit.), M.A.(Medit.)

Faculty Research Ethics Committee
Faculty of Medicine and Surgery
Medical School, Mater Dei Hospital
+356 2340 1214

<https://www.um.edu.mt/ms/students/researchethics>

On Mon, 29 Mar 2021 at 10:35, FACULTY RESEARCH ETHICS COMMITTEE <research-ethics.ms@um.edu.mt> wrote:

Dear David Zammit Dimech,

Kindly send also the supervisor endorsement.



Ruth Stivala | Secretary
B.A.(Hons)(Medit.), M.A.(Medit.)

Faculty Research Ethics Committee
Faculty of Medicine and Surgery
Medical School, Mater Dei Hospital
+356 2340 1214

<https://www.um.edu.mt/ms/students/researchethics>

On Sat, 27 Mar 2021 at 17:43, David Zammit Dimech <david.zammit-dimech.03@um.edu.mt> wrote:

Good afternoon.

Kindly find attached the documents related to my UREC submission in relation to my PhD dissertation, entitled 'Clinical Application And Use Of Medicinal Cannabis'.

Should you require additional information please do not hesitate to contact me.

Kind Regards,

David

David Zammit Dimech <david.zammit-dimech.03@um.edu.mt>

to FACULTY, Anthony, Louise ▾

Good evening Ms. Stivala.

I confirm that all documents required have been sent.

Kind Regards,

David

APPENDIX 2

Dear participant,

It would be appreciated if you could take 15 minutes to fill in this short questionnaire which captures your perception and concern, as a healthcare professional, with regards to the use of medicinal cannabis to alleviate patient symptoms. The questionnaire is part of a research study, 'Clinical Application And Use Of Medicinal Cannabis', conducted through the University of Malta under the supervision of Prof. Anthony Serracino Inglott and Dr. Louise Grech. Complete anonymity is ensured. Data handling, processing and publication will be in line with General Data Protection Regulations.

Demographics

Sex

- ☐ Female
- ☐ Male
- ☐ Other

Age: _____

Profession

- ☐ Doctor
- ☐ Pharmacist
- ☐ Other: _____

For doctors: What is your area of practice?

- ☐ Hospital
- ☐ Community
- ☐ Primary Care
- ☐ Academia
- Other

For pharmacists: What is your area of practice?

- ☐ Hospital
- ☐ Clinical
- ☐ Academia
- ☐ Community
- ☐ Regulatory
- ☐ Industry
- Other

Question 1. For each of these statements, kindly tick your level of agreement.

Statement	Strongly Agree 1	Mostly Agree 2	Somewhat Agree 3	No Opinion 4	Somewhat Disagree 5	Mostly Disagree 6	Strongly Disagree 7
There are patients who could benefit from use of medicinal cannabis.							
I feel comfortable discussing medicinal cannabis with patients.							
I am knowledgeable about the therapeutic effects of medicinal cannabis.							
I am knowledgeable about the side effects of medicinal cannabis.							
I am confident in dealing with patients exhibiting side effects due to use of medicinal cannabis.							
I am confident in answering questions put forward by patients on the use of medicinal cannabis.							
I do not prescribe medicinal cannabis because it is not an ethical form of therapy.							

Question 1 cont. For each of these statements, kindly tick your level of agreement.

Statement	Strongly Agree 1	Mostly Agree 2	Somewhat Agree 3	No Opinion 4	Somewhat Disagree 5	Mostly Disagree 6	Strongly Disagree 7
I am knowledgeable about which patients can derive beneficial effects from medicinal cannabis.							
I feel comfortable prescribing medicinal cannabis to patients.							
I do not prescribe medicinal cannabis because the harm caused outweighs the benefit.							
I do not prescribe medicinal cannabis because the risk of abuse and dependence is higher than for conventional therapy.							
I do not prescribe medicinal cannabis because the risk of side effects is higher than for conventional therapy.							
I am knowledgeable about the modalities and indications for medical cannabis prescribing.							

Question 2. Medicinal cannabis should be used in addressing (select as many as you wish):

- ☐ Multiple Sclerosis Spasticity
- ☐ Chemotherapy-Induced Nausea and Vomiting
- ☐ Post-Traumatic Stress Disorder
- ☐ Epilepsy
- ☐ Neuropathic Pain
- ☐ Mood Disorders
- ☐ Palliative Care
- ☐ Insomnia
- ☐ Chronic Cancer Pain
- ☐ Chronic Non-Cancer Pain

Other : _____

Question 3. Medicinal cannabis is safer than:

Drug	Agree	Don't Know	Disagree
Anxiolytic drugs			
Benzodiazepines			
Opioids			
Anticonvulsant drugs			
Antidepressant drugs			
Statins			
Antipsychotic drugs			

Question 4. For each of these statements, kindly tick your level of agreement.

Statement	Strongly Agree 1	Mostly Agree 2	Somewhat Agree 3	No Opinion 4	Somewhat Disagree 5	Mostly Disagree 6	Strongly Disagree 7
Among the general population there is little understanding of medicinal cannabis.							
I agree that students of medicine and pharmacy should be required to learn about medicinal							

cannabis as part of their curriculum.							
I have received satisfactory formal education about medicinal cannabis.							

Question 5. Via which modalities have you gained insight on the use of medicinal cannabis?

Question 6. Kindly tick your level of agreement for the below statement.

Statement	Strongly Agree 1	Mostly Agree 2	Somewhat Agree 3	No Opinion 4	Somewhat Disagree 5	Mostly Disagree 6	Strongly Disagree 7
I would be interested in attending educational activities to learn more about medicinal cannabis.							

Question 7. What would be your preferred method/s for acquiring more knowledge about medicinal cannabis?

- ☐ Webinars
- ☐ Face To Face Seminars
- ☐ Expert-Driven Online Lectures
- ☐ Medical Conference / Symposium
- ☐ Pharmaceutical Company-Organized Webinar
- Hybrid form (face to face/online)
- ☐ Other: _____

APPENDIX 3

Dear participant,

It would be appreciated if, as part of a select number of professionals invited for this validation panel, you could dedicate a few minutes to evaluate a questionnaire which is part of a study on the clinical use and application of medicinal cannabis.

The total number of items on the questionnaire is 21. You are being asked to evaluate each item on two different scales - clarity and relevance - on a 5-point scale, with 1 indicating the item is very clear or very relevant and 5 indicating that the item is not clear or not relevant.

Please follow the link below to access the validation form and fill it in.

<https://forms.gle/KDj15373sdtFxzEj7>

Attached, you will find the questionnaire in PDF form.

Your collaboration is considered particularly valuable, and it would be appreciated if you could kindly assist in validating the questionnaire that will be used for the study.

Please rate each statement on criteria of clarity and relevance, with 1 indicating that the questionnaire item is very clear or very relevant and 5 indicating that the item is not clear or not relevant. 3 indicates neutrality.

Statement	Criterion	Very Clear / Relevant 1	Clear / Relevant 2	Neutral 3	Unclear / Irrelevant 4	Very Unclear / Irrelevant 5
There are patients who could benefit from use of medicinal cannabis.	Clarity					
	Relevance					

Statement	Criterion	Very Clear / Relevant 1	Clear / Relevant 2	Neutral 3	Unclear / Irrelevant 4	Very Unclear / Irrelevant 5
I feel comfortable discussing medicinal cannabis with patients.	Clarity					
	Relevance					

Statement	Criterion	Very Clear / Relevant 1	Clear / Relevant 2	Neutral 3	Unclear / Irrelevant 4	Very Unclear / Irrelevant 5
I am knowledgeable about the therapeutic effects of medicinal cannabis.	Clarity					
	Relevance					

Statement	Criterion	Very Clear / Relevant 1	Clear / Relevant 2	Neutral 3	Unclear / Irrelevant 4	Very Unclear / Irrelevant 5
I am knowledgeable about the side effects of medicinal cannabis.	Clarity					
	Relevance					

Statement	Criterion	Very Clear / Relevant 1	Clear / Relevant 2	Neutral 3	Unclear / Irrelevant 4	Very Unclear / Irrelevant 5
I am confident in dealing with patients exhibiting side effects due to use of medicinal cannabis.	Clarity					
	Relevance					

Statement	Criterion	Very Clear / Relevant 1	Clear / Relevant 2	Neutral 3	Unclear / Irrelevant 4	Very Unclear / Irrelevant 5

I am confident in answering questions put forward by patients on the use of medicinal cannabis.	Clarity					
	Relevance					

Statement	Criterion	Very Clear / Relevant 1	Clear / Relevant 2	Neutral 3	Unclear / Irrelevant 4	Very Unclear / Irrelevant 5
I do not prescribe medicinal cannabis because it is not an ethical form of therapy.	Clarity					
	Relevance					

Statement	Criterion	Very Clear / Relevant 1	Clear / Relevant 2	Neutral 3	Unclear / Irrelevant 4	Very Unclear / Irrelevant 5
I am knowledgeable about which patients can derive beneficial effects from medicinal cannabis.	Clarity					
	Relevance					

Statement	Criterion	Very Clear / Relevant 1	Clear / Relevant 2	Neutral 3	Unclear / Irrelevant 4	Very Unclear / Irrelevant 5
I feel comfortable prescribing medicinal cannabis to patients.	Clarity					
	Relevance					

Statement	Criterion	Very Clear / Relevant 1	Clear / Relevant 2	Neutral 3	Unclear / Irrelevant 4	Very Unclear / Irrelevant 5
I do not prescribe medicinal cannabis because the harm caused outweighs the benefit.	Clarity					
	Relevance					

Statement	Criterion	Very Clear / Relevant 1	Clear / Relevant 2	Neutral 3	Unclear / Irrelevant 4	Very Unclear / Irrelevant 5
I do not prescribe medicinal cannabis because the risk of abuse and dependence is higher than for conventional therapy.	Clarity					
	Relevance					

Statement	Criterion	Very Clear / Relevant 1	Clear / Relevant 2	Neutral 3	Unclear / Irrelevant 4	Very Unclear / Irrelevant 5

		1				5
I do not prescribe medicinal cannabis because the risk of side effects is higher than for conventional therapy.	Clarity					
	Relevance					

Statement	Criterion	Very Clear / Relevant 1	Clear / Relevant 2	Neutral 3	Unclear / Irrelevant 4	Very Unclear / Irrelevant 5
I am knowledgeable about the modalities and indications for medical cannabis prescription.	Clarity					
	Relevance					

Statement	Criterion	Very Clear / Relevant 1	Clear / Relevant 2	Neutral 3	Unclear / Irrelevant 4	Very Unclear / Irrelevant 5
Medicinal cannabis should be used in addressing (select as many as you wish): a) Multiple Sclerosis Spasticity b) Chemotherapy-induced Nausea And Vomiting c) Post-Traumatic Stress Disorder d) Epilepsy e) Neuropathic Pain f) Mood Disorders g) Palliative Care h) Insomnia i) Chronic Cancer Pain j) Chronic Non-Cancer Pain	Clarity					
	Relevance					

Statement	Criterion	Very Clear / Relevant 1	Clear / Relevant 2	Neutral 3	Unclear / Irrelevant 4	Very Unclear / Irrelevant 5
Medicinal cannabis is less dangerous than: a) Anxiolytic Drugs b) Benzodiazepines c) Opioids d) Anticonvulsant Drugs e) Antidepressant Drugs f) Statins g) Antipsychotic Drugs	Clarity					
	Relevance					

Statement	Criterion	Very Clear / Relevant 1	Clear / Relevant 2	Neutral 3	Unclear / Irrelevant 4	Very Unclear / Irrelevant 5
Among the general population there is little understanding of medicinal cannabis.	Clarity					
	Relevance					

Statement	Criterion	Very Clear / Relevant 1	Clear / Relevant 2	Neutral 3	Unclear / Irrelevant 4	Very Unclear / Irrelevant 5
I agree that students of medicine and pharmacy should be required to learn about medicinal cannabis as part of their curriculum.	Clarity					
	Relevance					

Statement	Criterion	Very Clear / Relevant 1	Clear / Relevant 2	Neutral 3	Unclear / Irrelevant 4	Very Unclear / Irrelevant 5
I have received satisfactory formal education about medicinal cannabis.	Clarity					
	Relevance					

Statement	Criterion	Very Clear / Relevant 1	Clear / Relevant 2	Neutral 3	Unclear / Irrelevant 4	Very Unclear / Irrelevant 5
Via which modalities have you gained insight on the use of medicinal cannabis?	Clarity					
	Relevance					

Statement	Criterion	Very Clear / Relevant 1	Clear / Relevant 2	Neutral 3	Unclear / Irrelevant 4	Very Unclear / Irrelevant 5
I would be interested in attending educational activities to learn more about medicinal cannabis.	Clarity					
	Relevance					

Statement	Criterion	Very Clear / Relevant 1	Clear / Relevant 2	Neutral 3	Unclear / Irrelevant 4	Very Unclear / Irrelevant 5
What would be your preferred method/s for acquiring more knowledge about medicinal cannabis? a) Webinars b) Face-To-Face Seminars c) Expert-Driven Online Lectures d) Medical Conference / Symposium e) Pharmaceutical Company-Organized Webinar g) Hybrid Learning (Face-To-Face And Online) f) Other	Clarity					
	Relevance					

APPENDIX 4

Section A. Introduction to Medicinal Cannabis

Lecture 1. Historical Context of Cannabis as Medicine

Rationale: Understanding the historical use of cannabis in various cultures can provide insight into its therapeutic potential and how perceptions of the plant have evolved over time. This context is crucial for appreciating the complexity of current debates around its medical use.

Learning Objectives:

- To explore the historical significance of cannabis in medicine across different cultures and eras.
- To understand the shift in perception of cannabis from a medicinal herb to a regulated substance.
- To recognize the impact of historical context on current medicinal cannabis research and legislation.

Lecture 2. Understanding the Cannabis Plant and its Components

Rationale: A thorough knowledge of the cannabis plant, including its chemical constituents such as cannabinoids and terpenes, is essential for understanding its therapeutic effects and potential medical applications.

Learning Objectives:

- To identify the main components of the cannabis plant, including THC, CBD, and other cannabinoids.
- To understand the roles of terpenes and flavonoids in the therapeutic effects of cannabis.
- To discuss the importance of the entourage effect and how different components interact to enhance medicinal benefits.

Lecture 3. Mechanisms of Action in the Body and the Endocannabinoid System

Rationale: The endocannabinoid system plays a crucial role in regulating various physiological processes. Understanding how cannabis interacts with this system is key to comprehending its therapeutic potential.

Learning Objectives:

- To outline the components of the endocannabinoid system and their functions in the human body.
- To examine how cannabinoids interact with the endocannabinoid system to produce therapeutic effects.
- To discuss the implications of these interactions for treating various medical conditions.

Lecture 4. Adverse Effects and Risk Management

Rationale: While cannabis has therapeutic potential, it is also associated with risks and adverse effects. Medical practitioners need to be aware of these to effectively manage patient care.

Learning Objectives:

- To identify common adverse effects associated with medicinal cannabis use.
- To understand patient risk factors and contraindications for cannabis therapy.
- To develop strategies for monitoring and managing adverse effects in patients using medicinal cannabis.

Section B. Clinical Applications of Cannabis

Lecture 5. Dosage Principles and Considerations

Rationale: Proper dosing is crucial in medicinal cannabis to maximize therapeutic benefits while minimizing adverse effects. Understanding dosing principles is essential for personalized patient care.

Learning Objectives:

- To understand the factors influencing cannabis dosing, including patient tolerance, condition severity, and cannabinoid profiles.
- To learn about titration methods and starting low and going slow.
- To discuss the challenges and strategies in dosing due to the variability of cannabis potency and patient response.

Lecture 6. Different Forms and Delivery Methods of Cannabis

Rationale: The effects of cannabis can vary significantly depending on the form and delivery method, influencing onset, duration, and intensity of effects.

Learning Objectives:

- To compare the pharmacokinetics and pharmacodynamics of different cannabis delivery methods (inhalation, oral, topical, etc.).
- To understand the implications of each delivery method for specific medical conditions.
- To evaluate the pros and cons of each method in clinical practice.

Lecture 7. Overview of Cannabis Varieties and Their Medical Implications

Rationale: Cannabis strains vary in their cannabinoid and terpene profiles, which can influence their therapeutic effects. Knowledge of these variations is important for selecting the appropriate strain for specific conditions.

Learning Objectives:

- To learn about the major cannabis strains (Indica, Sativa, Hybrid) and their general effects.
- To understand how different cannabinoid and terpene profiles can influence medical outcomes.
- To discuss the current evidence and limitations in strain-specific research for medical use.

Section C. Medical Conditions and Cannabis Therapy

Lecture 8. Discussion on Medical Conditions that Might Benefit from Cannabis Use

Rationale: A deep dive into specific conditions allows for a nuanced understanding of how cannabis may alleviate symptoms or affect disease progression, tailored to the complexities of each condition.

Learning Objectives:

- To examine the potential therapeutic effects of cannabis on neurological conditions, mental health disorders, oncological symptoms, and chronic pain.
- To review current research, including clinical trials and epidemiological studies, on cannabis use for these conditions.
- To discuss the limitations and gaps in current research and the need for future studies.

Lecture 9. Case Studies and Clinical Evidence Supporting Cannabis Use

Rationale: Real-world examples and clinical evidence can provide practical insights into the effectiveness of cannabis therapy and inform best practices in patient management.

Learning Objectives:

- To analyze case studies where cannabis has been used to manage symptoms of specific medical conditions.
- To evaluate the strength and implications of clinical evidence supporting cannabis use in treatment protocols.
- To discuss the role of healthcare professionals in monitoring and adjusting cannabis therapy based on patient outcomes.

Lecture 10. Cannabis in Special Populations (Children, Pregnant Women, Elderly)

Rationale: Special populations may have different physiological responses, risk profiles, and ethical considerations when using cannabis for therapeutic purposes.

Learning Objectives:

- To understand the considerations and contraindications of using cannabis in vulnerable populations such as children, pregnant women, and the elderly.
- To review the existing literature and guidelines on cannabis use in these groups.
- To discuss ethical considerations and the importance of informed consent in cannabis therapy for special populations.

Section D. Practical Aspects of Medicinal Cannabis Use

Lecture 11. Legal and Ethical Considerations in Prescribing Cannabis

Rationale: Navigating the legal landscape and ethical responsibilities is crucial for healthcare professionals prescribing cannabis, ensuring compliance and patient safety.

Learning Objectives:

- To understand the legal framework surrounding medicinal cannabis in various jurisdictions.
- To discuss ethical considerations in prescribing cannabis, including patient autonomy, informed consent, and non-maleficence.
- To explore the role of healthcare professionals in advocating for patient access and evidence-based cannabis policies.

Lecture 12. Cannabis in the Workplace and Implications for Healthcare Professionals

Rationale: Healthcare professionals must be aware of the implications of cannabis use in the workplace, including policy, patient care, and professional conduct.

Learning Objectives:

- To review workplace policies regarding medicinal cannabis use, particularly in healthcare settings.
- To discuss the implications of cannabis use for healthcare professionals, including issues related to impairment, confidentiality, and patient safety.
- To explore strategies for addressing cannabis use among healthcare staff and patients within legal and ethical guidelines.

Lecture 13. Patient Education and Safety Measures

Rationale: Effective patient education and safety measures are essential in mitigating risks associated with cannabis use and ensuring optimal therapeutic outcomes.

Learning Objectives:

- To identify key components of patient education on medicinal cannabis use, including dosing, administration, and side effects.
- To discuss strategies for monitoring and managing potential risks and adverse effects in patients using cannabis.
- To emphasize the importance of ongoing patient-provider communication and education in the context of medicinal cannabis therapy.

Section E. Future Directions and Research

Lecture 14. Emerging Research on Cannabis and Its Compounds

Rationale: Staying abreast of the latest research is essential for understanding the evolving landscape of cannabis medicine, including new therapeutic targets and compounds.

Learning Objectives:

- To explore recent discoveries in cannabis research, focusing on novel cannabinoids and their potential medical applications.
- To discuss advancements in understanding the mechanisms of action of cannabis and its components.
- To assess the impact of new research on clinical practice and drug development.

Lecture 15. Integrative Approaches to Cannabis Therapy

Rationale: An integrative approach to cannabis therapy considers the holistic use of cannabis in conjunction with other treatments to optimize patient outcomes.

Learning Objectives:

- To examine how cannabis can be integrated with conventional and alternative therapies for a comprehensive treatment plan.
- To discuss the principles of holistic health in the context of cannabis therapy, including lifestyle, nutrition, and psychological well-being.
- To evaluate the evidence and best practices for using cannabis as part of an integrative treatment approach.

Lecture 16. Challenges and Opportunities in Cannabis Medicine

Rationale: Recognizing the challenges and opportunities in cannabis medicine is crucial for advancing the field and improving patient care.

Learning Objectives:

- To identify the current challenges in cannabis research, regulation, and clinical application.
- To explore opportunities for innovation in cannabis therapeutics, including personalized medicine and technological advancements.
- To discuss the future of cannabis policy and its implications for healthcare professionals and patients.

Educational Programme Validation Form

Well-organized, with a clear progression from introductory to advanced topics.

Yes ☐ No ☐

Lecture series structure enhances learning and engagement.

Yes ☐ No ☐

The rationale delineated for each section is relevant and logical.

Yes ☐ No ☐

Learning objectives for each lecture are clearly defined and achievable.

Yes ☐ No ☐

Ample coverage of background theme for gradual instructional development.

Yes ☐ No ☐

Provide a comprehensive overview of the practical aspects of medicinal cannabis use.

Yes ☐ No ☐

Risk management and safety measures are prioritized.

Yes ☐ No ☐

Ethical considerations in the use of medicinal cannabis are addressed.

Yes ☐ No ☐

Lectures contemplate future advancement in the field, discussing research and challenges.

Yes ☐ No ☐

APPENDIX 5

Section A. Introduction to Medicinal Cannabis

Lecture 1. Historical Context of Cannabis as Medicine

1. Which ancient civilization is credited with one of the earliest recorded uses of cannabis for medicinal purposes?

- A) Roman Empire
- B) Ancient Greece
- C) Ancient China
- D) Ancient Egypt

2. In which ancient text is cannabis mentioned as a treatment for various ailments, including sleeplessness and pain?

- A) The Bible
- B) Ebers Papyrus
- C) Rigveda
- D) Hippocratic Corpus

3. During which century did European physicians begin to document the medical uses of cannabis?

- A) 19th Century
- B) 16th Century
- C) 17th Century
- D) 18th Century

4. What role did cannabis play in traditional Ayurvedic medicine in India?

- A) Solely as a spiritual enhancer
- B) As a poison
- C) As a treatment for various conditions
- D) It was not used in Ayurvedic medicine

5. How was cannabis used in Ancient Egypt, according to historical medical texts?

- A) As a cure for baldness
- B) As an aphrodisiac
- C) To relieve pain and inflammation
- D) To improve eyesight

6. In the 19th century, which country's pharmacopeia included cannabis, marking its acceptance in Western medicine?

- A) France
- B) United States
- C) Germany
- D) United Kingdom

7. What significant event in the 20th century led to the global regulation and decline in medicinal cannabis use?

- A) Discovery of penicillin
- B) World War I
- C) International drug treaties
- D) The Great Depression

8. Which U.S. pharmacologist is known for his extensive research on cannabis in the early 20th century?

- A) John Harvey Kellogg
- B) Harvey Cushing
- C) Sigmund Freud
- D) William Brooke O'Shaughnessy

9. How did the perception of cannabis change in the United States during the early to mid-20th century?

- A) It became widely accepted for medical and recreational use
- B) It became associated with crime and was heavily regulated
- C) It was promoted by the government for its medical benefits
- D) It was used primarily in religious ceremonies

10. What was the role of cannabis in traditional Chinese medicine, particularly in the context of pain relief and anaesthesia?

- A) There was no recorded use of cannabis in Chinese medicine
- B) Used only in acupuncture
- C) As an analgesic and anaesthetic
- D) As a dietary supplement only

Lecture 2. Understanding the Cannabis Plant and its Components

1. What is the primary psychoactive component in cannabis?

- A) Cannabigerol (CBG)
- B) Cannabichromene (CBC)
- C) Tetrahydrocannabinol (THC)
- D) Cannabinol (CBN)

2. Which component of cannabis is known for its non-psychoactive therapeutic benefits?

- A) Cannabidiol (CBD)
- B) THC
- C) Terpinolene
- D) Myrcene

3. What are terpenes in the context of the cannabis plant?

- A) Psychoactive compounds
- B) Synthetic additives
- C) Toxic substances
- D) Aromatic oils that determine the scent and flavour

4. Which of the following is not a cannabinoid found in the cannabis plant?

- A) Cannabicyclol (CBL)
- B) Cannabivarin (CBV)
- C) Salicylic acid
- D) Tetrahydrocannabivarin (THCV)

5. What is the 'entourage effect' in cannabis?

- A) The feeling of euphoria from high-THC strains
- B) The legal impact of cannabis legislation
- C) The synergistic interaction of cannabinoids, terpenes, and other compounds
- D) The side effects experienced by first-time users

6. Flavonoids in cannabis are responsible for:

- A) Producing the plant's psychoactive effects
- B) Generating the plant's root system
- C) The addictive properties of cannabis
- D) Contributing to the plant's colour, flavour, and potential health benefits

7. Which cannabinoid is known for its potential to treat epilepsy and seizures?

- A) CBD
- B) THC
- C) CBC
- D) CBN

8. Myrcene, a common terpene in cannabis, is known for its:

- A) Ability to increase THC absorption
- B) Ability to induce hallucinations
- C) Psychoactive properties
- D) Sedative and relaxing effects

9. The presence of which compound is primarily responsible for the 'high' associated with cannabis use?

- A) CBD
- B) THC
- C) Limonene
- D) Linalool

10. Cannabinol (CBN) is known for its:

- A) Strong psychoactive effects similar to THC
- B) Role in the plant's photosynthesis
- C) Potential sedative properties and as a byproduct of THC degradation
- D) Ability to enhance cognitive performance

Lecture 3. Mechanisms of Action in the Body and the Endocannabinoid System

1. What are the primary components of the endocannabinoid system?

- A) Amygdala and hippocampus
- B) Insulin and glucagon
- C) CB1 and CB2 receptors
- D) White and red blood cells

2. How do cannabinoids like THC interact with the endocannabinoid system?

- A) By blocking neurotransmitter release
- B) By binding to cannabinoid receptors
- C) By inhibiting enzyme activity in the brain
- D) By promoting the synthesis of new cells

3. What role does the endocannabinoid system play in the human body?

- A) Blood clotting
- B) Regulating physiological and cognitive processes
- C) Oxygen transport
- D) Nutrient absorption

4. CBD is known to have therapeutic effects through:

- A) Direct activation of CB1 receptors
- B) Blocking the production of endocannabinoids
- C) Indirect effects on the endocannabinoid system
- D) Direct activation of CB2 receptors

5. Anandamide and 2-AG are examples of:

- A) Endocannabinoids produced by the human body
- B) Synthetic cannabinoids
- C) Terpenes found in cannabis
- D) Enzymes that degrade cannabinoids

6. The psychoactive effects of THC are primarily due to its action on:

- A) Dopamine receptors
- B) GABA receptors
- C) Serotonin receptors
- D) CB1 receptors in the brain

7. CB2 receptors are primarily found in:

- A) The central nervous system
- B) The peripheral nervous system and immune cells
- C) The digestive tract
- D) The respiratory system

8. The endocannabinoid system is involved in:

- A) Modulating pain perception
- B) Producing insulin
- C) Synthesizing vitamin D
- D) Filtering blood toxins

9. The therapeutic potential of targeting the endocannabinoid system lies in its ability to:

- A) Increase adrenaline production
- B) Suppress immune system activity
- C) Restore balance in physiological systems
- D) Increase blood glucose levels

10. Endocannabinoid system deficiency could be linked to:

- A) Excessive energy levels
- B) Certain pathological conditions
- C) Overactive immune responses
- D) High blood pressure

Lecture 4. Adverse Effects and Risk Management

1. Which of the following is a common short-term adverse effect of cannabis use?

- A) Hypertension
- B) Weight loss
- C) Increased appetite
- D) Dry mouth

2. Long-term cannabis use can potentially lead to:

- A) Improved lung function
- B) Cognitive impairments
- C) Increased bone density
- D) Lowered blood sugar levels

3. In the context of cannabis therapy, contraindications may include:

- A) Vitamin D deficiency
- B) History of psychotic disorders
- C) Low blood pressure
- D) Iron deficiency anaemia

4. A risk management strategy for patients using medicinal cannabis includes:

- A) Regular monitoring for adverse effects
- B) Increasing dosage steadily over time
- C) Using cannabis with high THC content for all conditions
- D) Advising against the use of other medications

5. Cannabis use may exacerbate symptoms in patients with:

- A) Anxiety disorders
- B) Vitamin C deficiency
- C) Muscle soreness
- D) Insomnia

6. Cannabis-induced psychosis is more likely in:

- A) Elderly patients with arthritis
- B) Individuals with a family history of mental illness
- C) Patients using CBD-dominant strains
- D) Patients with chronic pain

7. A possible adverse effect of cannabis that can impact driving ability is:

- A) Heightened alertness
- B) Impaired coordination and reaction time
- C) Reduced aggression
- D) Improved vision

8. Risk factors for adverse effects from cannabis use include:

- A) Use in well-ventilated areas
- B) Use of topical cannabis products
- C) Consumption of CBD-only products
- D) High doses of THC

9. To manage the risk of dependency, healthcare providers should:

- A) Encourage the use of high-THC strains for pain management
- B) Avoid discussing potential adverse effects
- C) Recommend cannabis use as a first-line treatment
- D) Assess the patient's history of substance use

10. In patients with cardiovascular disease, cannabis use may increase the risk of:

- A) Lowered cholesterol levels
- B) Myocardial infarction
- C) Decreased heart rate
- D) Improved blood circulation

Lecture 5. Dosage Principles and Considerations

1. The principle of "start low and go slow" in cannabis dosing primarily aims to:

- A) Increase the speed of onset of effects
- B) Maximize the psychoactive effects
- C) Minimize the risk of adverse effects
- D) Reduce the cost of treatment

2. Patient tolerance to cannabis is influenced by:

- A) Previous cannabis use and exposure
- B) The patient's weight and height
- C) The time of day cannabis is consumed
- D) The patient's dietary habits

3. When considering cannabis dosing, the severity of the condition:

- A) Is irrelevant to the dosing decision
- B) Is less important than the patient's age
- C) Should only be considered for terminal conditions
- D) Directly influences the initial dose and titration approach

4. Cannabinoid profiles are important in dosing because:

- A) Different cannabinoids can have varied therapeutic effects
- B) They indicate the flavour and aroma of the cannabis product
- C) They determine the colour of the cannabis product
- D) All cannabinoids have the same effects and benefits

5. A titration method in cannabis therapy involves:

- A) Mixing different strains to achieve a specific effect
- B) Switching between ingestion methods weekly
- C) Gradually adjusting the dose based on patient response
- D) Using the highest possible dose for the shortest duration

6. Variability in cannabis potency affects dosing because:

- A) It alters the plant's colour and texture
- B) It can lead to inconsistent effects from the same dose
- C) It changes the method of administration
- D) High potency strains are less effective medicinally

7. To address variability in patient response, healthcare providers should:

- A) Use a one-size-fits-all dosing strategy
- B) Only prescribe cannabis for acute conditions
- C) Always start with the maximum recommended dose
- D) Monitor and adjust doses based on individual patient outcomes

8. In the context of cannabis dosing, the entourage effect implies that:

- A) The therapeutic effects can be enhanced by the presence of multiple cannabis compounds
- B) Only THC is effective medicinally
- C) CBD should be avoided in medicinal cannabis
- D) Terpenes interfere with the absorption of cannabinoids

9. For patients new to cannabis therapy, an initial dosing strategy should:

- A) Focus on achieving immediate symptom relief
- B) Begin with the highest possible dose for the condition
- C) Start with a very low dose to assess tolerance
- D) Use THC-dominant strains exclusively

10. When considering the method of cannabis administration in dosing:

- A) Oral methods should be avoided due to lower efficacy
- B) Topical applications are the most effective for systemic conditions
- C) Inhalation is the only method suitable for medicinal purposes
- D) The onset and duration of effects vary significantly between methods

Lecture 6. Different Forms and Delivery Methods of Cannabis

1. Which delivery method of cannabis has the fastest onset of effects?

- A) Oral ingestion
- B) Sublingual
- C) Topical application
- D) Inhalation

2. Edible cannabis products are an example of which delivery method?

- A) Inhalation
- B) Oral ingestion
- C) Transdermal
- D) Intravenous

3. Topical cannabis products are primarily used for:

- A) Localized relief of pain and inflammation
- B) Psychoactive effects
- C) Treating systemic conditions
- D) Rapid onset of effects

4. The sublingual delivery of cannabis involves:

- A) Swallowing a cannabis-infused product
- B) Placing cannabis under the tongue for absorption
- C) Applying cannabis directly to the skin
- D) Inhaling cannabis vapours

5. Which delivery method is known for providing prolonged effects of cannabis?

- A) Inhalation
- B) Sublingual
- C) Topical application
- D) Oral ingestion

6. Vaporization is a form of which cannabis delivery method?

- A) Oral ingestion
- B) Inhalation
- C) Topical application
- D) Sublingual

7. Cannabis tinctures are typically administered via:

- A) Oral ingestion
- B) Inhalation
- C) Sublingual
- D) Topical application

8. The main advantage of transdermal cannabis patches is:

- A) Immediate onset of psychoactive effects
- B) Sustained release of cannabinoids into the bloodstream
- C) Localized skin treatment
- D) Rapid relief of gastrointestinal symptoms

9. Which factor is most critical when considering the oral ingestion of cannabis for medical use?

- A) The flavour of the product
- B) The colour of the product
- C) The variability in absorption and onset time
- D) The temperature at which the product is consumed

10. Inhalation methods of cannabis delivery are characterized by:

- A) Slow onset of effects
- B) Rapid onset but shorter duration of effects
- C) Lack of psychoactive effects
- D) Primarily topical benefits

Lecture 7. Overview of Cannabis Varieties and Their Medical Implications

1. Cannabis Indica strains are typically associated with:

- A) Heightened creativity
- B) Increased energy and alertness
- C) Relaxing and sedative effects
- D) Improved focus and concentration

2. Cannabis Sativa strains are most commonly used for:

- A) Energizing and uplifting effects
- B) Deep relaxation and sleep
- C) Localized pain relief
- D) Appetite suppression

3. Hybrid cannabis strains:

- A) Are not used for medicinal purposes
- B) Combine characteristics of both Indica and Sativa strains
- C) Have no psychoactive effects
- D) Are less potent than pure strains

4. The cannabinoid profile of a cannabis strain refers to:

- A) The colour and texture of the plant
- B) The method of cultivation
- C) The plant's resistance to pests
- D) The concentration of cannabinoids like THC and CBD

5. Terpenes in cannabis:

- A) Are only present in synthetic varieties
- B) Are toxic to humans in small amounts
- C) Decrease the potency of cannabinoids
- D) Contribute to the aroma, flavour, and therapeutic effects

6. A strain high in CBD and low in THC is typically used for:

- A) Managing pain without strong psychoactive effects
- B) Achieving strong psychoactive effects
- C) Enhancing creativity and focus
- D) Stimulating appetite

7. The entourage effect in the context of cannabis refers to:

- A) The social experience of using cannabis in a group
- B) The process of cross-breeding different strains
- C) The adverse effects experienced by first-time users
- D) The synergistic interaction between cannabinoids and terpenes

8. A strain with a high concentration of the terpene Myrcene is likely to:

- A) Be energizing and uplifting
- B) Have sedative and relaxing properties
- C) Improve cognitive function
- D) Increase appetite significantly

9. In medical cannabis research, the limitation of strain-specific studies often lies in:

- A) Variability in plant chemistry and lack of standardization
- B) The high cost of cannabis
- C) The placebo effect in clinical trials
- D) The short duration of most studies

10. When selecting a cannabis strain for medicinal use, it's important to consider:

- A) The plant's size and yield
- B) The popularity of the strain
- C) The patient's specific symptoms and desired outcomes
- D) The strain's name and branding

Lecture 8. Discussion on Medical Conditions that Might Benefit from Cannabis Use

1. Cannabis has been shown to have potential therapeutic effects in the treatment of:

- A) Common cold
- B) Chronic pain
- C) Broken bones
- D) Acute appendicitis

2. In the context of neurological conditions, cannabis may be beneficial for patients with:

- A) Migraines only
- B) Multiple sclerosis
- C) Cerebral palsy only
- D) Alzheimer's disease only

3. Cannabis use might alleviate symptoms of mental health disorders such as:

- A) Anxiety
- B) Bipolar disorder only
- C) Schizophrenia only
- D) Obsessive-compulsive disorder only

4. Regarding oncological symptoms, cannabis is primarily used to manage:

- A) Tumour growth directly
- B) Nausea and vomiting associated with chemotherapy
- C) Skin cancer
- D) Leukaemia

5. Current research on cannabis and epilepsy has focused on the efficacy of:

- A) THC in reducing seizure frequency
- B) THC in improving memory
- C) CBN in improving cognitive function
- D) CBD in reducing seizure frequency

6. One of the limitations in cannabis research for medical conditions is:

- A) The universal acceptance of cannabis in medical communities
- B) The complete understanding of the endocannabinoid system
- C) The low interest in cannabis studies
- D) The variability in cannabis strains and potency

7. Cannabis might be used in palliative care to:

- A) Cure terminal illnesses
- B) Increase life expectancy significantly
- C) Improve the quality of life and manage symptoms
- D) Replace all other forms of medication

8. In the treatment of chronic pain, cannabis is valued for its:

- A) Analgesic properties
- B) Ability to completely cure chronic pain conditions
- C) Immediate surgical pain relief
- D) Long-term use without tolerance development

9. Clinical trials investigating cannabis for medical conditions often assess:

- A) Only the psychoactive effects of THC
- B) Symptom relief and quality of life improvements
- C) The potential for cannabis addiction only
- D) The impact of cannabis on social interactions

10. The use of cannabis in treating gastrointestinal disorders may help with:

- A) Symptoms like nausea and lack of appetite
- B) Surgical repair of gastrointestinal injuries
- C) Total regeneration of damaged gastrointestinal tissues
- D) Immediate elimination of gastrointestinal pathogens

Lecture 9. Case Studies and Clinical Evidence Supporting Cannabis Use

1. Clinical evidence supporting the use of cannabis for chronic pain primarily demonstrates its:

- A) Ability to increase pain sensitivity
- B) Tendency to lead to rapid pain escalation
- C) Efficacy in pain management and reduction
- D) Ineffectiveness in treating pain

2. In case studies of cannabis use for epilepsy, a significant finding has been:

- A) The complete ineffectiveness of cannabis
- B) The sole effectiveness of THC
- C) An increase in seizure activity
- D) The reduction in seizure frequency with CBD-enriched treatments

3. Clinical trials on cannabis for multiple sclerosis have focused on its ability to:

- A) Improve spasticity and neuropathic pain
- B) Worsen mobility issues
- C) Decrease cognitive function
- D) Increase the progression of the disease

4. In the context of oncology, cannabis has been found to help manage:

- A) Tumour growth directly
- B) Chemotherapy-induced nausea and vomiting
- C) The spread of metastatic cancer cells
- D) The need for radiation therapy

5. Case studies involving cannabis for anxiety disorders have shown:

- A) A universal increase in anxiety symptoms
- B) No change in anxiety levels
- C) Potential for symptom relief in certain patients
- D) An immediate cure for all anxiety disorders

6. One of the challenges in interpreting clinical evidence for cannabis use is:

- A) The overwhelming number of studies showing its negative effects
- B) The variability in study designs and cannabis strains used
- C) The unanimous agreement on its effectiveness
- D) The lack of any real-world case studies

7. Patient outcomes in cannabis therapy are best monitored through:

- A) Ignoring patient feedback and relying solely on clinical data
- B) The exclusive use of high-THC strains
- C) Standardized dosing regimens with no adjustments
- D) Regular assessments and adjustments based on individual responses

8. The role of healthcare professionals in cannabis therapy includes:

- A) Guiding patients on dosing, strains, and monitoring adverse effects
- B) Discouraging its use regardless of patient condition
- C) Recommending cannabis as a first-line treatment for all conditions
- D) Avoiding any discussion of cannabis due to legal concerns

9. In palliative care, case studies of cannabis use have highlighted its role in:

- A) Accelerating disease progression
- B) Decreasing life expectancy
- C) Improving quality of life and symptom management
- D) Increasing the need for hospitalization

10. Clinical evidence for the use of cannabis in treating PTSD suggests it may:

- A) Lead to a worsening of symptoms in all cases
- B) Only be effective in combination with other psychoactive drugs
- C) Have no impact on PTSD symptoms
- D) Offer relief for certain symptoms like nightmares and insomnia

Lecture 10. Cannabis in Special Populations (Children, Pregnant Women, Elderly)

1. Cannabis use in children is primarily considered for:

- A) Recreational purposes
- B) Enhancing academic performance
- C) Common colds and flu
- D) Severe epilepsy syndromes

2. The primary concern with cannabis use during pregnancy relates to:

- A) Improved maternal nutrition
- B) Potential impact on foetal development
- C) Reduced morning sickness
- D) Enhanced maternal mood

3. In elderly patients, cannabis may be used to manage:

- A) Paediatric conditions
- B) Chronic pain and sleep disturbances
- C) Growth spurts
- D) Adolescent behavioural issues

4. Ethical considerations in prescribing cannabis to special populations include:

- A) Informed consent and assessing risk-benefit ratios
- B) Ensuring recreational use only
- C) Guaranteeing immediate cure
- D) Promoting long-term dependency

5. Contraindications for cannabis use in children might include:

- A) Lack of any medical condition
- B) History of psychotic episodes or severe anxiety
- C) Need for immunizations
- D) Participation in sports

6. The impact of cannabis on pregnant women's health is:

- A) Completely understood with unanimous consensus
- B) Under-researched, with potential risks to foetal health
- C) Known to enhance foetal development
- D) Recommended for all pregnant women by healthcare professionals

7. When considering cannabis for the elderly, a key factor is:

- A) The preference for high-THC strains
- B) Promoting its use as a primary treatment option
- C) Ensuring use in educational settings
- D) The potential for drug interactions with existing medications

8. Guidelines on cannabis use in special populations often emphasize:

- A) The absence of any risks or side effects
- B) The superiority of cannabis over other treatments
- C) Caution and close monitoring due to limited research data
- D) The use of cannabis as a first-line treatment

9. Potential benefits of cannabis use in children with severe epilepsy include:

- A) Increased seizure frequency
- B) Immediate and complete cure of epilepsy
- C) Development of new epilepsy syndromes
- D) Reduced seizure frequency and improved quality of life

10. In the context of special populations, informed consent for cannabis therapy involves:

- A) Thorough discussion of potential risks, benefits, and alternative treatments
- B) Only informing the patient about the benefits
- C) Waiving the need for consent in urgent cases
- D) Assuming consent if the patient does not explicitly decline

Lecture 11. Legal and Ethical Considerations in Prescribing Cannabis

1. A key legal consideration for healthcare professionals prescribing cannabis is to:

- A) Ensure it is used for recreational purposes
- B) Prescribe the highest possible doses
- C) Verify compliance with local medicinal cannabis regulations
- D) Encourage self-medication

2. Ethical prescribing of cannabis involves:

- A) Ignoring patient preferences and clinical evidence
- B) Withholding information about potential risks
- C) Focusing solely on potential profits
- D) Considering patient autonomy and informed consent

3. Informed consent in the context of cannabis therapy means that the patient:

- A) Is unaware of the treatment being cannabis-based
- B) Understands the potential risks and benefits of cannabis use
- C) Consents to treatment without any information
- D) Is only informed about the positive aspects of cannabis

4. Non-maleficence in prescribing cannabis implies:

- A) Intentionally harming the patient for educational purposes
- B) Using cannabis regardless of potential adverse effects
- C) Avoiding harm and ensuring the potential benefits outweigh the risks
- D) Prioritizing experimental treatments over proven therapies

5. Patient access to medicinal cannabis may be influenced by:

- A) The colour and branding of cannabis products
- B) The legal status and availability of cannabis in the jurisdiction
- C) The patient's ability to cultivate cannabis plants
- D) Popular media and celebrity endorsements

6. Advocacy for evidence-based cannabis policies by healthcare professionals involves:

- A) Promoting the unregulated use of cannabis
- B) Encouraging anecdotal evidence over scientific research
- C) Opposing any form of cannabis legalization
- D) Supporting research and policies that reflect clinical evidence

7. Ethical considerations in cannabis therapy include addressing:

- A) Potential conflicts of interest and ensuring unbiased patient care
- B) Only the financial interests of the healthcare provider
- C) The promotion of cannabis for all patient populations
- D) The exclusive use of synthetic cannabinoids

8. When prescribing cannabis, healthcare professionals must consider:

- A) The specific medical condition and evidence supporting cannabis use
- B) The most aggressive marketing campaigns
- C) The highest possible profit margins
- D) Popular trends in cannabis consumption

9. The principle of justice in cannabis therapy refers to:

- A) Ensuring fair and equal access to cannabis for eligible patients
- B) Providing cannabis only to high-profile patients
- C) Prioritizing access based on social status
- D) Limiting treatment to patients who can afford it

10. Continuous education on cannabis for healthcare professionals is important to:

- A) Discourage the use of cannabis under any circumstances
- B) Promote a single method of cannabis consumption
- C) Stay updated on research, legal changes, and best practices
- D) Focus exclusively on the historical use of cannabis

Lecture 12. Cannabis in the Workplace and Implications for Healthcare Professionals

1. Workplace policies on medicinal cannabis use in healthcare settings typically aim to:

- A) Balance patient care needs with staff health and safety
- B) Encourage the recreational use of cannabis by staff
- C) Ban the use of all forms of medication
- D) Promote the use of cannabis among patients only

2. The primary concern regarding healthcare professionals' use of cannabis is related to:

- A) Increasing work hours
- B) Reducing workplace stress only
- C) Enhancing productivity and focus
- D) Potential impairment and its impact on patient safety

3. Addressing cannabis use among healthcare staff requires:

- A) Ignoring legal and ethical guidelines
- B) Clear policies, education, and support mechanisms
- C) Mandatory cannabis use for all staff
- D) Focusing solely on punitive measures

4. In healthcare settings, patient confidentiality regarding cannabis therapy must be:

- A) Optional, based on staff discretion
- B) Shared with all patients and visitors
- C) Disclosed in all team meetings
- D) Strictly maintained according to privacy laws and ethical standards

5. Strategies for managing cannabis use in healthcare professionals may include:

- A) Routine impairment tests for all patients
- B) Encouraging self-reporting without any support
- C) Regular training on the effects of cannabis and workplace safety
- D) Complete prohibition of cannabis discussion

6. When a healthcare professional is prescribed medicinal cannabis, they should:

- A) Automatically be exempt from all work duties
- B) Use cannabis openly in the workplace
- C) Consult workplace policies and professional guidelines
- D) Advise patients on personal cannabis use

7. Legal implications of cannabis use for healthcare professionals can involve:

- A) Unlimited personal use rights
- B) The right to prescribe cannabis to themselves
- C) Understanding the legal status of cannabis and professional regulations
- D) Ignoring jurisdictional laws in favour of personal choice

8. Ethical guidelines for healthcare professionals and cannabis use emphasize:

- A) The moral superiority of cannabis over other treatments
- B) The promotion of cannabis as a universal cure
- C) Professional responsibility, patient safety, and non-maleficence
- D) Personal benefit and preference in treatment options

9. Healthcare professionals should address cannabis use with patients by:

- A) Providing evidence-based information and considering patient needs
- B) Discouraging all conversations about cannabis
- C) Recommending cannabis for all conditions
- D) Sharing personal opinions and experiences

10. In managing cannabis use and workplace safety, healthcare settings should prioritize:

- A) The preferences of the healthcare professionals
- B) A culture of safety, education, and open communication
- C) The most lenient approach to cannabis use
- D) Strict penalties without education or support

Lecture 13. Patient Education and Safety Measures

1. Effective patient education on medicinal cannabis should include information on:

- A) Recreational use in social settings
- B) The best cannabis strains for recreational use
- C) Proper dosing and potential side effects
- D) Legal ways to cultivate cannabis at home

2. A key safety measure for patients using medicinal cannabis involves:

- A) Avoiding all other forms of medication
- B) Regular monitoring for adverse effects
- C) Using cannabis in public places to reduce stress
- D) Sharing medication with family members for feedback

3. To manage the risks associated with cannabis use, healthcare providers should:

- A) Educate patients on the importance of starting with low doses
- B) Recommend the highest dose for quick results
- C) Encourage experimentation with different strains
- D) Focus solely on the benefits, ignoring potential risks

4. Patient-provider communication in medicinal cannabis therapy should be:

- A) One-time, during the initial prescription
- B) Limited to written communication only
- C) Ongoing, to adjust treatment and address concerns
- D) Conducted only if the patient experiences severe side effects

5. Safety measures for cannabis therapy include advising patients to:

- A) Avoid operating heavy machinery if experiencing impairment
- B) Drive immediately after use to assess their response
- C) Increase the dose if no effects are felt immediately
- D) Consume alcohol to enhance the effects of cannabis

6. When educating patients about cannabis administration methods, it's important to highlight:

- A) The superiority of inhalation over all other methods
- B) The use of synthetic cannabinoids exclusively
- C) That only edible forms are safe
- D) The differences in onset and duration of effects

7. Discussing potential risks and adverse effects of cannabis with patients helps to:

- A) Ensure informed decision-making and risk awareness
- B) Discourage any use of medicinal cannabis
- C) Promote the use of higher doses for better efficacy
- D) Focus on the recreational aspects of cannabis

8. Strategies for monitoring patient responses to cannabis therapy include:

- A) Ignoring mild side effects as insignificant
- B) Waiting for emergency situations to make adjustments
- C) Regular check-ups and patient feedback sessions
- D) Relying solely on family reports without patient input

9. Patient education materials on medicinal cannabis should be:

- A) Complex and detailed, requiring specialized knowledge
- B) Clear, accessible, and tailored to individual needs
- C) Focused on the history and politics of cannabis
- D) Exclusively in written form, without visual aids

10. In the context of medicinal cannabis therapy, the importance of ongoing education is to:

- A) Adapt to changes in patient condition and emerging research
- B) Promote the transition to recreational use
- C) Encourage patients to self-prescribe additional cannabis products
- D) Limit the discussion to the initial consultation

Lecture 14. Emerging Research on Cannabis and Its Compounds

1. Emerging research on cannabis is likely to reveal:

- A) New snack recipes
- B) Ways to increase the psychoactive effects of THC
- C) Novel cannabinoids with unique therapeutic properties
- D) Methods to eliminate all medicinal properties

2. A significant area of advancement in cannabis research involves:

- A) Developing more potent recreational strains
- B) Enhancing the plant's aesthetic qualities
- C) Reducing the plant's growth time
- D) Understanding the mechanisms of action of cannabinoids and terpenes

3. The discovery of new cannabinoids could lead to:

- A) A decrease in cannabis research funding
- B) A decline in medicinal cannabis use
- C) The elimination of all cannabis regulations
- D) New treatments for previously unmanageable conditions

4. Advancements in cannabis research might impact clinical practice by:

- A) Encouraging a return to traditional treatments only
- B) Informing more targeted and effective therapeutic applications
- C) Discouraging any use of cannabis in medicine
- D) Limiting cannabis therapy to acute conditions only

5. One of the objectives of recent cannabis research is to:

- A) Identify the full spectrum of cannabinoids and their effects
- B) Confirm the absence of any medicinal benefits
- C) Focus solely on the recreational aspects
- D) Prove the effectiveness of a single compound

6. Research into the entourage effect aims to understand:

- A) How to eliminate it completely
- B) How different cannabis compounds interact for enhanced benefits
- C) Ways to market cannabis based on its complexity
- D) The effect of cannabis on group social dynamics

7. The impact of new research on drug development in the cannabis industry could include:

- A) Decreasing the variety of available cannabis-based medications
- B) Stopping all development of cannabis-based drugs
- C) Creating more specific and effective formulations
- D) Focusing exclusively on THC

8. Studies on the mechanisms of action of cannabinoids contribute to:

- A) A better understanding of recreational use
- B) The cultural aspects of cannabis use
- C) Reducing the effectiveness of cannabis treatments
- D) Improved targeting of therapies to specific conditions

9. Future research on cannabis may explore:

- A) Ways to completely phase out its medicinal use
- B) The plant's history rather than its compounds
- C) Methods to increase dependency
- D) The potential of minor cannabinoids and terpenes in therapy

10. The role of healthcare professionals in the context of emerging cannabis research is to:

- A) Stay informed and integrate evidence-based advancements into patient care
- B) Dismiss new findings and adhere to traditional practices
- C) Focus solely on the legal aspects of cannabis
- D) Encourage patients to self-educate and self-prescribe

Lecture 15. Integrative Approaches to Cannabis Therapy

1. Integrative cannabis therapy involves combining cannabis with:

- A) Conventional and alternative medical treatments
- B) High-intensity exercise programs
- C) Recreational drug use
- D) Strictly pharmaceutical medications

2. A holistic approach to cannabis therapy emphasizes:

- A) The exclusive use of cannabis for all health issues
- B) Ignoring traditional medical practices
- C) The consideration of the patient's overall well-being, including lifestyle and nutrition
- D) Focusing on the psychological aspects only

3. When integrating cannabis into a treatment plan, it's important to consider:

- A) The patient's preference for cannabis strains only
- B) The cost of cannabis compared to other treatments
- C) The popularity of cannabis products
- D) The interaction between cannabis and other therapies

4. Best practices for using cannabis in an integrative approach include:

- A) Tailoring the therapy to individual patient needs and conditions
- B) Avoiding discussion of cannabis with patients
- C) Using the highest doses of cannabis for effectiveness
- D) Limiting treatment options to cannabis only

5. The role of nutrition in integrative cannabis therapy is to:

- A) Support overall health and enhance the efficacy of cannabis
- B) Replace cannabis with dietary changes
- C) Discourage the use of cannabis in favour of supplements
- D) Focus solely on weight management

6. Psychological well-being in the context of integrative cannabis therapy:

- A) Is unrelated to the effectiveness of cannabis
- B) Is the only factor to consider when prescribing cannabis
- C) Should be ignored in favour of physical symptoms
- D) Is considered alongside physical health for a comprehensive treatment approach

7. Evidence supporting integrative cannabis therapy includes studies on:

- A) The use of cannabis as a standalone treatment
- B) The benefits of ceasing all other treatments in favour of cannabis
- C) The synergistic effects of combining cannabis with other therapies
- D) The superiority of recreational cannabis use over medicinal use

8. In integrative therapy, cannabis can be particularly useful for:

- A) Patients who reject all other forms of medical treatment
- B) Managing symptoms that are inadequately addressed by conventional treatments alone
- C) Completely curing chronic diseases
- D) Serving as the sole treatment modality

9. Patient education in integrative cannabis therapy should focus on:

- A) The historical use of cannabis only
- B) Understanding how cannabis complements other treatment modalities
- C) The legal implications of cannabis use exclusively
- D) Cannabis cultivation techniques

10. The principle of personalized care in integrative cannabis therapy means:

- A) Treating all patients with the same cannabis regimen
- B) Assessing and adapting treatments to meet the unique needs of each patient
- C) Prioritizing cannabis over other effective treatments
- D) Recommending cannabis based on general trends rather than individual assessments

Lecture 16. Challenges and Opportunities in Cannabis Medicine

1. A major challenge in cannabis medicine is:

- A) The universal agreement on its effectiveness
- B) Overregulation that stifles all research
- C) The lack of patient interest in cannabis-based treatments
- D) Variability in cannabis strains and their effects

2. An opportunity in cannabis medicine includes:

- A) Decreasing the availability of cannabis for medical use
- B) Limiting research to recreational use only
- C) Personalized medicine approaches based on genetic profiles
- D) Ignoring technological advancements in cannabis cultivation

3. The future of cannabis policy could impact healthcare by:

- A) Potentially expanding access to cannabis-based therapies
- B) Ensuring cannabis is never used medicinally
- C) Reducing the quality of patient care
- D) Eliminating the need for clinical trials

4. Regulation challenges in cannabis medicine often involve:

- A) Balancing patient access with safety and control
- B) The absence of any legal framework
- C) Complete deregulation and unrestricted access
- D) The lack of interest from regulatory bodies

5. Technological advancements in cannabis medicine could lead to:

- A) A reduction in research funding
- B) Decreased efficacy of cannabis-based treatments
- C) Improved extraction techniques and formulation of cannabis compounds
- D) The elimination of all traditional treatments in favour of cannabis

6. Clinical application challenges in cannabis medicine include:

- A) The overwhelming preference for cannabis over other treatments
- B) Patients' complete understanding of cannabis therapy
- C) The rapid resolution of all regulatory issues
- D) Understanding the best use cases and dosing for different conditions

7. Research in cannabis medicine is hampered by:

- A) The complete understanding of cannabis and its effects
- B) The lack of any ethical concerns or debates
- C) The absence of any clinical or anecdotal evidence of efficacy
- D) Limited access to high-quality, standardized cannabis materials

8. Opportunities for innovation in cannabis therapeutics might include:

- A) Focusing solely on THC and ignoring other cannabinoids
- B) Reducing the variety of available cannabis-based products
- C) Avoiding any use of technology in cannabis research
- D) Exploring the therapeutic potential of minor cannabinoids and terpenes

9. One of the objectives for the future of cannabis policy is to:

- A) Create an evidence-based framework that supports patient care and safety
- B) Limit research to a small number of government-approved studies
- C) Completely ban the medical use of cannabis
- D) Promote recreational use over medicinal use

10. In addressing challenges in cannabis medicine, healthcare professionals should:

- A) Avoid discussing cannabis with patients due to legal uncertainties
- B) Discourage any form of cannabis use, regardless of evidence
- C) Stay informed about the evolving landscape of cannabis research and regulation
- D) Rely solely on anecdotal evidence in making treatment decisions

APPENDIX 6

Medicinal Cannababis

A patient information brochure



**Submitted in partial fulfilment
of the requirements for the
degree of Doctor of Philosophy**

David Zammit Dimech



MEDICINAL CANNABIS

Welcome to our medicinal cannabis information brochure. This guide is designed to provide you with a clear understanding of medicinal cannabis, its potential uses, and important considerations. Medicinal cannabis, derived from the cannabis plant, is increasingly recognized for its potential to alleviate symptoms associated with various medical conditions, including chronic pain, epilepsy, multiple sclerosis, and chemotherapy-induced nausea and vomiting. It is important to distinguish medicinal cannabis from its recreational use. Although both are under strict legal regulation, this brochure deals exclusively with information pertaining to medicinal cannabis, which is subject to stringent quality controls to ensure safety and efficacy. The purpose of this brochure is to equip you with information about benefits, risks and the correct treatment approach to help you make informed decisions in consultation with your healthcare provider.



What is Medicinal Cannabis?



Medicinal cannabis refers to cannabis-derived products prescribed by healthcare professionals to treat specific medical conditions and symptoms. Unlike recreational cannabis, medicinal cannabis is regulated for quality and safety. Its efficacy stems from active compounds known as cannabinoids, with THC (tetrahydrocannabinol) and CBD (cannabidiol) being the most prominent. THC is known for its psychoactive properties, whereas CBD is valued for its therapeutic effects without inducing a "high." Medicinal cannabis can be administered in various forms, including oils, capsules, and dried plant material, tailored to meet individual patient needs while minimizing adverse effects. The goal of medicinal cannabis is to improve quality of life through symptom management in a controlled and medically supervised manner.

Quality of Medicinal Cannabis

The quality of medicinal cannabis is paramount to its safety and efficacy. Strict regulations ensure that medicinal cannabis products are consistently produced and controlled to meet quality standards. These standards involve rigorous testing for cannabinoid content, ensuring the accurate dosage of active ingredients like THC and CBD. Additionally, quality control measures include testing for contaminants such as pesticides, heavy metals, and microbial organisms to ensure patient safety. By adhering to these high standards, medicinal cannabis products provide a reliable and effective option for patients under the guidance of healthcare professionals.





MEDICINAL CANNABIS

Medicinal Cannabis Benefits

Medicinal cannabis and its derivatives have been explored for various therapeutic uses, with some studies supporting a level of efficacy in certain conditions.



Commonly Observed Clinical Effects

- **Appetite Stimulation in HIV/AIDS and Cancer:** THC has shown efficacy in managing weight loss and appetite in both cancer patients and HIV/AIDS patients.
- **Chemotherapy-Induced Nausea and Vomiting:** Nabilone (Cesamet) and Dronabinol (Marinol) are recognized for their efficacy with managing nausea and vomiting associated with chemotherapy.
- **Spasticity:** Cannabis has been beneficial for spasticity related to spinal cord injuries and multiple sclerosis, with various studies confirming its positive effects.
- **Epilepsy:** Epidiolex is approved for treating specific forms of epilepsy, such as Dravet syndrome and Lennox-Gastaut syndrome, especially in children.
- **Chronic Pain:** Particularly effective in neuropathic pain, cannabis has been a therapeutic option for patients with chronic painful conditions.



Potential Therapeutic Uses

- **Movement Disorders:** Could be beneficial in conditions like Tourette's syndrome, dystonia, and dyskinesia induced by levodopa treatment.
- **Sleep Disorders:** May improve sleep quality for conditions such as insomnia, sleep apnea, and other disorders characterized by disrupted sleep patterns.
- **Glaucoma:** Although less commonly used today due to better alternatives, cannabis has been explored for reducing intraocular pressure in glaucoma.
- **Anxiety and PTSD:** CBD may help reduce anxiety symptoms in conditions like generalized anxiety disorder, social anxiety disorder, and post-traumatic stress disorder.
- **Inflammatory Bowel Disease:** Can potentially reduce symptoms of Crohn's disease and ulcerative colitis, such as abdominal pain, diarrhea, and inflammation.



Further studies are needed to fully understand and confirm these therapeutic effects.



MEDICINAL CANNABIS

Approach to Treatment

Treatment with medicinal cannabis involves a careful and personalized approach, guided by healthcare professionals. It ensures that therapy is safe, effective, and tailored to your specific health needs. The process typically moves through the following stages:

1 Assessment

A THOROUGH EVALUATION BY A HEALTHCARE PROVIDER TO DETERMINE IF MEDICINAL CANNABIS IS SUITABLE FOR YOUR CONDITION AND SYMPTOMS



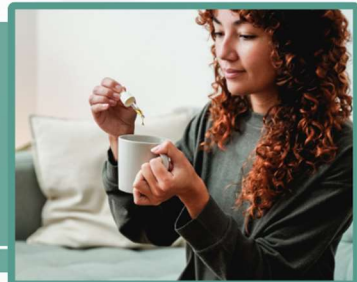
2 Prescription

MEDICINAL CANNABIS MUST BE PRESCRIBED BY A QUALIFIED DOCTOR, WHO WILL SELECT THE APPROPRIATE TYPE AND DOSAGE BASED ON YOUR NEEDS



3 Administration

MEDICINAL CANNABIS CAN BE ADMINISTERED IN VARIOUS FORMS - OILS, CAPSULES, DRIED FLOWERS - TAILORED TO YOUR NEEDS AND THE MEDICAL ADVICE



4 Monitoring

REGULAR FOLLOW-UPS ARE ESSENTIAL TO MONITOR THE EFFECTIVENESS AND ADJUST THE TREATMENT AS REQUIRED





MEDICINAL CANNABIS

Use of Medicinal Cannabis

Medicinal cannabis is available in several forms, catering to different needs and preferences. Dosage should begin low and gradually increase, under medical supervision, to ensure safety and efficacy.



Oil

Cannabis oils, consumed orally for therapeutic purposes, come equipped with droppers for precise dosing.



Tea

Cannabis leaves or flowers steeped in hot water. Dosage is controlled by the amount used and steeping time.



Inhalation

Vaporizing dried cannabis flowers offers quick relief, with dosage determined by vaporizer capacity and user's intake.



Orally-Administered Medications

- Cesamet (Nabilone): Synthetic cannabinoid similar to THC, used for nausea and vomiting, especially in chemotherapy patients.
- Marinol (Dronabinol): Synthetic THC used to treat nausea and vomiting from chemotherapy and to increase appetite in AIDS patients.
- Epidiolex: CBD-based medicine for treating seizures in specific forms of epilepsy.
- Sativex (Nabiximols): A cannabis extract spray with a balanced THC/CBD ratio, used for spasticity in MS, and neuropathic and cancer pain.



MEDICINAL CANNABIS

Conditions Benefitting from Medicinal Cannabis

Medicinal cannabis has shown promise in treating a variety of medical conditions, each with its unique set of symptoms.



Chronic Pain

Useful in managing persistent pain, particularly neuropathic pain, by interacting with pain receptors in the brain.



Multiple Sclerosis

May alleviate symptoms like muscle stiffness and spasms, and nerve pain, improving mobility and quality of life.



Epilepsy

Certain cannabis-derived medications are approved for severe forms of epilepsy, reducing the frequency and severity of seizures.



Chemotherapy-Induced Nausea and Vomiting

Can help manage nausea and stimulate appetite, aiding in weight maintenance during treatment.



Palliative Care

Offers symptom relief for terminal conditions, including pain, anxiety, and insomnia, enhancing comfort and well-being.



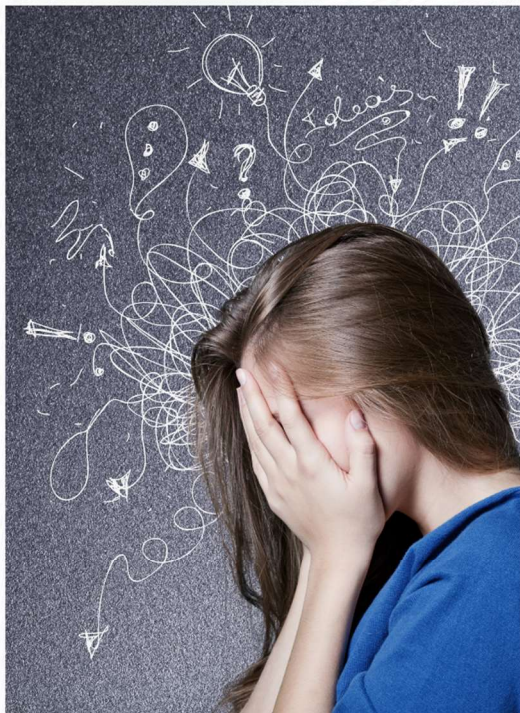
MEDICINAL CANNABIS

Risks and Side Effects of Medicinal Cannabis

While medicinal cannabis offers therapeutic benefits, it's essential to be aware of its potential risks and side effects to ensure safe and informed use.

Potential Risks

- **Psychological Conditions:** Individuals with a family history of psychosis or other psychological conditions should exercise caution, as cannabis may trigger psychotic episodes in susceptible individuals.
- **Cardiovascular Diseases:** Those with heart-related issues should be aware that cannabis can affect blood pressure and heart rate.
- **Age Considerations:** Young people, particularly those under 23, may be more sensitive to cannabis's effects, making its use less advisable.



Side Effects

Medicinal cannabis is generally well-tolerated, especially at low doses. Common side effects, which are more likely at higher doses or when combined with alcohol, include:

- Insomnia and heart palpitations
- Increased feelings of anxiety and depression
- Relaxation, dry mouth, increased appetite, and a more vivid sensory experience
- Drowsiness and altered perception of time and space
- Impaired responsiveness, especially in the initial hours of use
- A 'high' feeling at very high doses, transitioning to calmness and tranquility



MEDICINAL CANNABIS

Special Considerations

Dependency and Addiction

While dependency is less common with medical use at low dosages, long-term or high-dose use can lead to dependency and withdrawal symptoms like restlessness, irritability, insomnia, and nausea upon cessation.



Driving

Cannabis can impair concentration and reaction time, which are critical for safe driving, thereby increasing the risk of accidents due to delayed decision-making and motor control.



Pregnancy and Breastfeeding

Cannabis use is not recommended during pregnancy or breastfeeding due to potential developmental impacts on the child and the presence of THC in breastmilk.



Sourcing and Misinformation

In the digital age, the accessibility of information and products online, including those related to cannabis, has grown exponentially. However, this ease of access comes with significant risks, especially when it involves unregulated markets and misleading information.

Unverified Sources

Online hotspots for the buying and selling of cannabis products, ranging from dried flowers to oils, should be avoided. The origins and manufacturing processes of these products often remain unknown, raising concerns about their quality, composition, and cleanliness.

Misinformation

The internet is rife with claims about the curative powers of cannabis, with some suggesting it as a remedy for an array of illnesses, including various forms of cancer. It is crucial to approach such claims with skepticism, especially when they are not supported by scientific evidence.

Commercial Motives

A significant portion of online content, especially on platforms aiming to sell products, might be driven more by commercial interests than by the welfare of patients or consumers. This commercial slant can lead to biased or inaccurate information that prioritizes sales over safety and efficacy.



Recommendations

- **Seek Professional Advice:** For reliable information and guidance on the use of medicinal cannabis, always consult healthcare professionals. Your doctor or pharmacist can provide evidence-based advice tailored to your health needs.
- **Beware of Online Claims:** Be cautious of the miraculous benefits touted by online sources, particularly those claiming that cannabis is a panacea for all ailments. Remember, medicinal cannabis is a treatment that complements, but does not replace, standard medical treatments for serious conditions like cancer.
- **Regulated Sources:** If considering the use of cannabis for medicinal purposes, ensure that any products are obtained from regulated, reputable sources to guarantee their quality and safety.



MEDICINAL CANNABIS

Further Research on Medicinal Cannabis

The current landscape of medicinal cannabis research underscores the necessity for more comprehensive, high-quality studies to delineate its benefits, limitations, and safety profiles. Despite accumulating anecdotal evidence and preliminary studies indicating potential therapeutic uses, a significant gap remains in our understanding of medicinal cannabis in treating a wide array of health conditions and symptoms.



Extensive

Enhanced research efforts are essential to validate the therapeutic potential of medicinal cannabis across diverse medical conditions, ensuring that treatments are based on robust scientific evidence.



Specific

Future studies should aim to provide clear evidence on the most effective forms, dosages, and methods of administration, catering to the nuanced needs of patients and medical conditions.



Comparative

It's crucial to conduct comparative research to evaluate how medicinal cannabis stacks up against standard medication options, offering insight into its efficacy and safety relative to established treatments.



Interaction

Understanding the interactions with other medications is paramount, as many patients may be on concurrent drug therapies. This will help prevent adverse interactions and optimizing patient care.



As the scientific community continues to explore the multifaceted potential of medicinal cannabis, it is hoped that future research will illuminate its role in modern medicine, backed by a foundation of rigorous, evidence-based studies.

As the body of evidence grows, healthcare professionals will gain the necessary confidence and knowledge to prescribe medicinal cannabis as a viable option alongside or over traditional treatments, when appropriate.

Patient Information Leaflet Validation Form

The brochure clearly identifies its target audience.

Yes ☐ No ☐

The purpose of the brochure is clearly stated and easy to understand.

Yes ☐ No ☐

The language and terminology used in the brochure are appropriate for the intended audience.

Yes ☐ No ☐

The brochure provides accurate and relevant health information.

Yes ☐ No ☐

The information is presented in a logical and coherent order.

Yes ☐ No ☐

The brochure avoids medical jargon and explains terms that might be unfamiliar to the general public.

Yes ☐ No ☐

Key messages and instructions are highlighted effectively.

Yes ☐ No ☐

The brochure uses visual aids to enhance understanding.

Yes ☐ No ☐

The font size and style are easy to read.

Yes ☐

No ☐

There is sufficient contrast between the text and background for easy reading.

Yes ☐

No ☐

The layout (including white space, headings, and bullet points) facilitates easy navigation through the content.

Yes ☐

No ☐

The information provided in the brochure is consistent with current best practices and guidelines in healthcare.

Yes ☐

No ☐

There is a clear call-to-action for the reader, such as seeking further advice from a healthcare professional.

Yes ☐

No ☐

APPENDIX 7

Clinical Trial Framework - Evaluation Form

Instructions

Please review the proposed clinical trial framework for medicinal cannabis and provide your evaluation based on the points outlined below. Use the provided Likert scale to grade your level of agreement for each of the points. If necessary, include comments. Your feedback will help refine and optimize the framework.

1. Ethical Planning

The framework emphasizes the importance of addressing ethical considerations, including participant safety, informed consent, and regulatory compliance.

Agree ☐ Somewhat Agree ☐ Somewhat Disagree ☐ Disagree ☐

Comments:

2. Facility Preparation

The framework highlights the need for ensuring facilities are equipped and secured for handling medicinal cannabis products.

Agree ☐ Somewhat Agree ☐ Somewhat Disagree ☐ Disagree ☐

Comments:

3. Protocol Development

The framework underscores the significance of developing a detailed and scientifically rigorous protocol.

Comments:

4. Dosage Determination

The framework stresses the importance of establishing guidelines for determining appropriate dosages for participants.

Agree ☐ Somewhat Agree ☐ Somewhat Disagree ☐ Disagree ☐

Comments:

5. Dosing Control

The framework outlines the need for measures to ensure sufficient control over dosing for consistency, safety, and compliance.

Agree ☐ Somewhat Agree ☐ Somewhat Disagree ☐ Disagree ☐

Comments:

6. Participant Screening

The framework highlights the importance of developing robust inclusion and exclusion criteria and a clear process for participant screening.

Agree ☐ Somewhat Agree ☐ Somewhat Disagree ☐ Disagree ☐

Comments:

7. Adverse Event Management

The framework emphasizes the need for procedures to identify, report, and manage adverse events effectively.

Agree ☐ Somewhat Agree ☐ Somewhat Disagree ☐ Disagree ☐

Comments:

8. Security Measures

The framework stresses the importance of implementing sufficient security measures for storage, handling, and distribution of cannabis products.

Agree ☐ Somewhat Agree ☐ Somewhat Disagree ☐ Disagree ☐

Comments:

9. Inclusion/Exclusion Criteria

The framework emphasizes the importance of defining inclusion and exclusion criteria that align with the study objectives.

Agree ☐ Somewhat Agree ☐ Somewhat Disagree ☐ Disagree ☐

Comments:

10. Long-Term Considerations

The framework addresses the need to plan for long-term monitoring and follow-up of participants.

Agree ☐ Somewhat Agree ☐ Somewhat Disagree ☐ Disagree ☐

Comments:

11. Overall Evaluation

The framework effectively addresses the unique challenges of medicinal cannabis clinical trials.

Agree ☐ Somewhat Agree ☐ Somewhat Disagree ☐ Disagree ☐

Comments:

APPENDIX 8

Current Publications and Research

- International Pharmaceutical Federation

Poster presentation at the Brisbane 2023 Conference

- Doctors' and pharmacists' perspectives on the clinical use of medicinal Cannabis: a cross-sectional study

Publication in the Harm Reduction Journal (2025) 22:167

PMID: 41084005

<https://doi.org/10.1186/s12954-025-01317-6>

- Cannabinoid exposure for therapeutic targets in substance use disorders: Endpoint-specific findings from a systematic review

(provisional title)

PROSPERO Registration: CRD420251151193