Development of Guidelines for

High-Risk Medication Dispensing

Submitted in partial fulfilment

of the requirements of the

Degree of Master of Pharmacy

Nicole Schembri

Department of Pharmacy

2024

Dedicated with love to my family for their constant encouragement, patience and support throughout my journey at the University of Malta

Abstract

High-risk medications can cause an increased risk of significant harm to patients when misused or used in error. The aims were to evaluate whether high-risk medications are treated differently to non-high-risk drugs during dispensing and to develop guidelines for pharmacists dispensing high-risk medications. A high-risk documentation sheet (HiRisk) was developed and validated by four community pharmacists and two general practitioners. The tool captures the frequency of high-risk medication dispensing. Fifty observational studies using the HiRisk developed tool assessing the most common high-risk medication being dispensed were conducted in five community pharmacies chosen by random sampling from five different districts. Patient interview questions were developed and validated by the same panel. Fifty patient interviews were conducted on a separate cohort of patients in two community pharmacies chosen by convenience sampling aiming to assess patient knowledge and level of awareness of the high-risk medication being dispensed. From the fifty observational studies carried out using the HiRisk documentation sheet, thirty pharmacists being observed have been practicing community pharmacy for more than ten years. From 50 prescriptions observed using the HiRisk documentation sheet, the direct oral anticoagulants rivaroxaban and apixaban were the most commonly dispensed (n=20) high-risk medications followed by warfarin (n=11) and insulin (n=7). Throughout the dispensing process, all pharmacists (N=50) ensured that patients understood well how to administer the high-risk medication and if they are experiencing any issues. All pharmacists repeated major key points during the dispensing process. From the fifty patient interviews conducted, the direct oral anticoagulants were also the most commonly dispensed high-risk medication (n=16), followed by warfarin (n=13) and zolpidem (n=11). Guidelines to improve the dispensing

process were developed for the three most commonly dispensed high-risk medications namely the direct oral anticoagulants, warfarin and insulin. A focus group consisting of four general practitioners and four community pharmacists was set up to validate the developed guidelines. Observing the commonly dispensed high-risk medications and implementing strategies to reduce high-risk medication-associated side-effects through proposed guidelines makes dispensing a streamlined process contributing towards enhanced patient safety.

Acknowledgements

I would like to express my sincere gratitude towards my supervisor, Dr Maresca Attard Pizzuto for her guidance and invaluable advice throughout this study. Her constant feedback has been instrumental in guiding the path of this study.

A heartfelt thank you also goes to Professor Lilian M. Azzopardi, Head of the Pharmacy Department, and to all the staff at the Department of Pharmacy who have contributed to my academic development throughout the entire course of study.

I would also like to express my gratitude to all those, who participated and contributed to this research in any way.

Last but not least, the completion of this dissertation would not have been possible without the support of Timothy, whose love, unwavering patience and encouragement throughout my academic journey has been the driving force behind my accomplishments.

Table of Contents

List of Tables

List of Figures

List of Appendices

List of Abbreviations

ADEs	Adverse Drug Events
ADRs	Adverse Drug Reactions
APTT	Activated Partial Thromboplastin Time
DMARDs	Disease Modifying Antirheumatic Drugs
DOACs	Direct Oral Anticoagulants
ECRI	Emergency Care Research Institute
EMA	European Medicines Agency
EU	European Union
FDA	Food and Drug Administration
ISMP	Institute for Safe Medication Practices
LMWH	Low Molecular Weight Heparin
NSAIDs	Non-Steroidal Anti-Inflammatory Drugs
NSQHS	National Safety and Quality Health Service
REMS	Risk Evaluation and Mitigation Strategies
SSRIs	Selective Serotonin Re-Uptake Inhibitors
UH	Unfractionated Heparin
WHO	World Health Organisation

Chapter 1: Introduction

1.1 Background

"High-risk medications are medications with an increased risk of significant harm to the patient. The consequence of this harm can be more serious than with other medications" (Dumitrescu et al., 2020). This increased risk of significant harm can lead to a patient being more exposed to adverse drug events (ADEs). Some ADEs can be avoided and are predicted whilst other drug reactions are unpredictable. The latter are known as adverse drug reactions (ADRs) defined as "a response to a medicinal product which is noxious and unintended" as discussed by Montané and Santesmases (2020). Khalil and Huang (2020) highlighted that many adverse drug reaction events are a result of prescription errors in community practice. An adverse drug event occurs when a medication error causes injury or harm to the patient (Aljabari and Kadhim, 2021). This harm may also be non-preventable and occur unintentionally during administration of normal drug doses.

Narrow therapeutic index drugs, complex administration techniques, severe side-effects, drug interactions and monitoring requirements are all characteristics of high-risk medications. Medications having a small difference between the therapeutic dose and the toxic dose can lead to significant adverse effects of treatment failure (Habet, 2021). High-risk medications such as insulin and warfarin require precise timing and careful patient individualised dose calculations (Mason *et al*., 2022). High-risk medications can have significant interactions with other drugs, supplements and foods which may complicate their use (Zawiah *et al*., 2020). Many high-risk medications necessitate regular monitoring of drug levels as well as organ function to ensure safety and efficacy of the high-risk medication (Hanni *et al*., 2020).

1.2 Medication Errors

The process of prescribing, dispensing and administering medications involves different health care professionals, mainly general practitioners, pharmacists and nurses, working in many settings. Assiri *et al*., (2019) defined medication errors as "any preventable event that may cause or lead to inappropriate medication use or patient harm while the medication is in the control of the health care professional, patient or consumer". Medication errors can occur at various stages of the medication process including prescribing, dispensing, administering and monitoring. Addressing medication errors is crucial for enhancing patient safety and improving healthcare outcomes (Koeck *et al*., 2021). Prescribing errors include the choice of a wrong medication for the patient. Prescribing an incorrect dose, frequency or route of administration for a high-risk medication can cause severe patient harm resulting in hospital admissions and potentially death (Lemos *et al*., 2021). Inappropriate drug selection and prescribing a drug to which the patient has an allergy for can also be fatal. Dispensing errors include the dispensing of the wrong medication, mislabeling the medication with incorrect information, dosage instructions or drug name (Reiner *et al*., 2020). Failure to monitor patient's response to the high-risk medication can lead to unrecognised side-effects or else ineffective treatment (Levy, 2023).

There are various causes of medication errors which include human factors, systemic issues, technological issues as well as environmental factors. Overburdened healthcare professionals working long hours may rush through tasks which increases the likelihood of medication errors (Menon *et al*., 2020). Emotional toll on healthcare providers leads to burnout and reduced job satisfaction.

Interruptions and multitasking can also lead to mistakes (Enz *et al*., 2021). Lack of knowledge by healthcare professionals about medications and their drug interactions can also result in error. Missing or incomplete patient records can lead to incorrect medication decisions which can be of risk to the patient's wellbeing (Weiner *et al*., 2020).

The main impact of medications errors is on the patient. Medication errors can cause harmful side-effects and toxic reactions which can lead to ineffective treatment and prolonged illness. Medication errors involving high-risk medications may result in hospital admissions. Medication errors also have an impact on financial costs, with prolonged hospital stays requiring prolonged treatment (Jermini *et al*., 2024).

Various strategies are in place for preventing medication errors. Training of healthcare professionals including pharmacists is vital. This includes training on safe medication practices, new medications including high-risk medications, and updated technologies (Aldosari *et al*., 2020). E-prescribing helps with reducing errors associated with illegible handwritten prescriptions by electronically transmitting prescriptions directly to the pharmacy of the patient's choice (Gates *et al*., 2020). Improved communication between prescribers and pharmacists dispensing high-risk medications ensures accurate and comprehensive documentation in patient records. Standardised procedures should be set in place for transferring patient care information between healthcare professionals (Mercer *et al*., 2021). Educating patients about their medications, including dosage, timing of medication administration, potential side-effects and the importance of adherence is a major key point throughout the dispensing process especially in the case of high-risk medications. Ensuring adequate staffing levels for better workload management is a strategy to minimise and eliminate overburdened healthcare

professionals. Keeping medication preparation areas clean and free from distractions as well as creating 'no interruption zones' is important when high-risk medication dispensing is being executed. Regularly reviewing and updating patient medication history is important as it allows for better monitoring and reporting. Thorough investigations of medication errors to identify underlying causes, drug related problems and any possible side-effect is vital to allow for implementation of corrective actions (Nagappa and Naik, 2022).

Song *et al.,* (2021) agree that pharmacists may intervene in improving drug usage to minimise prescription medication errors and provide patient care services. In 2017, the World Health Organisation (WHO) launched its third "Global Patient Safety Challenge, Medication Without Harm",[1] which is an initiative that aims to reduce severe avoidable medication errors. This initiative proposes a strategic framework with three key action ideas as priorities for action which include polypharmacy, transition of care and high-risk situations.

Polypharmacy is defined by the National Institute for Health and Clinical Excellence (NICE) as "the use of multiple medicines by a person".[2] The global population's increasing life expectancy and comorbidities have led to polypharmacy becoming more prevalent in modern times. The occurrence of polypharmacy is becoming more frequent among adults over the past twenty years with the introduction of novel drugs and the expanding comorbidities requiring treatment.

[1] World Health Organisation (WHO). Medication Without Harm. [Internet] (Geneva) WHO;2017 [cited 2024 Jun 19]. Available from: https://www.who.int/initiatives/medication-without-harm

[2] National Institute for Health and Care Excellence (NICE). Medicines optimization: the safe and effective use of medicines to enable the best possible outcomes. [Internet] (UK) NICE;2015 [cited 2024 Jul 24]. Available from: https://www.nice.org.uk/guidance/ng5/chapter/recommendations#polypharmacy

Polypharmacy regimens carry a non-adherence risk, increasing the probability of disease and hospital admission (Wang *et al*., 2023). Polypharmacy is recognised as a significant factor that contributes to errors in treatment and is named as the strongest risk factor when it comes to adverse drug reactions by the US Department of Health and Human Services.[3] An important intervention to tackle polypharmacy is the use of regular medication reviews carried out by the pharmacist. The benefit/risk of medications should be re-evaluated with each medication review through the monitoring of patient blood tests and other relevant monitoring requirements. If the risk outweighs the benefit, the medication may be deprescribed by the physician (Scott *et al*., 2015). The implementation of periodic medication reviews has been proven to improve the health status of patients who are being dispensed multiple medications, reducing ADRs and hospitalisation (Varas-Doval *et al*., 2020).

Transitions of care through different care settings and various relationships with healthcare professionals may lead to medication errors. The patient's history must be recorded throughout all the care settings for the healthcare professionals to avoid medication errors. The digital recording of patient's history and clinical records is effective in reducing medication errors during transitions of care (Avery *et al*., 2012). The pharmacist's role is critical during the transition of care process. A pharmacist-led transition of care is both financially favourable for the institution and beneficial for patients as it decreases the number of readmissions (Rafferty *et al*., 2016).

[3] Patient Safety Network (PSNet). Medication Errors and Adverse Drug Events. [Internet] (USA) PSNet;2019 [cited 2024 Jul 24]. Available from: https://psnet.ahrq.gov/primer/medication-errors-and-adverse-drug-events#:~:text=Polypharmacy-taking%20more%20medications%20than,are%20particularly%20vulnerable%20to%20ADEs.)

High-risk medications, besides patient factors and setting of care may contribute to the occurrence of medication errors. Therefore, strategies must be implemented to address the risk with high-risk medications.

The Institute for Safe Medication Practices (ISMP) is an organisation dedicated for the prevention of medication errors. In 2020, ISMP affiliated with the Emergency Care Research Institute (ECRI) forming one of the largest healthcare quality and safety institutions in the world.[4] The ISMP Medication Safety Self-Assessment® for High-Alert Medications is designed to increase healthcare providers' understanding of the importance of safe medication systems and practices associated with high-risk medications. ISMP also aims to assist healthcare providers during prescribing, preparing and dispensing of high alert medications to recognise and prioritise opportunities that minimise patient harm. High-risk medications, as stipulated by the ISMP include but are not limited to antithrombotic agents, antiarrhythmics, chemotherapeutic agents, sedative agents, neuromuscular blocking agents, insulin, opioids and parenteral nutrition preparations.[5]

[4] Emergency Care Research Institute. [Internet] (USA) ECRI;2024 [cited 2021 Jun 19]. Available from: https://home.ecri.org/pages/ismp

[5] Institute for Safe Medication Practices List of High-Alert Medications in Acute Care Setting. [Internet] (United States): ISMP;2018 [cited 2024 Jun 19]. Available from: https://www.ismp.org/sites/default/files/attachments/2018-08/highAlert2018-Acute-Final.pdf

1.3 Management of High-Risk Medications

Managing high-risk medications involves a systematic approach to ensure patient safety and ultimately minimise the risk of dispensing errors. Goode *et al.,* (2019) argued that improving the quality of patient care and patient safety is always an increasing priority for health care systems.

Key strategies for effective management of high-risk medications include the identification and segregation of high-risk medications, education and training of pharmacists and other healthcare professionals, standardised protocols, patient education, patient monitoring and pharmacist involvement.[6] High-risk medications should be clearly identified using labels, colour coding or specific storage areas contrasting them from non-high-risk medications (Ruutiainen *et al.*, 2020). Healthcare professionals should be regularly trained on handling and dispensing high-risk medications. Ongoing education about potential safety risks should be provided. Standardised protocols and guidelines for dispensing and monitoring of high-risk medications should be disseminated in pharmacies and utilised by community pharmacists (Watkins, 2015). High-risk medications, like warfarin, are medications that should be closely monitored to ensure that the risk-benefit ratio remains favourable (Dreischulte and Guthrie, 2012). The direct oral anticoagulants (DOACs), being another example of high-risk medications, are increasingly prescribed instead of warfarin because they provide a better risk-benefit ratio and because therapeutic drug monitoring is no longer deemed necessary (Afzal *et al.*, 2021).

[6] Core Prescribing Solutions. High-Risk Medication Monitoring: A UK Healthcare Perspective. [Internet] (United Kingdom) CPS;2023 [cited 2024 Jul 26]. Available from: https://coreprescribingsolutions.co.uk/high-risk-medication-monitoring/

High-risk medications that were identified and which will be referred to in this study are insulin, opioids namely morphine and fentanyl, sedative agents namely zolpidem, warfarin, the direct oral anticoagulants rivaroxaban and apixaban, heparin, biologics and the disease-modifying antirheumatic drugs (DMARDs) methotrexate and sulphasalazine.

Insulin

Insulin is a widely used medication for the management of hyperglycaemia (Sanz-Pastor *et al*., 2024). It is classified as a high-risk medication as its misuse is associated with significant risks of hypoglycaemia. Failing to recognise signs of hypoglycaemia such as palpitations, anxiety, hunger, weakness and confusion can lead to unconsciousness and progress to death (Hölzen *et al*., 2024). Administration of insulin can be via various routes including subcutaneous, intramuscular or intravenous. Janež *et al*., (2020) agree that the route of administration is dependent on the patient condition, preference, setting and availability of reimbursement. Adequate patient counselling and monitoring is required with the dispensing and administration of insulin ensuring patient safety and adherence to treatment.

Opioids

Opioids are known to suppress pain (Brody *et al*., 2019). Nicholson and Hellman (2020) argue that opioids can be harmful even when prescribed in proper doses. The risk of opioid toxicity has increased owing to an increase of its use (Strang *et al*., 2020).

Opioid overdose deaths in the Unites States have increased from 2019 to 2022 with more than 107,941 deaths reported in 2022.[7] Adverse drug reactions caused by opioids that can lead to potential harm include respiratory depression, lethargy, dizziness and nausea and vomiting (Gustafsson *et al*., 2023). Opioid use and interactions should be closely monitored. Adverse effects precipitating from opioid usage lead not only to prolonged hospital admissions but also to addiction and hyperalgesia (Chia *et al*., 2020).

Opioids are classified as high-risk medications because if side-effects of excessive sedation, narcotisation and respiratory depression are not treated, they can lead to lethal overdosage (Montandon, 2022). Multidisciplinary efforts from pharmacists and other healthcare professionals are required to manage pain by opioid usage. Pharmacist intervention contributes positively during dispensing and through patient education as it leads to a reduction in negatively perceived barriers about opioids (Ayoub *et al*., 2022). When it comes to dispensing narcotics, the process require the maintenance of records. Proper handling is necessary to adopt proper narcotic use (Sonawale *et al*., 2022).

Sedative Agents

Zolpidem, a high-risk sedative agent, is associated with the increased incidence of dizziness, lightheadedness and falls especially in older persons (Amari *et al*., 2022). Although it is administered at bedtime, it may cause drowsiness and reduced alertness even on arising. Sedatives are central nervous system depressants used for various conditions such as anxiety and sleep disorders (Alkattan *et al*., 2021).

[7] National Institute on Drug Abuse. Drug Overdose Death Rates [Internet] (United States): 2024 [cited 2024 Jun 21]. Available from: https://nida.nih.gov/research-topics/trends-statistics/overdose-death-rates

A multi-disciplinary team approach should be adopted when treating insomnia with a focus on improving sleep hygiene, controlling stresses and drug therapy. Edinoff *et al*., (2021) agreed that when compared to other sedatives such as benzodiazepines and melatonin agonists, zolpidem has shown a reduced incidence of residual daytime sleepiness and a lower risk of falls, however, adverse effects shown through its administration include nausea, dizziness, drowsiness and short-term memory loss (Shih *et al*., 2015).

Warfarin

Warfarin is an antithrombotic agent that is most widely used long term (Ma *et al*., 2019). Being a narrow therapeutic index drug, warfarin needs to be closely monitored as it is associated with a number of significant drug-drug interactions. Common drug-drug interactions that are observed in long term patient care include interactions with non-steroidal anti-inflammatory drugs (NSAIDs) leading to potential gastrointestinal bleeding, interactions with macrolides, sulfonamides and fluoroquinolones which can all lead to potential bleeding, and interactions with anticonvulsants which can lead to increased effects of warfarin (Wang *et al*., 2021). DOACs are used in the treatment and prophylaxis of thromboembolisms as well as prophylactically when hip and knee surgery is due.

The direct oral anticoagulants have shown significant advantages over Vitamin K antagonists, namely warfarin given that they do not require international normalised ratio (INR) laboratory monitoring (Sarode, 2019). Direct oral anticoagulants are more susceptible to changes in renal function and result in poorer adherence (Burn and

Pirmohamed, 2017). Baseline renal function is tested for when DOACs are first prescribed. Periodic monitoring of renal function is required, especially in renally impaired patients. Direct oral anticoagulants have generally better safety profile than warfarin, however, there is still controversy on whether DOACs are more likely to cause gastrointestinal bleeding than Vitamin K antagonists. For this reason, direct oral anticoagulants are classified as high-risk medications due to this increased risk of bleeding which can be uncontrolled and life-threatening (Benamouzig *et al*., 2022).

Heparin

Qiu *et* al., (2021) agree that heparin is the earliest and widely used anticoagulant in clinical medicine. Drug related problems with heparin are not necessarily related to medication errors. Such can include heparin-induced thrombocytopenia, haemorrhage, hyperkalaemia, rebound hyperlipidaemia upon withdrawal and osteoporosis. Bleeding can also occur with therapeutic doses and therefore, patient monitoring is important (Lucatelli *et al*., 2020). The risk of bleeding with heparins resulting from over anticoagulation and its narrow therapeutic index are characteristics classifying heparin as a high-risk medication. Heparin has also been widely used as therapy for COVID-19 for its antiviral and anti-inflammatory effects (Vitiello and Ferrara, 2023). Due to their numerous advantages over unfractionated heparin (UH), low molecular weight heparin (LMWH) has been most widely prescribed and administered. These advantages include superior efficacy, greater bioavailability and safety when administered subcutaneously, decreased frequency of thrombocytopenia and osteopenia. The ease of administration of low molecular weight heparin makes it easier to administer by patients at home and therefore, increases patient compliance.

Another advantage is that LMWH does not require routine daily monitoring of the activated partial thromboplastin time (APTT) unlike UH (Shaikh *et al*., 2023).

Biologic Drugs

Therapy with biologic agents such as methotrexate and sulfasalazine has greatly improved the treatment of immune mediated disease such as inflammatory bowel disease, rheumatoid arthritis as well as psoriasis (Papamichael *et al*., 2019). Piovani *et* al., (2020) agree that biologics are likely to increase the risk of serious infections. Potential approaches to risk mitigation with the use of biologics include patient pre-treatment screening, monitoring of infections if present and the cessation of treatment or alternative therapy at first signs of infection. For the majority of patients, the benefit-risk ratio of biologic agents is considered favourable (Adami *et al*., 2019).

1.4 Dispensing of High-Risk Medications

The dispensing process of high-risk medications is a process demanding vigilance and adherence to protocols with the main aim of preventing medication errors and ensuring patient safety (Kallio *et al*., 2020). Each high-risk medication prescription should be reviewed by the pharmacist for prescription appropriateness, dosing and any present drug interactions (Petrovic *et al*., 2022). Verification of the medication by another pharmacist before dispensing is crucial for double-checking and minimising dispensing errors (Alsaloom *et al*., 2022). Clear and written instructions should be communicated with the patient receiving the high-risk medication including administration techniques, possible side-effects and dosage regimen. Pharmacists should ensure that the patient understands

correctly how to self-administer the medication as well as the importance of adherence. Any additional labelling for proper drug administration should include the drug name, dosage regimen, administration instructions and storage requirement (Advinha *et al*., 2021).

Throughout the dispensing process, the pharmacist is responsible of ensuring that the patient receives the right medication, and that necessary advice is provided to comply with the dosage regimen (Paulino *et al*., 2019). Dispensing is a multi-stage process which includes "pharmacist involvement, identification of patient, assessing patient knowledge, decision making, rechecking of prescription, advice given, confidentiality and patient profile. When one fails, the risk of medication errors increases" (Azzopardi, 2000).

Throughout the dispensing process, it is the pharmacists' professional responsibility to make sure the patient receives the appropriate high-risk medication and the guidance the patient needs to follow the dosage regimen (Gurwitz *et al*., 2021). Upon receiving a prescription, the pharmacist is responsible of checking patient's details. This would enable the pharmacist to obtain relevant information required for the dispensing of the high-risk medication. To be able to offer guidance and appropriate patient counselling, the pharmacist must first evaluate the patient's knowledge (Qudah *et al*., 2021). Nowadays, patients are increasingly showing interest to obtain information about the high-risk medications they are continuously being prescribed and dispensed (Kvarnström *et al*., 2021). The pharmacist holds the position of providing this information which is relevant to the medication the patient is being administered. What information should be kept private in the patient's best interest is the basis for the decision. The provision of information allows for better patient compliance and adherence to treatment.

Well-informed patients are more likely to use their medications correctly. The pharmacist is also responsible in verifying with the patient the indication for which the high-risk medication is prescribed and to gauge the patient's understanding. Before opting to dispense the prescribed high-risk medications, the pharmacist reviews the prescription for inadvertent prescription errors. This ultimately reflects on the patient's well-being. Decision making also influences the choice of medication chosen. The pharmacist should offer to contact the prescriber and be able to assist the patient in getting the required high-risk medication if it is not readily available. Pharmacists double-checking prescriptions is crucial. Comparing the high-risk medication prescribed and the medication selected for dispensing ensures proper treatment. Better patient management is obtained by the advice given by the pharmacists during the dispensing process, whether advice given verbally, or instructions written on the high-risk medication itself (Suppiah *et al*., 2023). Pharmacists need to adapt their advice given based on patient characteristics. The counselling process should be developed according to each individual patient's needs.

The dispensing of a high-risk medication prescription raises ethical concerns about confidentiality and recommends the consultation with other healthcare professionals. Pharmacies should have designated private areas for discussing with the patient, reassuring the patient during the dispensing process without alarming them. All prescriptions and patient records should be segregated preventing any unauthorised access (Semantha *et al*., 2021).

Throughout the dispensing process, the pharmacist discusses with the patient pharmacological and non-pharmacological measures in concordance with the high-risk medication being dispensed. The pharmacist also provides advice on the health condition

being treated and how symptoms can be alleviated non-pharmacologically. Pharmacists also have a role in informing the patient about concomitant medications that should be avoided or taken in conjunction with the high-risk medication being dispensed.

The most common factors associated with dispensing errors include high workload and low staffing, sound-alike drugs, distractions as well as lack of knowledge or experience (Aldhwaihi *et al*., 2022). Factors that aid in reducing the incidence of errors during high-risk medication dispensing include improvement of the dispensary area, reducing pharmacy interruptions, reducing the pharmacist's workload and keeping the pharmacist's knowledge up to date (Gogazeh, 2020).

The dispensing of high-risk medications across European countries involves regulatory frameworks and practices to ensure patient safety and therapeutic efficacy. The European Medicines Agency[8] (EMA) provides guidelines whilst individual countries develop and implement protocols tailored to their healthcare system. Each country within the European Union (EU) has its own regulatory body. In Malta, this is the Malta Medicines Authority which implements EMA guidelines and enforces local regulations. Pharmacovigilance systems are in place for the reporting of adverse effects especially with effects reported with high-risk medication use. Systems are in place for reporting and monitoring adverse drug reactions. Pharmacists and other healthcare professionals must report significant adverse effects to national pharmacovigilance institutes. Manufacturers are then required to implement risk management plans to explain how

[8] European Medicines Agency (EMA). [Internet] (Netherlands) EMA;2024 [cited 2024 Jun 20]. Available from: https://www.ema.europa.eu/en/homepage

risks will be minimised.[9] Clear protocols proposed by the MMA are in place for prescribing high-risk medications. Throughout the dispensing of a high-risk medication, pharmacists are to follow dispensing guidelines, including the double-checking of procedures and patient counselling. On-going training programs for pharmacists are in place to ensure that pharmacists are up to date on best practices for the handling of high-risk medications.

When dispensing a high-risk medication such as insulin, the pharmacist should verify with the patient the type on insulin being used, ensuring it matches the high-risk medication prescription received. Proper self-administration techniques using pens or syringes should be ensured with the patient (Alhindi *et al*., 2020). Special storage requirements should also be ensured with the patient, maintaining unopened insulin vials or cartridges refrigerated and opened ones at room temperature.

Dispensing of warfarin requires verification of the most recent INR test undertaken and ensuring the prescribed dose aligns with the INR range. Pharmacists should review the patient's medication records for any possible interactions that could affect warfarin efficacy and safety. Patients should be encouraged to carry an alert card indicating that they are on warfarin therapy which can be crucial in emergency situations (Jani *et al*., 2021).

In a community pharmacy, the pharmacist has to accept the prescription and checks details such as the patient's date of birth especially for children and whether the

[9] Malta Medicines Authority (MMA). Safety. [Internet] (Malta) MMA;2024 [cited 2024 Jul 25]. Available from: https://medicinesauthority.gov.mt/safety?l=1

prescription is genuine (Azzopardi, 2000). For medications that require additional monitoring such as the high-risk medication, warfarin, supporting documents are required. In a hospital setting, the dispensing process of high-risk medications occurs at a faster pace and is affected by internal and external factors as well as strengths and limitations. Internal factors include the requirement for a new prescription as well as the access to clinical information. External factors could be threats as well as patients' attitudes. Due to heavy workloads, low staff and overcrowding of patients, patient confidentiality and patient-pharmacist relationship is not always supported (Cassar and Serracino-Inglott, 2013).

Trying to reduce risks during the dispensing process of a high-risk medication is an ongoing process. Risk reduction strategies for process entailing high-risk during the dispensing of high-risk medications should be put forward. According to a systematic study carried out by Kallio *et al*., in 2020 to investigate the interventions of community pharmacists to high-risk medication management in Finland, it was found that community pharmacists could reduce medication related risks and improve adherence during dispensing of high-risk medications. Such risks could be reduced by discussing the problem with the patient, by advising the patient to contact the physician where need be and by offering prescription or medication review when needed (Kallio *et al*., 2020). The safe dispensing of high-risk medications such as insulin, warfarin and the direct oral-anticoagulants involves communication with the patient, patient education and continuous monitoring. By adhering to protocols, healthcare professionals and pharmacists can minimise the risk of high-risk medication dispensing errors and improve patient safety and compliance (Aradhya *et al*., 2023).

1.5 Aims and Objectives

The aims were to evaluate whether high-risk medications are treated differently to non-high-risk drugs during the dispensing process and to put forward guidelines to community pharmacists dispensing high-risk medications.

The objectives were:

1) To develop a high-risk documentation sheet to identify the most common high-risk medications being dispensed in five community pharmacies
2) To develop patient interview questions to assess patient knowledge and level of awareness of the high-risk medication being administered
3) To develop guidelines to be disseminated in community pharmacies and to set-up a focus group to validate developed guidelines.

Chapter 2: Methodology

2.1 Research Phase I: Observational Studies and Interviews

In the first research phase, observational studies in five community pharmacies and patient interviews in two community pharmacies were carried out. A 'HiRisk' documentation sheet was developed and validated, and the dispensing of fifty high-risk medication prescriptions throughout the observational studies was carried out. Interview questions were also developed and validated by the same panel. Patient interviews aimed to assess patient knowledge and level of awareness of the high-risk medication being dispensed.

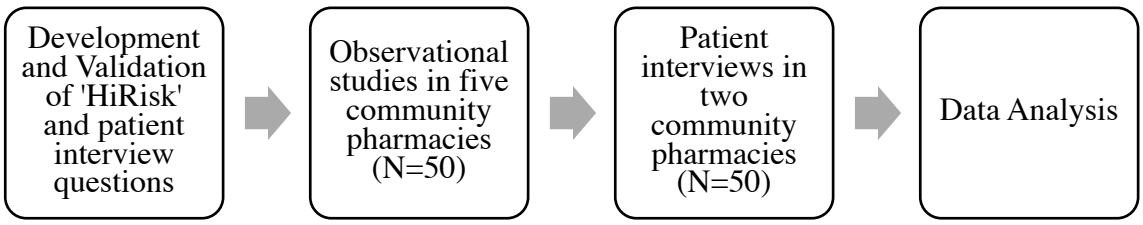


Figure 2. 1 Flowchart showing Phase 1 of the *study*

2.1.1 Development of HiRisk and Observational Studies

A documentation sheet titled 'HiRisk' (Appendix 2) was developed and validated by six experts; four community pharmacists and two general practitioners. The 'HiRisk' tool gathers data such as advice given during the dispensing process in a community pharmacy. Observational studies using the 'HiRisk' tool to assess the frequency of high-risk medication dispensing were carried out in five community pharmacies chosen by random sampling from the five statistical districts in Malta as per the National Statistic Office classification.

The dispensing of the first ten high-risk medication prescriptions from each pharmacy was observed amounting to a total of fifty prescriptions. A 'HiRisk' documentation sheet was filled in for every new prescription received.

The documentation sheet consisted of three main sections as follows:

Section 1: Demographic Data

Section 2: Pharmacists' Review and Advice

Section 3: Patient Issues

Section 1: Demographic Data

This section gathers data about the dispensing of high-risk medication. It includes information whether the pharmacist dispensing the high-risk medication is the managing pharmacist, a locum pharmacist, a pharmacist employed full time or part time. It also highlights the years of practice of the community pharmacist. The tool gathers information of which high-risk medication is being dispensed together with the dose dispensed and the dosage regimen. This section allows the identification of the high-risk medication being most commonly dispensed in community pharmacies.

Section 2: Pharmacists' Review and Advice

The documentation sheet aims to exhibit the communication between the pharmacist dispensing the high-risk medication and the patient receiving the medication. Identification of the patient is important ensuring that the right high-risk medication is being dispensed to the right patient. Rechecking of prescription and information provided as well as ensuring maximum benefit are all tasks carried out together with assessing patient knowledge as it allows for minimization of error and proper prescription

interpretation. This section highlights all necessary information needed for the proper dispensing of high-risk medications. The patient is questioned on the medication being dispensed and if the patient is taking other medications concomitantly with the high-risk medication. This section looks at whether the pharmacist explains to the patient how to administer the medication and the duration of treatment. It gathers how administration information was interpreted to the patient, whether any non-pharmacological advice was offered and whether the pharmacist dispensing the high-risk medication repeated major key points relevant to the high-risk medication being dispensed in relation to the patient.

Section 3: Patient Issues

This section aims to evaluate any adverse drug reactions exhibited by the high-risk medication in question whether allergic, non-allergic or toxic reactions were presented back to the pharmacist after the dispensing of the high-risk medication.

It reports whether any patient being administered a high-risk medication returned to the pharmacy with a presenting complaint associated with the high-risk medication. It also highlights issues related to the self-administration of the high-risk medication such as deliberately skipping doses or patients returning back to the pharmacy to confirm the dosage regimen. The pharmacies were visited during the same time period to allow for better comparison of results.

A review of the literature to identify which high-risk medications would be identified, the management of high-risk medications and their dispensing was carried out. The high-risk medications that were identified and which were referred to in this study are insulin, opioids namely morphine and fentanyl, sedative agents namely zolpidem, warfarin, the

direct oral anticoagulants rivaroxaban and apixaban, heparin, biologics and the disease-modifying antirheumatic drugs (DMARDs) methotrexate and sulphasalazine.

2.1.2 Patient Interviews

Patient interview questions (Appendix 3) in both Maltese and English were developed and validated by the same group of individuals who validated the 'HiRisk' documentation sheet comprising of four community pharmacists and two general practitioners. Ten-minute patient interviews were carried out on a separate cohort of patients in two out of the five community pharmacies, chosen by convenience sampling. Interview questions were composed of eight questions which aimed to assess the knowledge and level of awareness of the high-risk medication the patient was receiving. A total of fifty patient interviews were conducted. The first twenty-five patients being dispensed a high-risk medication, from each pharmacy, were interviewed after written consent was obtained from the pharmacist intermediary.

Private high-risk medication prescriptions presented to the community pharmacist during the observational studies were analysed using the 'HiRisk' developed tool. No patient details were recorded or divulged. Only data pertaining to what drug/s has/have been prescribed and the dose were analysed. Patient interview responses gathered were also thematically analysed.

2.2 Research Phase II: Guidelines

In the second phase of the research, the development of high-risk medication dispensing guidelines was carried out. A focus-group of healthcare professionals comprising of four community pharmacists and four general practitioners assessing the presented guidelines was set up to aid better dispensing processes.

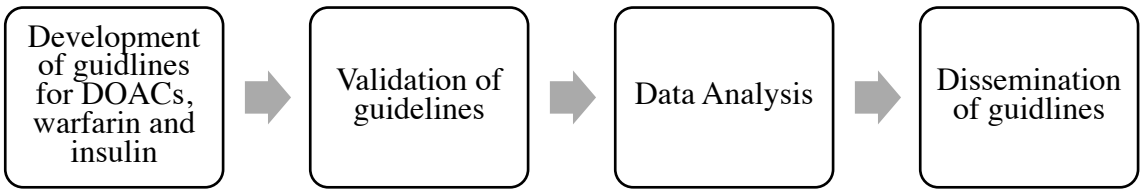


Figure 2. 2 Flowchart showing Phase 2 of the *study*

2.2.1 Development and Validation of Guidelines

The development of guidelines was carried out for four high-risk medications which were most commonly dispensed during the observational studies. These were the direct oral anticoagulants apixaban and rivaroxaban, warfarin and insulin. The guidelines consist of key points relevant to the high-risk medication being dispensed such as side-effects, drug-drug interactions, patient monitoring, patient counselling, information related to patients undergoing surgery and information related to special patient groups such as pregnant or breastfeeding women.

Guidelines to aid the dispensing process of high-risk medications (Appendix 4) were developed through research of current dispensing methods, incorporating advice given by the community pharmacists. Each guideline is adapted to the high-risk medication with special preference to monitoring and administration respectively.

Following the completion of the high-risk medication guidelines, a validation document was compiled to be used for validation purposes. The validation document consisted of questions about whether the guidelines are clear and understandable, if the statements are relevant to the high-risk medication being dispensed, if the developed guidelines are easy to follow and if there are any difficulties in understanding them. The guidelines were presented to a group of healthcare professionals consisting of four general practitioners and four community pharmacists. Participants were also given the opportunity to add any further comments at the end. After completion of the validation process, any suggested changes to the high-risk medication guidelines were made and amended respectively. These guidelines will then be disseminated to community pharmacists dispensing high-risk medications.

Chapter 3: Results

Qualitative and quantitative research results obtained are described in this chapter. Validation of the research tools used throughout the study was carried out. Results of the fifty high-risk medication prescriptions gathered from the 'HiRisk' documentation sheet throughout the observational studies are also presented. Results from the fifty patient interviews and responses gathered during the focus group are also described. The developed guidelines to be disseminated to community pharmacists dispensing high-risk medications are also discussed in this chapter.

3.1 Validation of Research Tools

When research tools are developed, validation of both the HiRisk documentation sheet and the patient interviews is essential ensuring the validity and good quality of the instrument as well as determining its reliability (Elangovan and Sundaravel, 2021). Both the HiRisk documentation sheet and the patient interview questions were well received and established to be clear in relation to the study. All experts from the validation panel suggested that both tools were sufficient. Recommendations regarding changes to the language used in the patient interviews were undertaken due to suggestions that some questions might not be understood by all patients. It was noted that the HiRisk documentation sheet will only be used by the researcher and for this reason development of this tool was done using only the English language.

3.2 Observational Studies Evaluation

In this section, results from the HiRisk documentation sheet developed tool and the patient interviews are presented.

3.2.1 Section 1: Demographic Data

From the 50 observational studies carried out, thirty of the high-risk medications were being dispensed by community pharmacists who have been practising community pharmacy for more than 10 years. Most pharmacists dispensing the high-risk medication were employed as full-time pharmacists. Table 3.1 shows the years of experience of each pharmacist being observed during the observational studies.

Table 3. 1 Pharmacists' Years of Professional Experience (N=50)

Years of Experience	Number of Pharmacists
<2	3
2 – 5	17
6 – 10	0
>10	30

Gathering results from all five community pharmacies, through fifty high-risk medication prescriptions received, the direct oral anticoagulants (n=20) were the most commonly dispensed high-risk medications having presented 13 rivaroxaban prescriptions and 7 apixaban prescriptions. This was closely followed by warfarin (n=11) and insulin (n=7). Table 3.2 shows the number of prescriptions per high-risk medication whilst Table 3.3 shows the most commonly dispensed high-risk medication in each of the five pharmacies. The direct oral anticoagulants were the most commonly dispensed high-risk medications in three community pharmacies whilst warfarin was the most commonly dispensed high-risk medication in the remaining two community pharmacies.

Table 3. 2 Number of prescriptions per high-risk medication

High-Risk Medication	Number of Prescriptions (N=50)
Direct Oral Anticoagulants • Rivaroxaban • Apixaban	20; 13 7
Warfarin	11
Insulin	7
Zolpidem	5
Disease Modifying Antirheumatic Drugs • Methotrexate • Sulphasalazine	 1 1
Biologics	2
Opioids	2
Heparin	1

Table 3. 3 Most commonly dispensed high-risk medication

Pharmacy	High-risk medication most commonly dispensed	Frequency of dispensing (N=10)
1	Warfarin	3
2	Direct oral anticoagulants	3
3	Direct oral anticoagulants	3
4	Warfarin	4
5	Direct oral anticoagulants	3

Warfarin was the most common high-risk medication being dispensed (n=3) in the first community pharmacy. This was closely followed by the direct oral anticoagulant apixaban (n=2) and insulin (n=2) with two prescriptions and rivaroxaban, zolpidem and fentanyl with one prescription each. The direct oral anticoagulant rivaroxaban was the most commonly dispensed high-risk medication (n=3) in the second community pharmacy followed by zolpidem (n=2). Warfarin, apixaban, morphine, heparin and the biologic drug; belimumab all presented with one prescription each. Rivaroxaban was also the most commonly dispensed high-risk medication from the third community pharmacy (n=3), followed by apixaban (n=2) and insulin (n=2) with two prescriptions each. Zolpidem, warfarin and methotrexate each presented with one prescription. Warfarin was the most commonly dispensed high-risk medication (n=4) in the fourth community pharmacy followed by rivaroxaban (n=3), insulin (n=2) and apixaban (n=1) with one prescription each. From the fifth pharmacy, rivaroxaban was the most commonly dispensed high-risk medication (n=3), followed by warfarin with two prescriptions (n=2). Zolpidem, apixaban, insulin, adalimumab and sulphasalazine all presented with one prescription each.

3.2.2 Section 2: Pharmacists' Review and Advice

All (N=50) pharmacists identified the patient and ensured that the prescription being presented is valid. When it comes to assessing patient knowledge, pharmacists (n=46) confirmed with the patient the indication for which the high-risk medication is being dispensed for. Thirty-eight pharmacists did not question if the patient is concomitantly taking other medications however, twelve pharmacists did. Throughout the dispensing process, fourty-one pharmacists explained how the medication should be administered.

Twenty-eight pharmacists explained when to take the medication and 23 explained what the duration of treatment should be. When it comes to the rechecking of prescription, pharmacists (n=49) re-checked the selected medication with the prescription confirming that the right high-risk medication was to be dispensed. All fifty pharmacists interpreted the prescription order by dispensing the exact quantities as prescribed on the prescription and all fifty pharmacists checked the medications expiration date before dispensing. Pharmacists (n=45) dispensed the medication in its original packaging. Three pharmacists dispensed the medication in single blister packs and two dispensed the medication in single blister packs labelled with high-risk medication name, quantity dispensed, expiry date and dosage regimen. No loose high-risk medication was dispensed to the patient. Throughout the dispensing process, pharmacists (n=29) offered verbal advice and administration information to patients.

Fourteen pharmacists (n=14) wrote the dispensing information on the original packaging itself and three pharmacists printed the information on a separate label. Four pharmacists gave their advice both as instructions written on the medication packaging and verbally. All fifty pharmacists double-checked the prescription to minimise dispensing errors. All pharmacists (n=50) advised the patient on proper storage conditions. Patients were advised not to store the medication in direct sunlight, in its original packaging and to store in the refrigerator any medication which requires storage conditions at temperature between 2°C and 8°C such as insulin.

All pharmacists ensured that the patient understood how to administer the high-risk medication. All pharmacists asked whether the patient is experiencing any difficulties

with the high-risk medication and all pharmacists repeated major key points such as the dosage regimen during the dispensing process.

Community pharmacists exhibited good dispensing practices which account for the positive outcome obtained from the observational studies.

3.2.3 Section 3: Patient Issues

No patients returned to the pharmacy presenting with an adverse drug reaction of allergic, non-allergic or toxic origin during the observational studies. All fifty pharmacists ensured that any drug-drug interactions, common side-effects as well as pharmacological and non-pharmacological advice was communicated with the patient during the dispensing of the high-risk medication ensuring patient safety.

3.3 Patient Interviews Evaluation

The aim of the patient interviews was to assess patient knowledge and level of awareness of the high-risk medication that they are being dispensed. Ten-minute interviews were carried out on a separate cohort of patients in two out of the five community pharmacies chosen by convenience sampling. From the fifty patient interviews carried out, 28 interviewees were male and 22 were female.

When it comes to the interviewed patient's level of education responses varied from primary education up until tertiary education. The majority of patients (n=22) had a primary level of education, followed by eighteen patients who had secondary education,

six patients having post-secondary education and four patients having tertiary education. When asked whether the patient knew which high-risk medication is being dispensed and its indication, all fifty patients knew the medication they were being dispensed and for which condition the medication was prescribed for.

Figure 3.1 shows for how long the patient had been taking the high-risk medication. The majority of patients (n=20) had been taking the high-risk medication for a period between one and five years, followed by 12 patients who had been on their high-risk medication between 6 months and 1 year and 10 patients who had been taking their medication for more than five years. Only eight patients had been taking their medication for less than 6 months.

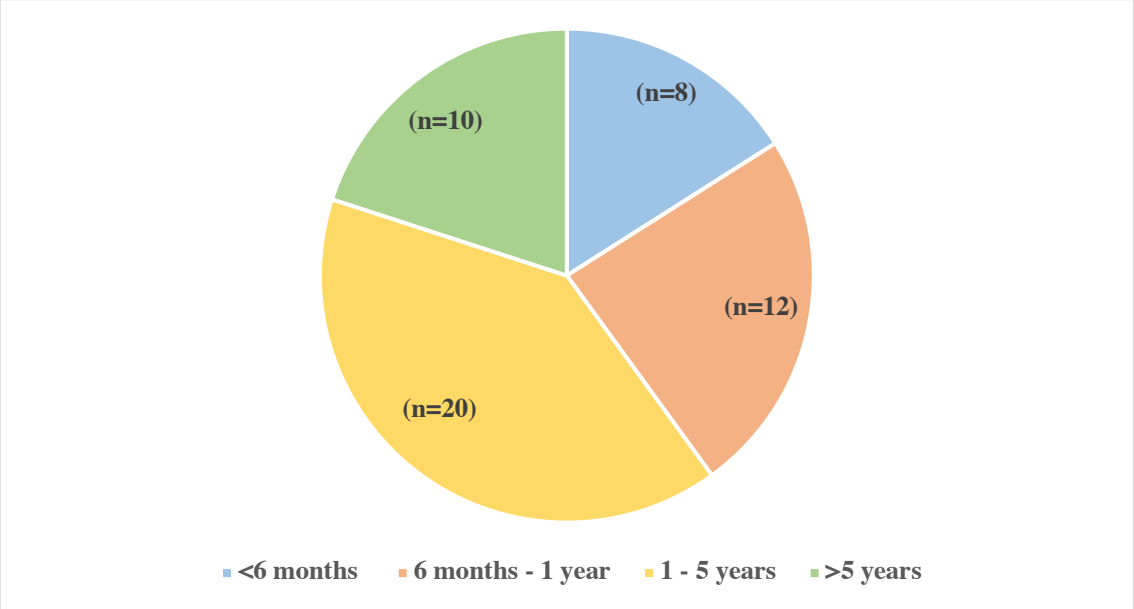


Figure 3. 1 Duration of treatment of the high-risk medication (N=50)

Another question asked throughout the patient interviews was whether the patient ever experienced any side-effect whilst being treated with the high-risk medication. Fourty-six patients (n=46) explained how they never experienced any side-effect. Four patients exhibited side-effects with rivaroxaban, warfarin, zolpidem and insulin at any point during treatment (Table 3.4).

Table 3. 4 Associated side-effect with the High-Risk Medication (N=4)

High-Risk Medication	**Side-Effect and Occurrence**
Rivaroxaban	Bleeding (n=1)
Warfarin	Bleeding (n=1)
Zolpidem	Short-term amnesia (n=1)
Insulin	Blurred vision and confusion (n=1)

Patients communicated that when they experienced side-effects, they referred to their healthcare provider and were frequently being monitoring. Three out of the four patients experiencing side-effects have been on the high-risk medication for a period of more than five years. The other patient had been on the high-risk medication for a period between six months and one year. All four patients explained how side-effects occurred throughout the first weeks of treatment and resolved within weeks.

From all fifty patient interviews carried out, the direct oral anticoagulants were the most commonly prescribed high-risk medication with a total of sixteen patients (Table 3.5).

Table 3. 5 Number of prescriptions per high-risk medication

High-Risk Medication	Number of Patients (N=50)
Direct Oral Anticoagulants	16
Warfarin	13
Zolpidem	11
Insulin	9
Biologics	1

3.4 Focus Group Evaluation

A focus group was set up to evaluate and validate developed guidelines. The focus group consisted of four general practitioners and four community pharmacists. The guidelines were presented together with the guideline's validation form for reviewing and validation. All eight members agreed that the presented guidelines are clear and understandable, and that the advice reflects on the dispensing of the specific high-risk medication. Pharmacists (N=4) also agreed that there were no unnecessary or repetitive statements. Changes to the language used in one statement was amended, due to suggestions from one pharmacist suggesting that the statement might be misunderstood. It was noted that the developed guidelines were to be disseminated to community pharmacists, assuming certain terminology would be understood.

3.5 Guidelines

The guidelines were based on the most commonly observed high-risk medications being dispensed in community pharmacies, namely the direct oral anti-coagulants rivaroxaban and apixaban, warfarin and insulin. Guidelines titled: "Guidelines for Improving Dispensing Procedures and Enhancing Patient Safety" (Appendix 4) were developed. These guidelines were based on existing literature and recommendations put forward by the focus group, ensuring the mentioning of important key points as suggested by the focus group, to avoid errors during the dispensing process.

Chapter 4: Discussion

The aims of this study were to evaluate whether high-risk medications are treated differently to non-high-risk drugs during the dispensing process and to put forward guidelines for community pharmacists dispensing high-risk medications. The drug dispensing process was studied using the 'HiRisk' documentation sheet and through patient interviews. Guidelines to improve the dispensing process and patient safety were developed from existing literature together with the opinions of general practitioners and community pharmacists gathered through the focus group. Findings from both the observational studies carried out using the 'HiRisk' documentation sheet and from patient interviews resulted in the direct anti-coagulants being the most commonly dispensed high-risk medication followed closely by warfarin and insulin. During the observational studies in the five different community pharmacies, positive outcomes were observed. All pharmacists ensured the validity of the prescription and not even one high-risk medication was inappropriately dispensed. Forty-one pharmacists explained to the patient how to take the medication, and instructions were not only given verbally but also labelled on the medication packaging. No loose high-risk medication with no labelling was dispensed during the observational studies which decreases chances or error. Throughout patient interviews, it was noted that all patients being dispensed a high-risk medication knew which medication they were being dispensed and the indication for what it was prescribed.

4.1 Good Dispensing Practices

Good dispensing practices for high-risk medications have several significant benefits. Proper medication dispensing reduces the risk of medication errors such as wrong medication selected, wrong dose or wrong route of administration which can lead to adverse drug reactions (Al-Worafi, 2020). Accurate selection of medication, accurate

dosing, clear labelling and appropriate patient counselling and monitoring ensure that the high-risk medication is taken correctly. Ensuring that the right high-risk medication reaches the patient in the correct form and dose helps in achieving the desired therapeutic outcomes. Proper and effective high-risk medication dispensing can prevent complications and adverse reactions which can lead to hospitalisation (Manias *et al*., 2020). Therefore, effective dispensing lowers healthcare costs and burden on hospital resources.

Patient compliance is increased throughout the dispensing process by pharmacists encouraging proper education and clear instructions on how to take the high-risk medication (Anderson *et al*., 2020). Patient adherence to treatment enhances the overall effectiveness of therapy. Correct dispensing practices also ensure that the patient receives the exact quantity of medication required. This reduces high-risk medication wastage and unnecessary costs associated with excess or incorrect medications (Alhomoud, 2020). Adhering to good dispensing practices when dispensing high-risk medications also helps healthcare providers and pharmacists comply with legal and regulatory requirements. Pharmacists and healthcare professionals who consistently demonstrate good dispensing practices towards the patient build trust and a positive reputation which can enhance their professional standing and patient loyalty (Kentab *et al*., 2024). Educating patients about their medication empowers them to manage their own health better, recognise potential side-effects and possible interactions and increases patient compliance.

The benefits of good dispensing practices for high-risk medications extend beyond patient safety to encompass improved health outcomes, economic savings and enhances professional credibility.

4.2 Handling high-risk medications

Proper handling and dispensing requires various strategies ensuring patient safety upon administration of the medication. Adequate pharmacists' knowledge, training, communication between health care professionals and patient involvement are all vital components involved in the dispensing process (Alanezi *et al*., 2024). The existence of inappropriate high-risk medication drug dispensing indicates that guidelines are not thoroughly followed despite their presence. (Phipps *et al*., 2020). Improper high-risk medication dispensing can also be influenced by external factors such as interruptions and distractions throughout the dispensing process. Previous studies highlighted that one-third of medication errors involving high-risk medications resulted in moderate to severe harm due to miscommunication, lack of knowledge and lack of collaborative approach between health care professionals (Gaitan-Gómez *et al*., 2023). Risk evaluation with high-risk medication dispensing is important to discover ramifications which may impact patient safety and the community pharmacist (Ledlie *et al*., 2023). Evaluating the risk brought by improper high-risk medication drug dispensing in community pharmacies is estimable for determining whether the developed guidelines would be of good purpose.

Insulin is classified as a high-risk medication due to its narrow therapeutic index which can lead to hypoglycaemia (Hölzen *et al*., 2024). Insulin dosing must be precise as too much insulin leads to hypoglycaemia whilst too little can result in hyperglycaemia and ketoacidosis (Besen *et al*., 2023). Being a high-risk medication administered as a subcutaneous injection, proper injection technique must be ensured with the patient preventing lipodystrophy (Özen *et al*., 2020).

Throughout the dispensing process of insulin, pharmacists should ensure that patients are able to recognise symptoms of both hypoglycaemia and hyperglycaemia. Patients being administered insulin should always carry fast-acting glucose tablets to quickly manage these early symptoms. Hyperglycaemia symptoms include polyuria, polydipsia and fatigue (Mohajan and Mohajan, 2023). Patients should increase their insulin dose in episodes of hyperglycaemia. Insulin dosing is also affected by illness, exercise and alcohol intake. Patients should be aware on how to self-adjust insulin doses around their carbohydrate intake and exercise to prevent hypoglycaemia (Chambers *et al*., 2023). Pharmacists should encourage patients to keep logs of their blood glucose readings, insulin doses, meals and physical activity. Self-monitoring of blood glucose levels is an integral part of managing diabetes mellitus. Individualised blood glucose targets should be set to help patients interpret their readings and adjust their insulin dose accordingly. HbA1c testing is also important as it provides a long-term view of blood glucose levels (Pleus *et al*., 2022). Tracking tools should be encouraged for diabetes management. This helps patients track their blood glucose levels, insulin doses as well as dietary intake. Other features such as reminders, trend analysis and online communication with health care providers can be beneficial (Doupis *et al*., 2020).

Medicine reconciliation carried out during the dispensing process of an insulin prescription is important (Marinović *et al*., 2021). Pharmacist intervention in providing patient care by reviewing insulin regimens, identifying potential issues and making recommendations is important. Community pharmacists should be accessible both in-person and via telehealth to provide patient monitoring and counselling, addressing concerns and manage potential drug-drug interactions (Chess-Williams *et al*., 2024).

Gurwitz *et* al., (2021) agreed that handling insulin as a high-risk medication requires a multifaceted approach that includes patient education regarding the high-risk medication, patient monitoring, proper storage and the use of technology. A collaborative approach between prescribers and community pharmacists is essential for 43andomized insulin therapy and ensuring patient safety. By educating patients and providing support, pharmacists can effectively manage insulin therapy and improve outcomes for individuals with diabetes.

Warfarin is classified as a high-risk medication due to its narrow therapeutic index, the necessity for continuous regular monitoring and for its extensive drug and dietary interactions (Habet, 2021). Handling of warfarin requires strategies ensuring patient safety and therapeutic efficacy. Small changes in warfarin dosing can lead to significant deviations in efficacy causing excessive bleeding or insufficient anticoagulation. Warfarin interacts with various medications such as anti-infectives, antiepileptics and certain anti-virals all of which can alter its anticoagulant effect (Mar *et al*., 2022). Leafy green vegetables which are foods high in vitamin K can 43andomized the effect of warfarin. Dietary consistency is of utmost importance and patients need to inform their healthcare providers if there are any changes to diet (Grześk *et al*., 2021). Warfarin can be prescribed for common conditions including atrial fibrillation; reducing the risk of stroke, deep vein thrombosis and pulmonary embolism; two types of venous thrombosis, mechanical heart valve replacement and other hypercoagulable states when anticoagulation is required (Sokolova *et al*., 2022). When switching patient treatment from warfarin to a direct oral anticoagulant, warfarin treatment should be stopped before commencing DOAC treatment reducing the risk of over-anticoagulation and bleeding (Romoli *et al*., 2021).

Strategies for the safe management of warfarin should be practiced by all healthcare professionals including pharmacists ensuring patient safety. Patients on warfarin therapy all have individualised dosing based on their INR values (Fahmi *et al*., 2022). The INR should be frequently monitored to ensure target INR is within range. Dosing is also based on patient-specific factors such as age, renal function, hepatic function and medication history. It is essential that the INR be determined daily or on alternate days in the early days of treatment, then at longer intervals depending on patient response (McRae *et al*., 2021). Doses are adjusted based on INR readings, patient symptoms and changes in diet or medication. Patients should be advised to maintain a consistent intake of vitamin K foods. Pharmacists dispensing warfarin should discuss potential interactions with over-the-counter medications and supplements with the patient.

Educating patients on signs of bleeding is a pharmacist's priority. Healthcare professionals should advise their patients that unusual bleeding, prolonged bleeding, blood in urine or stools as well as nosebleeds should all be reported. Pharmacists should provide patients with instructions on what to do if they experience significant bleeding, including when to seek medical attention.

The direct oral anti-coagulants have improved anticoagulation therapy by offering effective alternatives to Vitamin K antagonists such as warfarin. When compared with warfarin, the direct oral anticoagulants have fewer dietary restrictions and have no routine monitoring requirements (Chen *et al*., 2020). However, they are still associated with significant risks associated with bleeding, renal function and drug-drug interactions.

Rivaroxaban and apixaban were the most commonly dispensed high-risk medications in this research.

Bleeding is the most significant risk with DOAC use. It can include both gastrointestinal bleeding and intracranial bleeding (Benamouzig *et al*., 2022). Pharmacists should advise patients to remain vigilant for signs and symptoms which can include bleeding gums, nosebleeds, blood in urine, blood in stools and coughing or vomiting blood. Patients should stop treatment if severe bleeding occurs and refer immediately to their healthcare provider. Healthcare professionals and pharmacists are also advised about the use of direct acting anticoagulants in renally impaired patients. Since DOACs are partially excreted by the kidneys, impaired renal function can lead to the accumulation of drug and increased bleeding risk (Rogula *et al*., 2022). DOACs should be avoided in patients with severe renal impairment and used with caution in mild to moderate impairment.

Although fewer drug-drug interactions are observed when compared with warfarin, DOACs still have prominent interactions with certain medications which can affect their safety and efficacy. Such medications include antiepileptics, certain antivirals, certain anti-infectives and other anticoagulants (Crawley and Anderson, 2020). Pharmacists should advise patients that missed doses can increase the risk of clotting and bleeding complications therefore, if a dose is missed, it should be administered as soon as remembered on the same day unless it is almost time for the next dose. No double doses can be accounted for missed doses.[10]

[10] NHS Greater Glasgow and Clyde. Direct Oral Anticoagulant (DOAC) Therapy. [Internet] (England) NHS;2023 [cited 2024 Jul 25]. Available from: https://ggcmedicines.org.uk/media/uploads/patient_information/278864_3_0_novel_oral_antic_therapy_web_version.pdf

When starting DOAC therapy, patient-specific factors such as age, body weight and renal function have to be assessed. Baseline assessment of renal function is essential to determine the appropriate dose and ensure patient safety (Smith *et al*., 2021). Periodic follow-up appointments should be carried out to monitor renal function, detect any decline and adjust dose if there is an increased bleeding risk. Pharmacists should encourage patients to adhere to anticoagulant therapy and ensure continuous anticoagulation given the shorter half-lives of direct oral anti-coagulants when compared to warfarin (Dunois, 2021).

Medication reconciliation should be carried out with every DOAC prescription received and at each follow-up appointment to identify any possible problems or drug interactions and ensure that all healthcare providers including pharmacists are aware of the patient's DOAC therapy. Pharmacists should refer patients in case of severe bleeding complications. Knowledge on antidotes and chelators is important when the reversal of anticoagulant effect is required. Andexanet alfa is used in the reversal of apixaban and rivaroxaban in life-threatening uncontrolled bleeding (Rauch *et al*., 2022).

Similarly to the National Safety and Quality Health Service (NSQHS)[11] standards which were developed by the Australian commission on safety and quality in health care, in this study guidelines were developed. These standards provide a "nationally consistent statement of the level of care consumers can expect from health service organisations". Their aims are to protect the public from harm and improve the quality of health services

[11] Australian Commission on Safety and Quality in Health Care. The NSQHS Standards. [Internet] (Australia) NSQHS;2024 [cited 2024 Jun 18]. Available from: https://www.safetyandquality.gov.au/publications-and-resources/resource-library/national-safety-and-quality-health-service-standards-second-edition

provided. One of the developed standards titled 'Medication Safety Standard' ensures that healthcare professionals are competent to prescribe, dispense and administer appropriate medications and to monitor medicines use. Within the standard, with respect to high-risk medicines, the health service organisation should identify the high-risk medications being used and the organisation should have a system in place to properly store, prescribe, dispense and administer high-risk medications in a safely manner.

Publications of updated recommendations for the safe use of high-risk medications is also being promoted by the Ministry of Health of Spain and the department of Health of Catalonia implementing dispensing practices that safeguard the patient. High-risk medication lists should be developed by each centre individually and lists should be updated every two years. From the developed list, the most effective risk reduction methods will be chosen.[12]

In the United States, a drug safety program 'Risk Evaluation and Mitigation Strategy' (REMS)[13] is in place to help ensure that the benefits of the medication outweigh the risks for medications with serious safety concerns. REMS are intended to encourage safe medication use by reinforcing actions and behaviours related to medication use. While all medications have proper labelling disclosing information on medication risks, only selected medications require a REMS. REMS focus on preventing, monitoring and managing risk by educating and reinforcing actions to reduce the occurrence of an event.

[12] Generalitat de Catalunya. Recommendations for the safe use of high-risk medications. [Internet] (Catalunya) Gencat;2023 [cited 2024 Jun 19]. Available from: https://seguretatdelspacients.gencat.cat/en/detalls/noticia/recomanacions-us-segur-medicaments-alt-risc

[13] Food and Drug Administration. Risk Evaluation and Mitigation Strategies (REMS). [Internet] (United States) FDA;2023 [cited 2024 Jun 19]. Available from: https://www.fda.gov/drugs/drug-safety-and-availability/risk-evaluation-and-mitigation-strategies-rems

Black box warnings were implemented in 1979 and these are the strictest labelling requirements that the Food and Drug Administration (FDA) provided (Greiwe *et al*., 2022). These issued warnings ensure to bring to the patient's attention serious and sometimes life-threatening adverse drug reactions. High-risk medications on the market can have a black box added, removed or updated on its packaging. Warfarin, fentanyl, morphine, methotrexate, infliximab, the selective COX-2 inhibitor celecoxib and selective serotonin re-uptake inhibitors (SSRIs) are all examples of medications with boxed warnings.

4.3 Evaluation of risk with improper drug dispensing

Improper drug dispensing can pose significant risks to the patient being administered the high-risk medication, healthcare professionals and the healthcare system. Incorrect drug dispensing can lead to adverse drug reactions which can be of allergic, non-allergic and toxic origin. Adverse drug reactions can also exacerbate existing conditions (Mirza and Khan, 2023). Dispensing the wrong high-risk medications or incorrect dose can render the treatment ineffective or worsen the patient's condition as it can be toxic (Prolay *et al*., 2023). Incorrect drugs can negatively interact with other concomitant medications that the patient is being administered. Interactions are not only present with drugs, however, than can occur also with food. Mislabeling, wrong dosages and wrong administration instruction can all lead to serious health consequences including overdose. Legal and ethical risks are also associated with improper drug dispensing (Malik *et al*., 2021). Pharmacists and healthcare professionals can be held liable for any harm which is caused by improper high-risk medication drug dispensing. Inaccurate dispensing can also result

in professional disciplinary actions including suspension or revocation of licenses. Loss of trust is also an issue (Soubra and Karout, 2021). Patients may lose trust in healthcare providers and the healthcare system, directly affecting the patient-provider relationship and adherence to treatment.

Treating complications that arise from medication errors can be costly. Additional medications, hospitalisations and longer treatment durations all directly affect cost (Mutair *et al*.,2021). Healthcare facilities and pharmacies may suffer reputational damage leading to loss of business and patient confidence. Patients may also experience psychological distress over potential medication errors which impacts their mental well-being (Prentice *et al*., 2020). By addressing risks through preventative strategies and safety protocols, the incidence of improper high-risk medication drug dispensing can be minimised improving the overall healthcare quality.

4.4 Strategies to improve the drug dispensing process

In research conducted by Mohamed *et al*., 2020, in the United Arab Emirates, the most common dispensing errors found included: wrong medication selected, wrong strength, wrong dosage form and wrong quantity of medication dispensed. The least dispensing errors included labelling errors and wrong instructions for drug usage. These dispensing errors occurred in community pharmacies. In another study carried out in community pharmacies in Jordan in 2021, similar drug errors were identified having the wrong drug selected, wrong strength and wrong dosage form as the most commonly observed dispensing errors. Abdel-Qader *et al*., 2021 agree how such dispensing errors are a cause of poor handwriting on prescriptions and heavy workload in the community pharmacy.

Both studies carried out in the United Arab Emirates and in Jordan correlate with having the same dispensing errors.

Koyama *et al*., 2020 suggest that strategies to improve the drug dispensing process is to double-check high-risk medications prescriptions received especially the dose prescribed. Counselling about the high-risk medication indication, verifying any contraindications to the high-risk medication being dispensed and counselling on non-pharmacological monitoring are important. Correct high-risk medication usage and medication adherence counselling is the leading strategy for proper drug dispensing (Santos *et al*., 2022). Another suggestion may include the avoidance of drug abbreviations, specifying the duration of treatment and the indication for which the high-risk medication is being prescribed for (Tariq *et al*., 2020).

Medication reconciliation to identify drug related problems and assess patient's knowledge is an important strategy (Camilleri, 2015). In Thailand, Chiewchantanakit *et al*., 2020, concluded that medication reconciliation lowers the incidence of medication errors among patients in both inpatient and outpatient settings. Medication review is a critical process that involves comparing a patient's current medication regimen to all medications the patient has been taking (Beuscart *et al*., 2021). Reviewing patients' treatment reduces the risk of errors such as medication omission, duplications as well as dosing errors. All medication regimens should be documented. Reviewing a patient's medication during transitions of care helps resolves any discrepancies in medication, promoting continuity of care (Bethishou *et al*., 2020). Seamless transitions between different care settings should be promoted by maintaining consistent and accurate medication information. Patients should also be engaged in their own care by being

involved in their review process which improves their understanding of their medications (Bucknall *et al*., 2020). Medication reconciliation gives an opportunity to pharmacists to make patients aware of their prescribed high-risk medication.

4.4.1 Pharmacist accessibility

Community pharmacists are thought to be one of the most accessible and readily available to patients (Ilardo and Speciale, 2020). The pharmacists' active role in patient care and safety improves the quality of life of the patient (Bethishou, 2024). The proposed guidelines may help pharmacists during the dispensing process and aid to correct for any current or possible problems. Pharmacists can help by utilizing their understanding of high-risk medications. The developed guidelines can help community pharmacists identify any present side-effect or drug-drug interaction and refer patient if the high-risk medication is posing an increased risk of patient harm.

The pharmacist's role is continually progressing despite the idea for simply dispensing medications. Pharmacists have a role in safeguarding patient's safety by re-checking high-risk medication prescriptions, dispense appropriately the high-risk medication indicated for the patient in the correct strength and dosage form as well as provide non-pharmacological advice throughout the dispensing process (Adams and Weaver, 2020). In a study carried out in 2020, it was concluded that the pharmacists' role has evolved throughout time and in community pharmacies nowadays pharmacists have gained the authority to "prescribe, administer and monitor drug therapies" in addition to dispensing (Raiche *et* al., 2020).

If pharmacists use the developed guidelines for proper drug dispensing, it may help in addressing safety concerns such as appropriateness of the high-risk medication. This study is mainly focused on the dispensing process of high-risk medications being carried out in community pharmacies across Malta. It exhibits patient safety from the pharmacist's perspective from when the high-risk medication prescription is received up until the high-risk medication is dispensed, taking into consideration all necessary key points required for proper drug dispensing.

4.4.2 Digitalisation

Another strategy aiding the dispensing process is the retrieval of high-risk medication prescriptions online. Medication errors due to illegible handwriting are eliminated, which is one of the main advantages of electronic prescribing. Electronic health records and e-prescribing systems streamline the dispensing process as well as making it easier to track and manage patient medications. Electronic prescribing is considered to be an important measure to reduce or completely prevent medications errors. Systems can also provide checks for allergies, previous laboratory test results, drug interactions as well as patient medication history.

Technology plays an important role in improving patient safety and improving the drug dispensing process. Better access to medical records and the usage of electronic prescriptions are made possible by computerised systems (Janett and Yeracaris, 2020). Computerised systems may also issue alerts when either the medication is inputted in the system or when a pharmacist comes to dispense the high-risk medication prescribed (Santos *et al*., 2019). Digital systems can reduce medication errors by providing accurate

and up to date patient information. Automation of routine tasks like processing a prescription allows pharmacists to focus more on patient care and on dispensing the correct high-risk medication. Automation will also be advantageous is minimising waste and reducing costs associated with expired or overstocked medications.

Digitilisation also allows for the integration of patient-specific data to provide randomised medication therapy management. It provides tools for patient education, reminders, adherence and monitoring which enhance patient engagement and health outcomes. Digital systems facilitate better communication and data sharing amongst all healthcare professionals leading to a more coordinated and comprehensive patient care. Pharmacists having access to patient medical records is beneficial as it gives pharmacists the opportunity to view patient's history, identify any other medications that the patient is being administered concomitantly with the high-risk medication and it allows for identification of any possible error. Incorporating computerised systems with other interventions can enhance patient safety and drastically decrease improper high-risk medication prescriptions (Santos *et al*., 2019).

4.5 Development and implementation of guidelines

The purpose of the guidelines is to establish standardisation, to establish consistent practices and procedures, ensuring uniformity and reducing variability. The aim of developed guidelines is to promote best practices and evidence-based approaches to enhance the quality of service. They also may provide community pharmacists vital information such as proper drug administration, patient counselling and monitoring when it comes to dispensing common high-risk medications which are frequently prescribed. Guidelines outline optimal ways to perform tasks in an organised manner. They serve as

a valuable resource providing a foundation of knowledge which is necessary for the dispensing process of high-risk medications. The guidelines may help community pharmacists to identify problems such as drug-drug interactions, improper patient administration and improper monitoring involving the high-risk medication. The guidelines will ensure proper drug dispensing information required by the pharmacist throughout the dispensing process of the high-risk medication. They act as a point of reference including information from administration techniques, associated side-effects and drug-drug interactions, patient monitoring and counselling required and miscellaneous information such as procedures to be carried out before surgical procedures and special groups like pregnant women. The guidelines were validated by four community pharmacists and four general practitioners.

The developed guidelines also serve as an educational tool to other healthcare professionals as well as to the public. Patient safety will increase as a result of few high-risk medication errors when pharmacists and other healthcare professionals are aware of the risks associated with inappropriate drug dispensing (Isaacs *et al*., 2021).

4.6 Impact of Study

The study has various implications as it recognises the most common high-risk medications being dispensed in the community pharmacy setting. This study may also act as a motive to increase the awareness associated with medication errors resulting from improper high-risk medication drug dispensing. The implementation of the guidelines developed during the research, to be utilised by community pharmacists may help in improving the dispensing process, increasing patient compliance and of utmost

importance, maximising patient safety by ensuring that pharmacists repeat necessary details during the dispensing process. A key factor in achieving seamless patient care may be by enhancing and changing the dispensing process. Improving pharmacist accessibility by allowing the pharmacist to check for all necessary information required before dispensing a high-risk medication is vital. Having the pharmacist being a point of reference for patients would result in improved patient quality of life (Santos *et al*., 2019). Pharmacists, especially those working in community are the most readily available and accessible to patients. The role of pharmacists to identify errors and practice safe dispensing before the high-risk medication reaches the patient.

The study highlights the importance of not only the dispensing process of high-risk medications by community pharmacists, but it identifies the critical role of the pharmacist. Throughout the dispensing process pharmacists have to be cautious of selecting the appropriate high-risk medication for the patient, safeguarding the patient's safety through appropriate dispensing. This study may also affect other healthcare professionals apart from community pharmacists such as the prescribing physicians. Pharmacist education is crucial in keeping up with the advancements of medications, supporting public health and in the research and development sector. Proper trained pharmacists are well equipped to provide comprehensive medication management, identifying and resolving medication relates problems and support chronic diseases. Pharmacists contribute to public health initiatives such as vaccination programmes, health screenings and patient education on preventative healthcare measures. Pharmacists' knowledge enables pharmacists to effectively collaborate with other healthcare professionals ensuring an integrated and coordinated care for patients. Ongoing education supports pharmacists' professional growth, career advancement, and fulfilment. Proper

education empowers pharmacists to fulfil their roles as medication experts and integral members of the healthcare team.

4.7 Limitations of the Study

Observational study bias was a noticeable limitation. This could have resulted from the pharmacist's attitudes throughout the dispensing process knowing that the process was being observed.

The choice of the pharmacists being observed was based on those working in the five community pharmacies chosen by random sampling. The pharmacies that participated in the observational studies did not take into account community pharmacies in Gozo as they were all pharmacies based in Malta.

A limitation of the study includes a small sample size, in terms of number of prescriptions observed during the observational studies as well as the number of interviews collected from the two pharmacies. With fewer participants, the ability to detect a true effect diminishes. Conclusions derived from a small sample size have wider confidence intervals, making them less precise and more variable. Small samples are more susceptible to sampling bias, where the sample may not accurately represent the broader population.

Regarding patient interviews, response bias, recall bias, lack of self-awareness and misinterpretation of questions were all limitations associated with self-reporting. Patients could have responded to provide socially desirable answers rather than their true thoughts

and behaviours. Patients might not have accurately remembered experiences leading to inaccurate or incomplete data throughout the patient interviews. The information gathered throughout the interviews was solely based on patient memory and self-reporting.

4.8 Recommendations for Future Studies

The aims of the research were to identify whether high-risk medications are treated differently to non-high-risk drugs during dispensing and to develop guidelines for high-risk medication drug dispensing. Suggestions to reduce medication errors throughout the dispensing process included digitalisation of prescriptions and the use of developed guidelines to ensure proper drug dispensing. Once the developed guidelines are implemented in community pharmacies, safer dispensing practices are expected with regards to patient monitoring and counselling, drug-drug interactions and proper administration with regards to strength and dosage form. Suggestions to evaluate the dispensing process after guideline dissemination is also a recommendation, observing any improvements in the dispensing process in community pharmacies. It is a possibility that future research on increasing pharmacist accessibility could pave the way for pharmacist prescribing high-risk medication prescriptions.

An increase in the number of prescriptions studied and an increase in the number of patient interviews carried out can also result in more accurate results. Other high-risk medications fit for this research can also be studied.

Further research about the dispensing process in a hospital setting rather than in community pharmacies may help identify errors throughout the dispensing process of the

high-risk medications and expand the need for the developed guidelines to be used in hospitals and public health centers, apart from private community pharmacies.

4.9 Conclusion

This research reviewed the dispensing process of high-risk medication when compared to the dispensing process of non-high-risk medications. Guidelines for improving the dispensing process and enhancing patient safety were developed by evaluating dispensing processes throughout the observational studies. Patient interviews carried out also identified the most common high-risk medication dispensed and gathered feedback from patients being administered high-risk medication.

Guidelines developed for this research may help fill in gaps in the dispensing process in both the public and private sector by allowing pharmacists to look for key points when dispensing high-risk medications. The guidelines will potentially serve as a tool in improving pharmacist accessibility, since pharmacists can work within a multidisciplinary team to identify errors throughout the dispensing process and enhance patient safety.

References

Abdel-Qader DH, Al Meslamani AZ, Lewis PJ, Hamadi S. Incidence, nature, severity, and causes of dispensing errors in community pharmacies in Jordan. International Journal of Clinical Pharmacy. 2021;43:165-173. Doi: 10.1007/s11096-020-01126-w.

Adami G, Saag KG, Chapurlat RD, Guañabens N, Haugeberg G, Lems WF et al. balancing benefits and risks in the era of biologics. Therapeutic Advances in Musculoskeletal Disease. 2019;11:1-6. Doi: 10.1177/1759720X19883973.

Adams AJ, Weaver KK. Pharmacists' patient care process: State "Scope of Practoce" priorities for action. Annals of Pharmacotherapy. 2020;55(4). Doi: 10.1177/1060028020950193.

Advinha AM, Nunes A, de Barros CT, Lopes MJ, de Oliveira-Martins S. Key factors of the functional ability of older people to self-manage medications. Scientific Reports. 2021;11:22196. Doi: 10.1038/s41598-021-01434-9.

Afzal A, Zaidi SYR, Merchand HA, Babar ZUD, Hasan SS. Prescribing trends of oral anticoagulants in England over the last decade: a focus on new and old drugs and adverse events reporting. Journal of Thrombosis and Thrombolysis. 2021;52(2):646-653. Doi: 10.1007/s11239-021-02416-4.

Al Mutair A, Alhumaid S, Shamsan A, Zaidi ARZ, Al Mohaini M, Al Mutairi A et al. The Effective Strategies to Avoid Medication Errors and Improving Reporting Systems. Medicines. 2021;8:46. Doi: 10.3390/medicines8090046.

Al-Worafi YM. Chapter 6- Medication errors. Drug Safety in Developing Countries. 2020;59-71. Doi: 10.1016/B978-0-12-819837-7.00006-6.

Alanezi HJ, Alenazi OJ, Sudi Alhazmi NA, Alanazi WJ, Alshammari SF, Awad Alhazmi AM. Safe handling and administration of high-risk medications a nursing perspective. Neuropsychopharmacologia Hungarica. 2024;22(2):26-32.

Aldhwaihi K, Schifano F, Pezzolesi C, Umaru N. A systematic review of the nature of dispensing errors in hospital pharmacies. Integrated Pharmacy Research and Practice. 2016;5:1-10. Doi: 10.2147/IPRP.S95733.

Aldosari H, Alsairafi Z, Waheedi S. Continuing education in pharmacy: A cross-sectional study exploring pharmacists' attitudes and perceptions. Saudi Pharmaceutical Journal. 2020;28(7):803-813. Doi: 10.1016/j.jsps.2020.05.008.

Alhindi Y, Sharaf S, Almeflahi A, Felemban R, Hamza E, Aljehani A et al. Investigating the effect of pharmacist eduational intervention of the proper use of insulin pen in older patients with Type 2 Diabetes Mellitus in primary health care and diabetic centres in Makkah Al-Mukarramah, Saudi Arabia. Indian Journal of Public Health Research and Development. 2020. Doi: 10.37506/IJPHRD.V11I12.13235.

Alhoumoud F. “Don’t Let Medicines Go to Waste”—A Survey-Based Cross-Sectional Study of Pharmacists’ Waste-Reducing Activities Across Gulf Cooperation Council Countries. Frontiers in Pharmacology. 2020;11:1334. Doi: 10.3389/fphar.2020.01334.

Aljabari S, Kadhim Z. Common Barriers to Reporting Medical Errors. The Scientific World Journal. 2021;1:6494889. Doi:10.1155/2021/6494889.

Alkattan, A.; Alsalameen, E.; Ahmed, A. Central Nervous System Depressant Drugs: Updated Review. Preprints 2021;2021010503. Doi: 10.20944/preprints202101.0503.v1.

Alsaloom MS, Alsaloom HA, Alsaloom HA, Humayyin MM, Lasloum MJ, Lsloom DN, et al. Enhancing Medication Safety through the Implementation of a Double Check System: Strategies, Benefits and Challenges. Advances in Clinical and Experimental Medicine. 2022;9(4).

Amari DT, Juday T, Frech FH, Wang W, Wu Z, Atkins Jr N et al. Falls, healthcare resources and costs in older adults with insomnia treated with zolpidem, trazodone, or benzodiazepines. BMC Geriatrics. 2022;22(484). Doi: 10.1186/s12877-022-03165-6.

Anderson LJ, Nuckols TK, Coles C, Le MM, Schnipper JL, Shane R et al. A systematic overview of systematic reviews evaluating medication adherence interventions. American Journal of Health-System Pharmacy. 2020;77(2):138-147. Doi: 10.1093/ajhp/zxz284.

Aradhya PJ, Ravi R, Subhash Chandra BJ, Ramesh M, Chalasani SH. Assessment of Medication Safety Incidents Associated with High-alert Medication Use in Intensive Care Setting: A Clinical Pharmacist Approach. Indian Journal of Critical Care Medicine. 2023;27(12): 917–922. Doi: 10.5005/jp-journals-10071-24588.

Assiri GA, Shebl NA, Mahmoud MA, Aloudah N, Grant E, Aljadhey H et al. What is the epidemiology of medication errors, error-related adverse events and risk factors for errors in adults managed in community care contexts? A systematic review of the international literature. BMJ Open 2018;8:e019101. Doi:10.1136/ bmjopen-2017-019101.

Avery AJ, Rodgers S, Cantrill JA, Armstrong A, Cresswell K, Eden M, et al. A pharmacist-led information technology intervention for medication errors (PINCER): A multicentre, cluster 62andomized, controlled trial and cost-effectiveness analysis. Lancet. 2012;379(9823):1310–9. Doi: 10.1016/S0140-6736(11)61817-5.

Ayoub NM, Jibreel M, Nuseir K, Al-Taani GM. A Survey of Knowledge and Barriers of Healthcare Professionals toward Opioid Analgesics in Cancer Pain Management. International Journal of Clinical Practice. 2022;1:1136430. Doi: 10.1155/2022/1136430.

Azzopardi LM. Validation instruments for community pharmacy: Pharmaceutical Care for the Third Millennium. Binghamton: Pharmaceutical Products Press®; 2000.

Benamouzig R, Guenoun M, Deutsch D, Fauchier L. Review Article: Gastrointestinal Bleeding Risk with Direct Oral Anticoagulants. Cardiovascular Drugs and Therapy. 2022;36:973-989. Doi: 10.1007/s10557-021-07211-0.

Besen BAMP, Ranzani OT, Singer M. Management of diabetic ketoacidosis. Intensive Care Medicine. 2023;46:95-98. Doi: 10.1007/s00134-022-06894-9.

Bethishou L, Herzik K, Fang N, Abdo C, Tomaszewski DM. The impact of the pharmacist on continuity of care during transitions of care: A systematic review. Journal of the American Pharmacists Association. 2020;60(1):167-177. Doi: 10.1016/j.japh.2019.06.020.

Bethishou L. The Role of Pharmacy in Supporting Safe and Effective Transitions of Care. Calif Pharmacy. 2024;71(2):23-33. Doi: 10.37901/cpha24-04.

Beuscart JB, Pelayo S, Robert L, Thevelin S, Marien S, Dalleur O. Medication review and reconciliation in older adults. European Geriatric Medicine. 2021;12:499-507. Doi: 10.1007/s41999-021-00449-9.

Bucknall TK, Hutchinson AM, Botti M, McTier L, Rawson H, Hitch D, et al. Engaging patients and families in communication across transitions of care: An integrative review. Patient Education and Counseling. 2020;103(6);1104-1117. Doi: 10.1016/j.pec.2020.01.017.

Burn J, Pirmohamed M. Direct oral anticoagulants versus warfarin: is new always better than the old?. Open Heart. 2018;5:e000712. Doi:10.1136/ openhrt-2017-000712.

Camilleri M, Azzopardi LM, Serracino-Inglott, A. Patient benefit of a medicines use review service. Poster session presented at the Nordic Social Pharmacy and Health Services Research Conference & The Nordic Networking Group for Clinical Pharmacy, Tartu, Estonia. 2015.

Cassar K, Serracino-Inglott A. Clinical analysis of the dispensing process at Mater Dei Hospital. Journal of Euromed Pharmacy. 2013; 8-11.

Cerqueira-Santos A, Santos Rocha KS, de Araújo DCSA, de Souza EV, Santos Caxico Vieira LJ, dos Santos SNP et al. Perception of community pharmacists about the work process of drug dispensing: a cross-sectional survey study. BMC Health Services Research. 2022;22:161. Doi: 10.1186/s12913-022-07528-y.

Chambers A, Mackay D, Farnsworth K, Morrisson AE, Witteman HO, Senior P. Do-It-Yourself Automated Insulin Delivery: A Health-care Practitioner User's Guide. Canadian Journal of Diabetes. 2023;47(5):389-397. Doi:10.1016/j.jcjd.2023.06.001.

Chen A, Stecker E, A Warden B. Direct Oral Anticoagulant Use: A Practical Guide to Common Clinical Challenges. Journal of the American Heart Association. 2020;9(13):e017559. Doi: 10.1161/JAHA.120.017559.

Chess-Williams LM, Broadbent AM, Hattingh L. Cross-sectional study to evaluate patients' medication management with a new model of care: incorporating a pharmacist into a community specialist palliative care telehealth service. BMC Palliative Care. 2024;23:172. Doi: 10.1186/s12904-024-01508-1.

Chia PA, Cannesson M, Myo Bui CC. Opioid free anesthesia: feasible? Current Opinion Anesthesiol. 2020;33(4):512-517. Doi: 10.1097/ACO.0000000000000878.

Chiewchantanakit D, Meakchai A, Pituchaturont N, Dilokthornsakul P, Dhippayom T. The effectiveness of medication reconciliation to prevent medication error: A systematic review and meta-analysis. Research in Social and Administrative Pharmacy. 2020;16(7):886-894.

Crawley RM, Anderson RL. Prevention and Treatment of Bleeding with Direct Oral Anticoagulants. Drugs. 2020;80:1293-1208. Doi: 10.1007/s40265-020-01345-5.

De Lemos J, Loewen P, Nagle C, McKenzie R, Dong You Y, Dabu A et al. Preventable adverse drug events causing hospitalisation: identifying root causes and developing a surveillance and learning system at an urban community hospital, a cross-sectional observational study. BMJ Open Quality. 2021;10:e001161. Doi: 10.1136/ bmjoq-2020-001161.

Dos Santos NS, Marengo LL, da Silva Moraes F, Barberato-Filho S. Interventions to reduce the prescription of inappropriate medicines in older patients. Revista de Saúde Pública. 2019;53:7. Doi: 10.11606/S1518-8787.2019053000781.

Doupis J, Festas G, Tsilivigos C, Efthymiou V. Smartphone-Based Technology in Diabetes Management. Diabetes Therapy. 2020;11:607-619. Doi: 10.1007/s13300-020-00768-3.

Dreischulte T, Guthrie B. High-risk prescribing and monitoring in primary care: how common is it, and how can it be improved? Therapeutic Advances in Drug Safety. 2012;3(4):175-184. Doi: 10.1177/ 2042098612444867.

Dumitrescu I, Casteels M, De Vliegher K, Dilles T. High-risk medication in community care: a scoping review. European Journal of Clinical Pharmacology2020;76:623-638. Doi: 10.1007/s00228-020-02838-8.

Dunois C. Laboratory Monitoring of Direct Oral Anticoagulants (DOACs). Biomedicines. 2021;9:445. Doi: 10.3390/biomedicines9050445.

Edinoff AN, Wu N, Ghaffar YT, Prejean R, Gremillion R, Cogburn M et al. Zolpidem: Efficacy and Side Effects for Insomnia. Health Psychology Research. 2021;9(1). Doi: 10.52965/001c.24927.

Elangovan N, Sundaravel E. Method of preparing a document for survey instrument validation by experts. MethodsX. 2021;8:101326. Doi: 10.1016/j.mex.2021.101326.

Enz S, Hall ACG, Williams KK. The Myth of Multitasking and What It Means for Future Pharmacists. American Journal of Pharmaceutical Education. 2021; 85(10):8267. Doi: 10.5688/ajpe8267.

Fahmi AM, Elewa H, El Jilany I. Warfarin dosing strategies evolution and its progress in the era of precision medicine, a narrative review. International Journal of Clinical Pharmacy 2022;44(3):599–607. Doi: 10.1007/s11096-022-01386-8.

Gaitan-Gómez OL, Bueno-Robles LS, Camargo-Figuera FA, Regina-Secoli S. Interruptions and distractions during the preparation and administration of high-risk medications: A cross-sectional study. Revista de Enfermagem Referência. 2024;6(3): e31983. Doi: 10.12707/RVI23.83.31983.

Gates PJ, Hardie RA, Raban MZ, Li L, Westbrook JI. How effective are electronic medication systems in reducing medication error rates and associated harm among hospital inpatients? A systematic review and meta-analysis. Journal of the American Medical Informatics Association. 2021;28(1):167-177. Doi: 10.1093/jamia/ocaa230.

Gogazeh E. Dispensing errors and self-medication practice observed by community pharmacists in Jordan. Saudi Pharmaceutical Journal. 2020;28(3):233-237. Doi: 10.1016/j.jsps.2020.01.001.

Goode JV, Owen J, Page A, Gatewood S. Community-Based Pharmacy Practice Innovation and the Role of the Community-Based Pharmacist Practitioner in the United States. Pharmacy. 2019;7:106. Doi: 10.3390/pharmacy7030106.

Greiwe J, Honsinger R, Hvisdas C, Chu DK, Lang DM, Nicklas R et al. Boxed Warnings and Off-Label Use of Allergy Medications: Risks, Benefits, and Shared Decision Making. The Journal of Allergy and Clinical Immunology: In Practice. 2022;10(12):3057-3063. Doi: 10.1016/j.jaip.2022.08.033

Grześk G, Rogowicz D, Wołowiec Ł, Ratajczak A, Gilewski W, Chudzińska M et al. The Clinical Significance of Drug–Food Interactions of Direct Oral Anticoagulants. International Journal of Molecular Sciences. 2021;22:8531. Doi: 10.3390/ijms22168531.

Gurwitz JH, Kapoor A, Garber L, Mazor KM, Wagner J, Cutrona SL et al. Effect of a multifaceted clinical pharmacist intervention on medication safety after hospitalization in persons prescribed high risk medications. A randomized clinical trial. JAMA Internal Medicine. 2021;181(5):610-618. Doi: 10.1001/jamainternmed.2020.9285.

Gustafsson M, Matos C, Joaquim J, Scholl J, van Hunsel F. Adverse Drug Reactions to Opioids: A Study in a National Pharmacovigilance Database. Drug Safety. 2023;46:1133-1148. Doi: 10.1007/s40264-023-01351-y.

Habet S. Narrow Therapeutic Index drugs: clinical pharmacology perspective. Journal of Pharmacy and Pharmacology. 2021;73:1285-1291. Doi: 10.1093/jpp/rgab102.

Hanni C, Petrovich E, Ali M, Gibson W, Giuliano C, Holzhausen J et al. Outcomes associated with apixaban vs warfarin in patients with renal dysfunction. Blood advances. 2020;4(11):2366-2371. Doi: 10.1182/bloodadvances.2019000972.

Hölzen L, Schultes B, Meyhöfer SM, Mayhöfer S. Hypoglycemia Unawareness—A Review on Pathophysiology and Clinical Implications. Biomedicines. 2024;12(2):391. Doi: 10.3390/biomedicines12020391.

Ilardo ML, Speciale A. The Community Pharmacist: Perceived Barriers and Patient-Centered Care Communication. International Journal of Environmental Research and Public Health. 2020;17(2):536. Doi: 10.3390/ijerph17020536.

Isaacs AN, Ch'ng K, Delhiwale N, Taylor K, Kent B, Raymond A. Hospital medication errors: a cross-sectional study. International Journal for Quality in Health Care. 2020;1-6. Doi: 10.1093/intqhc/mzaa136.

Janett RS, Yeracaris PP. Electronic Medical Records in the American Health System: challenges and lessons learned. Ciência & saúde coletiva. 2020;25(4):1293-1304. Doi: 10.1590/1413-81232020254.28922019.

Janež A, Guja C, Mitrakou A, Lalic N, Tankoca T, Czupryniak et al. Insulin Therapy in Adults with Type 1 Diabetes Mellitus: a Narrative Review. Diabetes Therapy. 2020;11:387-409. Doi: 10.1007/s13300-019-00743-7.

Jani YH, Hirani B, Livingstone C. Evaluation of patients' knowledge about oral anticoagulant medicines and use of alert cards by community pharmacists. International Journal of Clinical Pharmacy. 2021;43:203–211. Doi: 10.1007/s11096-020-01134-w.

Jermini M, Fonzo-Christe C, Blondon K, Milaire C, Stirnemann J, Bonnabry P et al. Financial impact on medication reviews by clinical pharmacists to reduce in-hospital adverse drug events: a return-on-incestment analysis. International Journal of Clinical Pharmacy. 2024;46:496-505.

Kallio S, Skola T, Pohjanoksa-Mäntylä M, Airaksinen M. Medication Risk Management in Routine Dispensing in Community Pharmacies. International Journal of Environmental Research and Public Health. 2020;17:8186. Doi: 10.3390/ijerph17218186.

Kentab, BY, Barry HE, Al-Aqeel SA, Hughes CM. Improving medication dispensing and counselling for patients with vision impairment: a qualitative study of pharmacist-reported barriers and facilitators. BMC Health Services Research. 2024;24:534. Doi: 10.1186/s12913-024-11009-9.

Khalil H, Huang C. Adverse drug reactions in primary care: a scoping review. BMC Health Services Research. 2020;20:5. Doi: 10.1186/s12913-019-4651-7.

Koeck JA, Young NJ, Kontny U, Orlikowsky T, Bassler D, Eisert A. Interventions to Reduce Medication Dispensing, Administration, and Monitoring Errors in Pediatric Professional Healthcare Settings: A Systematic Review. Frontiers in Pediatrics. 2021;9:633064. Doi: 10.3389/fped.2021.633064.

Koyama AK, Sheridan Maddox CS, Li L, Bucknall T, Westbrook JI. Effectiveness of double checking to reduce medication administration errors: a systematic review. BMJ Quality and Safety. 2020;29:595-603. Doi: 10.1136/bmjqs-2019-009552.

Kvarnström K, Westerholm A, Airaksinen M, Liira H. Factors Contributing to Medication Adherence in Patients with a Chronic Condition: A Scoping Review of Qualitative Research. Pharmaceutics. 2021;13(7):1100. Doi: 10.3390/pharmaceutics13071100.

Ledlie S, Gomes T, Dolovich L, Bailey C, Lallani S, Frigault DS et al. Medication errors in community pharmacies: Evaluation of a standardized safety program. Exploratory Research in Clinical and Social Pharmacy. 2023;9:100218. Doi: 10.1016/j.rcsop.2022.100218.

Levy HB. Maybe It's Your Medications: How to Avoid Unnecessary Drug Therapy and Adverse Drug Reactions. USA: Skyhorse Publishing; 2023.

Lucatelli P, De Rubeis G, Citone M, Lucarelli NM, Pasqualini V, Sturiale M et al. Heparin-Related Major Bleeding in Covid-19-Positive Patient: Perspective from the Outbreak. Cardiovascular and Interventional Radiology. 2020;42:1216-1217. Doi: 10.1007/s00270-020-02532-3.

Ma Z, Cheng G, Wang P, Khalighi B, Khalighi K. clinical Model for predicting Warfarin Sensitivity. Scientific Reports. 2019;9:12856. Doi: 10.1038/s41598-019-49329-0.

Malik F, Shah S, Shah SMM. The Role of Drug Regulatory Authority in Ethical Promotion of Pharmaceuticals in Pakistan: A Grounded Theory Study. City University Research Journal. 2021;11(1):209-228.

Manias E, Kusljic S, Wu A. Interventions to reduce medication errors in adult medical and surgical settings: a systematic review. Therapeutic Advances in Drug Safety. 2020;11:1-29. Doi:10.1177/2042098620968309.

Mar PL, Gopinathannair R, Gengler BE, Chung MK, Perez A, Dukes J et al. Drug Interactions Affecting Oral Anticoagulant Use. Circulation, Arrhythmia and Electrophysiology. 2022;15(6):e007956. Doi: 10.1161/CIRCEP.121.007956.

Marinović I, Vrca VB, Samardžić I, Marušić S, Grgurević I, Papić I et al. Impact of an integrated medication reconciliation model led by a hospital clinical pharmacist on the reduction of post discharge unintentional discrepancies. Journal of Clinical Pharmacy and Therapeutics. 2021;46(5):1326-1333. Doi: 10.1111/jcpt.13431.

Mason A, Lockard G, Cantrell V, Li SP, Patel K, Klein S, et al. Drug Dose and Therapy Individualization. Recent Advances in Therapeutic Drug Monitoring and Clinical Toxicology. 2022;285-301. Doi: 10.1007/978-3-031-12398-6_17.

McRae HL, Militello L, Refaai MA. Updates in Anticoagulation Therapy Monitoring. Biomedicines. 2021;9:262. Doi: 10.3390/biomedicines90302.

Menon NK, Shanafelt TD, Sinsky CA, Linzer M, Carlasare L, Brady KJS et al. Association of Physician Burnout With Suicidal Ideation and Medical Errors. JAMA Network Open. 2020;3(12):e2028780. Doi: 10.1001/jamanetworkopen.2020.28780.

Mercer K, Carter C, Burns C, Tennant R, Guirguis L, Grindrod K. Including the Reason for Use on Prescriptions Sent to Pharmacists: Scoping Review. JMIR Human Factors. 2021;8(4):e22325. Doi: 10.2196/22325.

Mirza S, Khan M. Dispensing errors turning into diseases: Pharmacists perspective. Comiogenic: A Novel Disease. 2023.

Mohajan D, Mohajan HK. Hyperglycaemia Among Diabetes Patients: A Preventive Approach. Innovation in Science and Technology. 2023;2(6). Doi: 10.56397/IST.2023.11.05.

Mohamed OI, Ibrahim RM, Al Meslamani AZ, Al Mazrouei A. Dispensing errors in community pharmacies in the United Arab Emirates: investigating incidence, types, severity, and causes. Pharmacy Practice. 2020;18(4):2111. Doi: 10.18549/PharmPract.2020.4.2111.

Montandon G. Chapter 12 – The pathophysiology of opioid-induced respiratory depression. Handbook of Clinical Neurology. 2022;188:339-355. Doi: 10.1016/B978-0-323-91534-2.00003-5.

Montané E, Santesmases J. Adverse drug reactions. Medicina Clinica. 2020;154(5):178-184. Doi: 10.1016/j.medcle.2019.08.005.

Nagappa AN, Naik V. Patients: Gaps in Knowledge, Medication Errors, and Their Impact on Outcomes, Quality of Life, and Cost of Treatments. 2022. Doi: 10.1007/978-981-16-9213-0_4.

Nicholson KM, Hellman D. Opioid Prescribing and the Ethical Duty to Do No Harm. American Journal of Law & Medicine. 2020;46:297-310. Doi: 10.1177/0098858820933500.

Özen S, Akinci B, Oral EA. Current Diagnosis, Treatment and Clinical Challenges in the Management of Lipodystrophy Syndromes in Children and Young People. Journal of Clinical Research in Pediatric Endocrinology. 2020;12(1):17-28. Doi: 10.4274/jcrpe.galenos.2019.2019.0124.

Papamichael K, Vogelzang EH, Lambert J, Wolbink G, Cheifetz AS. Therapeutic drug monitoring with biologic agents in immune mediated inflammatory diseases. Expert Review of Clinical Immunology. 2019;15(8):837-848. Doi: 10.1080/1744666X.2019.1630273.

Paulino E, Thomas D, Huey Lee SW, Cooper JC. Dispensing Process, Medication Reconciliation, Patient Counseling, and Medication Adherence. Clinical Pharmacy Education, Practice and Research. 2019;109-120. Doi: 10.1016/B978-0-12-814276-9.00008-8.

Petrovic M, O'Mahony D, Cherubini A. Inappropriate prescribing: hazards and solutions. Age and Ageing. 2022;51(2):afab269. Doi: 10.1093/ageing/afab269.

Phipps D, Ashour A, Riste L, Lewis P, Ashcroft D. Understanding dispensing errors and risk. The Pharmaceutical Journal. 2020;305:7943. Doi:10.1211/PJ.2020.20208528.

Piovani D, Danese S, Peyrin-Biroulet L, Nikolopoulos GK, Bonovas S. Systematic review with meta-analysis: biologics and risk of infection or cancer in elderly patients with inflammatory bowel disease. Aliment Pharmacology and Therapeutics. 2020;51(9):820-830. Doi: 10.1111/apt.15692.

Pleus S, Freckmann G, Schaeur S, Heinemann L, Ziegler R, Ji L et al. Self-Monitoring of Blood Glucose as an Integral Part in the Management of People with Type 2 Diabetes Mellitus. Diabetes Therapy. 2022;13:829-846. Doi: 10.1007/s13300-022-01254-8.

Prentice JC, Bell SK, Thomas EJ, Schneider EC, Weingart SN, Weissman JS et al. Association of open communication and the emotional and behavioural impact of medical error on patients and families: state-wide cross- sectional survey. BMJ Quality and Safety. 2020;29:883-894. Doi: 10.1136/bmjqs-2019-010367.

Qiu M, Huang S, Luo C, Wu Z, Liang B, Huang H et al. Pharmacological and clinical application of heparin progress: An essential drug for modern medicine. Biomedicine & Pharmacotherapy. 2021;139:111561. Doi: 10.1016/j.biopha.2021.111561.

Qudah B, Thakur T, Chewning B. Factors influencing patient participation in medication counseling at the community pharmacy: A systematic review. Research in Social and Administrative Pharmacy. 2021;17(11):1863-1876. Doi: 10.1016/j.sapharm.2021.03.005.

Rafferty A, Denslow S, Michalets EL. Pharmacist-provided medication management in interdisciplinary transitions in a community hospital (PMIT). The Annals of Pharmacotherapy. 2016;50(8):649-655. Doi:10.1177/1060028016653139.

Raiche T, Pammett R, Dattani S, Dolovich L, Hamilton K, Kennie-Kaulbach N, et al. Community pharmacists' evolving rold in Canadian Primary Health Care: A Vision of Harmonization in a patchwork system. Pharmacy Practice. 2020;18(4):2171. Doi: 10.18549/pharmpract.2020.4.2171.

Rauch S, Müller HP, Dreyhaupt J, Ludolph AC, Kassubek J, Althaus K. Andexanet Alfa for Reversal of Factor Xa Inhibitors in Intracranial Hemorrhage: Observational Cohort Study. Journal of Clinical Medicine. 2022;11:3399. Doi: 10.3390/jcm11123399.

Reiner G, Pierce SL, Flynn J. Wrong drug and wrong dose dispensing errors identified in pharmacist professional liability claims. Journal of the American Pharmacists Association. 2020;60(5):50-56. Doi: 10.1016/j.japh.2020.02.027.

Rogula S, Gasecka A, Mazurek T, Navarese EP, Szarpal L, Filipiak KJ. Safety and Efficacy of DOACs in Patients with Advanced and End-Stage Renal Disease. International Journal of Environmental Research and Public Health. 2022;19:1436. Doi: 10.3390/ijerph19031436.

Romoli M, Marchetti G, Bernardini F, Urbinati S. Switching between direct oral anticoagulants: a systematic review and meta-analysis. Journal of Thrombosis and Thrombolysis. 2021;52:560–566. Doi: 10.1007/s11239-020-02367-2.

Ruutiainen HK, Kallio MM, Kuitunen SK. Identification and safe storage of look-alike, sound- alike medicines in automated dispensing cabinets. European Journal of Hospital Pharmacy. 2021;28:e151-e156. Doi: 10.1136/ejhpharm-2020-002531.

Sanz-Pastor AG, Enríquez AJ, Sánchez Bao A, Ampudia-Blasco FJ. Current barriers to initiating insulin therapy in individuals with type 2 diabetes. Frontiers in Endocrinology. 2021;15:1366368. Doi: 10.3389/fendo.2024.1366368.

Sarode R. Direct oral anticoagulant monitoring: what laboratory tests are available to guide us? Hematology, the Education Program of the American Society of Hematology. 2019;(1):194-197. Doi: 10.1182/hematology.2019000027.

Scott IA, Hilmer SN, Reeve E, Potter K, Couteur DL, Rigby D, et al. Reducing inappropriate polypharmacy: The process of deprescribing. JAMA Internal Medicine. 2015;175(5):827–834. Doi: 10.1001/jamainternmed.2015.0324.

Semantha FH, Azam S, Shanmugam B, Yeo KC, Beeravolu AR. A Conceptual Framework to Ensure Privacy in Patient Record Management System. IEEE Access. 2021;9:165667-165689. Doi: 10.1109/ACCESS.2021.3134873.

Shaikh AA, Anbhule SJ, Banagr AA, Raykar MH, Pawar JB. A retrospective review on importance and various preparation of low molecular weight heparin for cardio vascular diseases. International Journal of Pharmaceutical Chemistry and Analysis. 2022;9(4):188-195.

Shih HI, Lin CC, Tu YF, Chang CM, Hsu HC, Chi CH et al. An Increased Risk of Reversible Dementia May Occur After Zolpidem Derivative Use in the Elderly Population A Population-Based Case-Control Study. Medicine. 2015;94(17). Doi: 10.1097/MD.0000000000000809.

Smith BR, DiDomenico RJ. Renal Function Assessment and Direct- Acting Oral Anticoagulants Dosing: Are We Entering a New Age? Circulation: Cardiovascular Quality and Outcomes. 2021;14:e008064. Doi: 10.1161/CIRCOUTCOMES.121.008064.

Sokolova AA, Kudriavtseva AA, Kostikova NV, Zaikina MP, Gebekova ZA, Napalkov DA et al. Risk of Venous Thromboembolic Complications in Patients with Atrial Fibrillation: a Systematic Review and Meta-analysis. Rational Pharmacotherapy in Cardiology. 2022;18(3):236-241. Doi:10.20996/1819-6446-2022-06-02.

Sonawale SC, Shelar SV, Kumbhar SB, Khakal NN, Shinde VR, Jadhao RG et al. Explaining the handling of prescription which contains the narcotic substances and habit forming drugs: An onfield report. GSC Biological and Pharmaceutical Sciences. 2022;19(2):180–186. Doi: 10.30574/gscbps.2022.19.2.0192.

Song Z, Hu Ym Zheng S, Yang L, Zhao R. Hospital pharmacists' pharmaceutical care for hospitalized patients with COVID-19: Recommendations and guidance from clinical experience. Research in Social and Administrative Pharmacy. 2021;17(1):2027-2031. Doi: 10.1016/j.sapharm.2020.03.027.

Soubra L, Karout S. Dispensing errors in Lebanese community pharmacies: incidence, types, underlying causes, and associated factors. Pharmacy Practice. 2021;19(1):2170. Doi: 10.18549/PharmPract.2021.1.2170.

Strang J, Volkow ND, Degenhardt L, Hickman M, Johnson K, Koob GF et al. opioid use disorder. Nature Reviews Disease Primers. 2020;6(3). Doi: 10.1038/s41572-019-0137-5.

Suppiah SD, Tan YW, Cheng Tay SS, Ying Tan VS, Tan NC, Tang WE, et al. Challenges encountered by pharmacy staff in using prescription medication labels during medication counselling with older adults and solutions employed: A mixed-methods study. Exploratory Research in Clinical and Social Pharmacy. 2023;9:100226. Doi: 10.1016/j.rcsop.2023.100226.

Tariq RA, Scherbak Y. Medication Errors. [Updated 2024 Feb 12]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2020 [cited 2024 Jul 25]. Available from: https://www.ncbi.nlm.nih.gov/books/NBK519065/

Varas-Doval R, Gastelurrutia MA, Benrimoj SI, García-Cárdenal V, Sáez-Benito L, Martinez-Martínez F. Clinical impact of a pharmacist-led medication review with follow up for aged polypharmacy patients: A cluster randomized controlled trial. Pharmacy Practice Granada. 2020;18(4):2133. Doi: 10.18549/PharmPract.2020.4.2133.

Vitiello A, Ferrara F. Low Molecular Weight Heparin, Anti-inflammatory/Immunoregulatory and Antiviral Effects, a Short Update. Cardiovascular Drugs and Therapy (2023) 37:277–281. Doi: 10.1007/s10557-021-07251-6.

Wang C, Liu K, Shirai K, Tang C, Hu Y, Wang Y. Prevalence and trends of polypharmacy in U.S. adults, 1999–2018. Global Health Research and Policy. 2023;8:25. Doi: 10.1186/s41256-023-00311-4.

Wang M, Zeraatkar D, Obeda M, Lee M, Garcia C, Nguyen L et al. Drug-drug interactions with warfarin: A systematic review and meta-analysis. British Journal of Clinical Pharmacology. 2021;87(11):4051-4100. Doi: 10.1111/bcp.14833.

Watkins K, Wood H, Schneider CR, Clifford R. Effectiveness of implementation strategies for clinical guidelines to community pharmacy: a systematic review. Implementation Science. 2015;15:151. Doi: 10.1186/s13012-015-0337-7.

Weiner SJ, Wang S, Kelly B, Sharma G, Schwartz A. How accurate is the medical record? A comparison of the physician's note with a concealed audio recording in unannounced standardized patient encounters. Journal of the American Medical Informatics Association. 2020;27(5):770-775. Doi: 10.1093/jamia/ocaa027.

Zawiah M, Yousef AM- Khan AH, Al-Ashwal FY, Mayar A, AlKhawaldeh B et al. Food-drug interactions: Knowledge among pharmacists in Jordan. PloS ONE. 2020;15(6):e0234779. doi: 10.1371/journal. pone.0234779.

List of Publications and Abstracts

Schembri N, Attard Pizzuto M, Azzopardi LM. Department of Pharmacy, University of Malta, Msida, Malta. Pharmacist Intervention in High-Risk Medication Dispensing. Poster session to be presented at the forthcoming FIP World Congress, 2024 September 1-4; Cape Town, South Africa.

Pharmacist Intervention in High-Risk Medication Dispensing

Nicole Schembri, Maresca Attard Pizzuto, Lilian M Azzopardi

Background:

High-risk medications are associated with an increased risk of significant harm when misused or used in error.

Purpose:

To evaluate whether high-risk medications are treated differently to non-high- risk drugs during dispensing in a community pharmacy.

Method:

A documentation sheet titled 'HiRisk' and patient interview questions were developed in English and Maltese. These were validated for relevance, comprehensiveness and presentation by four community pharmacists and two general practitioners. Observational studies were carried out using the developed tool in five community pharmacies chosen from five different districts chosen by stratified random sampling. The dispensing of the first ten prescriptions presenting with a high-risk medication was observed and the 'HiRisk' documentation sheet was filled in for every prescription received. Fifty patient

interviews were then conducted on a separate cohort of patients receiving HiRisk medication in two out of the five community pharmacies, chosen by convenience sampling.

Results:

From the dispensing of 50 high-risk medication prescriptions, the direct oral anticoagulants (DOACs) were the most commonly dispensed (n=20) having presented 13 rivaroxaban prescriptions and 7 apixaban prescriptions, followed by warfarin (n=11) and insulin (n=7). All pharmacists (n=50) ensured that the patient knew how to administer the medication and whether the patient had any problem with the high-risk medication being dispensed. All pharmacists (n=50) repeated major key advice points to ensure patient understanding. When carrying out patient interviews, 28 of the interviewees were male and 22 were female whose majority (n=20) have been taking their medication for a period between 1 and 5 years. Similarly, to the observational studies, DOACs were the most common high-risk medications dispensed (n=16). Only four patients presented with side-effects related to the high-risk medication

Conclusion:

Results gathered from the observational studies using the 'HiRisk' documentation sheet and from patient interviews correlate in having the direct oral anticoagulants being the most dispensed high-risk medication. The community pharmacist is in an ideal position to intervene to minimise risks and aid patient compliance during the dispensing process of high-risk medications.

Topic area: Community pharmacy

L-Università ta' Malta | Faculty of Medicine & Surgery | Department of Pharmacy

PHARMACIST INTERVENTION IN HIGH-RISK MEDICATION DISPENSING

Nicole Schembri, Maresca Attard Pizzuto, Lilian M. Azzopardi
Department of Pharmacy, Faculty of Medicine and Surgery, University of Malta, Msida, Malta
email: nicole.schembri.19@um.edu.mt

INTRODUCTION

"High-risk medications are associated with an increased risk of significant harm when misused or used in error. The consequence of this harm can be more serious than that with other medications"[1]

AIMS

- To evaluate dispensing of high-risk medications in a community pharmacy
- To develop guidelines for pharmacists dispensing high-risk medications

METHOD

Phase 1: Observational Studies and Patient Interviews

Development and Validation of 'HiRisk' documentation sheet and patient interview questions

↓

Observational Studies in five community pharmacies (N=50)

↓

Patient interviews in two community pharmacies (N=50)

↓

Data Analysis

Phase 2: Guidelines

Development of guidelines for Direct Oral Anticoagulants, warfarin and insulin

↓

Validation of guidelines by four community pharmacists and two general practitioners

↓

Data Analysis

↓

Dissemination of guidelines to community pharmacists dispensing high-risk medications

RESULTS

Phase 1: Observational Studies

- From the dispensing of high-risk medication prescriptions (N=50) observed in five community pharmacies the following were the most common;
  - Direct Oral Anticoagulants (n=20)
  - Warfarin (n=11)
  - Insulin (n=7)
- The direct oral anticoagulants were the most dispensed in three community pharmacies followed by warfarin in two pharmacies.

Phase 1: Patient Interviews

- From interviews with patients being dispensed a high-risk medication (N=50) in two community pharmacies the following were the most common;
  - Direct Oral Anticoagulants (n=16)
  - Warfarin (n=13)
  - Zolpidem (n=11)
- Twenty patients have been taking their medication for a period between 1 – 5 years, 12 patients between 6 months – 1 year, 10 patients for more than 5 years and 8 patients for less than 6 months.
- Four patients exhibited side-effects of bleeding with rivaroxaban and warfarin, short-term amnesia with zolpidem and blurred vision and confusion with insulin owing to the hypoglycaemic effect.

Phase 2: Guidelines

Guidelines to support the dispensing process were developed for the three most dispensed high-risk medications which are the direct oral anticoagulants, warfarin and insulin.

CONCLUSION

Observing the commonly dispensed high-risk medications and implementing strategies to reduce high-risk medication associated side-effects through the proposed guidelines contributes to a streamlined dispensing process enhancing patient safety. Guidelines potentially serve as a tool in improving pharmacist accessibility, since pharmacists can practice within a multidisciplinary team to identify errors throughout the dispensing process.

REFERENCE

1. Dumitrescu I, Casteels M, De Vliegher K, Dilles T. High-risk medication in community care: a scoping review. European Journal of Clinical Pharmacology. 2020;76:623-638. doi: 10.1007/s00228-020-02838-8.

Appendices

Appendix 1: Ethics Approval

L-Università ta' Malta

Faculty of Medicine & Surgery

University of Malta
Msida MSD 2080, Malta

Tel: +356 2340 1879/1891/1167
umms@um.edu.mt

www.um.edu.mt/ms

Ref No: MED-2022-00282

13 April 2023

Ms Nicole Schembri
12 ST MARY TUNNARA STREET
ZURRIEQ ZRQ 1180

With reference to your application submitted to the Faculty Research Ethics Committee in connection with your research entitled:

Pharmacist Intervention in High-Risk Medications

The Faculty Research Ethics Committee is granting ethical approval for the above-mentioned application.

Professor Anthony Serracino Inglott
Chair
Faculty Research Ethics Committee

Appendix 2: High-Risk Medications Documentation Sheet (HiRisk)

'HiRisk' Documentation Sheet

Section 1: Demographic Data

Pharmacy:	

Pharmacist present is:

The owner	
The managing pharmacist	
Employed full-time	
Employed part-time	
A locum pharmacist	

Pharmacists years of practice:

<2 years	
2-5 years	
6-10 years	
>10 years	

High-Risk medication being dispensed:

Trade Name	Active Ingredient	Dose Dispensed	Dosage Regimen	Duration of Treatment

Section 2: Pharmacists' Review and Advice

Identification of patient

	Yes	No
Pharmacist askes for patient:		
• Name		
• Age		

Assessing patient knowledge

	Yes	No
Pharmacist confirms with the patient the indications for which the medication(s) is/are being used.		
Pharmacist questioned if the patient is taking other medication. If yes, what medication? _____		
Pharmacist explains to the patient:		
1. How to take medication		
2. When to take the medication		
3. Duration of treatment		

Rechecking of prescription and dispensing and information provided

	Yes	No
Pharmacist compared medication with the prescription to confirm that the right product was selected.		
Pharmacist interpreted the prescription order by dispensing exact quantities of medication.		
Pharmacist checked expiration date before dispensing.		
The pharmacist dispensed medication in:		
1. Original packaging		

2. Single blister packs		
3. Single blister packs in a bag labelled with trade name, quantity, expiry date and regimen		
4. Loose		
Pharmacist gives information to the patient:		
1. Written form as a printed label		
2. Handwritten label		
3. Instructions written on the packet		
4. Verbal advice		
Pharmacist double checked the prescription.		
Pharmacist advised the patient on drug blood level monitoring (if applicable).		
Pharmacist advised the patient of any possible side-effects.		
Pharmacist highlighted any drug-drug interactions (DDI's) that might occur with drugs administered concomitantly.		
Pharmacist provided non-pharmacological advice.		
Pharmacist advised patient on modifiable risk factors.		
Pharmacist advised the patient of proper storage conditions:		
• Not in direct sunlight		
• In fridge (2-8 degrees) if required		
• In original blister pack or bottle		

Ensuring maximum benefit

	Yes	No
Pharmacist ensured that the patient understood how to administer the medication.		
Pharmacist asked whether the patient has any problems with the medication.		

Pharmacist repeated major points covered during dispensing.		

Section 3: Patient Issues

	Yes	No
Patient presented with an adverse drug reaction.		
• Allergy?		
• Non-allergic reaction?		
• Toxic reaction to the drug?		
• Other: _____		
If so, • Medication Trade Name: • ADR presented: • Action/Recommendation by pharmacist		
Pharmacist asked the patient to describe the nature and severity of symptom(s).		
Pharmacist asked about the onset and duration of the symptom(s).		
Pharmacist asked the patient whether he/she experienced any accompanying symptoms.		
Patient is experiencing difficulties with taking the drug:		
• Forgot regimen		
• Does not want to take the medication		
• Deliberately skipping doses		
• Other:		
Patient presented back at the pharmacy with relevant questions:		
• In relation to DDIs		
• Experiencing any side-effect		
• Other: _____		

Pharmacist stressed to the patient the importance of seeking medical advice immediately.		
Pharmacist recognises deviations from normality and suggests seeking medical advice if symptom(s) persist for more than 24 hours.		

Appendix 3: Patient Interview Questions in English and Maltese

'Interview Questions'

1. Gender

Male	
Female	
Other	

2. Level of Education

Primary	
Secondary	
Post-Secondary	
Tertiary	

3. Are you aware of which medication you are being dispensed?

Yes	
No	

4. Do you know for what you are being administered this medication?

Yes	
No	

5. For how long have you been on this medication?

< 6 months	
6 months – 1 year	
1-5 years	
>5 years	

6. Did you experience any side-effects whilst on this medication?

Yes	
No	

What was the side-effect?

_____

_____

_____

What did you do to treat the side-effect?

_____

_____

_____

7. Were you monitored more frequently by your doctor or pharmacist when you started taking this medication?

Yes	
No	

8. Do you take other medications besides this one?

Yes	
No	

If yes, can you name them?

_____

_____

‘Mistoqsijiet tal-intervista’

1. Sess

Raġel	
Mara	
Oħra	

2. Livell t’Edukazzjoni

Primarja	
Sekondarja	
Post-Sekondarja	
Terzjarja	

3. Taf liema mediċina qiegħed/qiegħda tiġi mqassam/mqassma?

Iva	
Le	

4. Taf għalxiex qiegħed/qiegħda tiġi mqassam/mqassma din il-mediċina?

Iva	
Le	

5. Kemm ilek tieħu din il-mediċina?

< 6 xhur	
6 xhur – 1 sena	
1-5 snin	
>5 snin	

6. Esperjenzajt xi effetti sekondarji waqt li qiegħed/qiegħda tieħu din il-mediċina?

Iva	
Le	

X'kienu l-effetti?

_____

_____

_____

X'għamilt biex ikkurajt l-effetti sekondarji?

_____

_____

_____

7. Kont immonitorjat/a aktar ta' spiss mit-tabib jew mill-ispiżjar tiegħek meta bdejt tieħu din il-mediċina?

Iva	
Le	

8. Tieħu xi mediċini ohra apparti din?

Iva	
Le	

Jekk iva, tista ssemmihom?

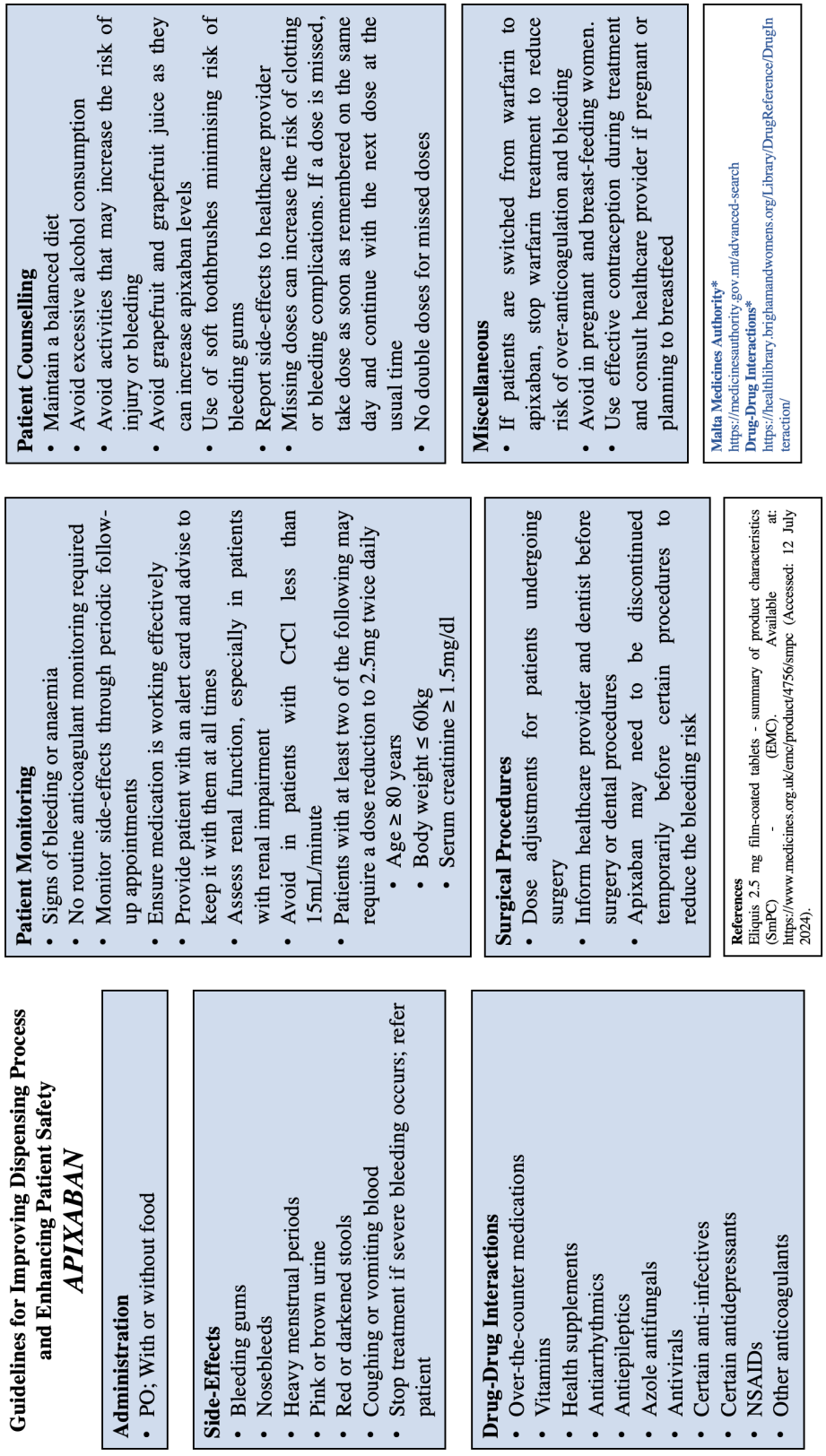
_____

_____

_____

Appendix 4: Guidelines to Improve the Dispensing Process

"Guidelines for Improving Dispensing Process and Enhancing Patient Safety"



Guidelines for Improving Dispensing Process and Enhancing Patient Safety

RIVAROXABAN

Administration
- PO; With food for enhanced absorption especially 15mg and 20mg
- Same time each day

Side-Effects
- Bleeding gums
- Nosebleeds
- Heavy menstrual periods
- Pink or brown urine
- Red or darkened stools
- Coughing or vomiting blood
- Stop treatment if severe bleeding occurs; refer patient

Miscellaneous
- If patients are switched from warfarin to rivaroxaban, stop warfarin treatment to reduce the risk of over-anticoagulation and bleeding
- Avoid in pregnant and breast-feeding women
- Use effective contraception during treatment and consult healthcare provider if pregnant or planning to breastfeed

Patient Monitoring
- Signs of bleeding or anaemia
- No routine anticoagulant monitoring required
- Monitor side-effects through periodic follow-up appointments
- Ensure the medication is working effectively
- Provide patient with an alert card and advise to keep it with them at all times
- Assess renal function, especially in patients with renal impairment
- Use with caution if CrCl is 15-29mL/minute
- Avoid if CrCl is less than 15mL/minute

Drug-Drug Interactions
- Over-the-counter medications
- Vitamins
- Health supplements
- Antiarrhythmics
- Antiepileptics
- Azole antifungals
- Antivirals
- Certain anti-infectives
- NSAIDs
- Other anticoagulants
- Strong CYP3A4 inhibitors; ketoconazole, ritonavir, rifampin and phenytoin

Patient Counselling
- Maintain a balanced diet
- Avoid excessive alcohol consumption
- Avoid activities that may increase the risk of injury or bleeding
- Tablets may be crushed and mixed with water or apple puree just before administration
- Use of soft toothbrushes minimising risk of bleeding gums
- Report side-effects to their healthcare provider
- Missing doses can increase the risk of clotting or bleeding complications. If a dose is missed, take dose as soon as remembered on the same day. For 15mg BD regimen, both tablets can be taken together

Surgical Procedures
- Dose adjustments for patients undergoing surgery
- Inform healthcare provider and dentist before surgery or dental procedures

Malta Medicines Authority*
https://medicinesauthority.gov.mt/advanced-search
Drug-Drug Interactions*
https://healthlibrary.brighamandwomens.org/Library/DrugReference/DrugInteraction/

References
Xarelto 10 mg film-coated tablets - summary of product characteristics (SmPC) - (EMC). Available at: https://www.medicines.org.uk/emc/product/6402/smpc (Accessed: 12 July 2024).

Guidelines for Improving Dispensing Process and Enhancing Patient Safety

WARFARIN

Administration
- PO; In the evening at the same time each day

Side-Effects
- Haemorrhage
- Nausea and vomiting
- Unusual bruising
- Nosebleeds
- Pink or brown urine
- Red or darkened stools
- Coughing up or vomiting blood

Drug-Drug Interactions
- Over-the-counter medications
- Vitamins
- Herbal supplements
- NSAIDs
- Aspirin
- Certain anti-infectives
- Antiepileptics
- Certain anti-virals

Colour coding
- 1mg - Brown
- 3mg - Blue
- 5mg - Pink

Patient Monitoring
- Baseline prothrombin time
- Regular INR monitoring. Target INR range: 2.0 -3.0
- Signs of bleeding and thromboembolic events.
- Provide patient with anticoagulant card and advise to keep it with them at all times
- Hepatic and Renal impairment
  - Caution in mild to moderate hepatic impairment
  - Avoid in severe renal impairment. Monitor INR more frequently in severe renal impairment

Surgical Procedures
- Stop warfarin five days before surgery
- Inform healthcare provider and dentist before surgery or dental procedures

Miscellaneous
- If patients are switched from warfarin to a DOAC, stop warfarin treatment to reduce risk of over-anticoagulation and bleeding
- Contra-indicated in pregnant and breast-feeding women
- Women of child-bearing age should be warned of the danger of teratogenicity
  - Use effective contraception

Patient Counselling
- Take warfarin exactly as prescribed
- Missed doses can significantly impact INR and increase risk of clotting and bleeding. If a dose is missed, take as soon as remembered
- Avoid cranberry juice
- Avoid alcohol consumption
- Consistent dietary vitamin K from leafy green vegetables, broccoli and Brussels sprouts is important; No significant changes to diet
- Consult healthcare provider if there are changed to diet
- Avoid activities that may increase the risk of injury or bleeding
- Use soft toothbrushes, electric razors with care
- Report serious bleeding symptoms to health care provider
  - Severe headaches
  - Dizziness
  - Fainting
  - Prolonged bleeding
  - Heavy menstrual period

Malta Medicines Authority*
https://medicinesauthority.gov.mt/advanced-search
Drug-Drug Interactions*
https://healthlibrary.brighamandwomens.org/Library/DrugReference/DrugInteraction/

References
Warfarin 1 mg tablets - patient information leaflet (PIL) - (EMC). Available at: https://www.medicines.org.uk/emc/product/4442/pil (Accessed: 12 July 2024).

Guidelines for Improving Dispensing Process and Enhancing Patient Safety

INSULIN

Administration
- SC injection

Storage
- Unopened insulin in fridge
- Opened insulin at room temperature for up to 28 days
- Do not freeze insulin or leave in direct sunlight

Side-Effects
- Hypoglycaemia
- Oedema, lipodystrophy and amyloidosis

Drug-Drug Interactions
- Oral anti-diabetic agents
- Beta-blockers
- Atypical antipsychotics

Patient Monitoring
- Train patients to self-monitor blood-glucose levels
- Maintain a blood glucose level between 4-9mmol/L
- HbA1c testing and monitoring for diabetic complications
- Hepatic impairment
  - Requirements may be decreased
- Renal impairment
  - Response to hypoglycaemia is impaired
  - Requirements may decrease therefore; dose reduction is necessary

Miscellaneous
- Increased demand in pregnancy; insulin dose is increased in 2nd and 3rd trimester of pregnancy

Types of Insulin

Rapid-acting insulin
- Example: insulin lispro (Humalog®), insulin aspart (Novorapid®)
- Onset: 10 – 30 minutes
- Peak: 30 minutes to 3 hours
- Duration: 3 – 5 hours

Short-acting insulin
- Example: soluble insulin (Humulin® R)
- Onset: 30 minutes – 1 hour
- Peak: 30 minutes to 1 hour
- Duration: 5-8 hours

Intermediate-acting insulin
- Examples: isophane insulin (Humulin® N), biphasic insulin (Humulin® M3)
- Onset: 1 – 2 hours
- Peak: 4 – 12 hours
- Duration: 12 – 18 hours

Long-acting insulin
- Examples: insulin glargine (Lantus®), insulin degludec (Tresiba®)
- Onset: 1 – 4 hours
- Peak: Minimal or none
- Duration: up to 24 hours or more

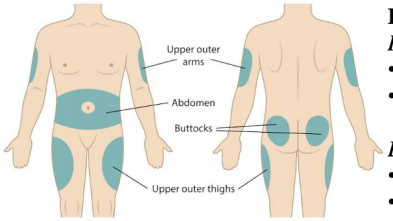
Patient Counselling
- Rotate injection sites to reduce lipodystrophy risk
- Rapid-acting insulin – just before or right after meals
- Long-acting insulin – once daily at the same time each day
- Adjust dose based on blood glucose levels and food consumed
- Do not skip long-acting insulin doses and do not double the dose if a dose is missed
- Maintain a balanced diet; consistent carbohydrate intake to stablise blood glucose levels
- Regular exercise
- Avoid alcohol consumption; increased risk of hypoglycaemia when consumed on an empty stomach
- Monitor more frequently blood glucose during illness
  - Rapid-acting insulin: based on food intake
  - Long-acting insulin: maintain usual daily dose
- Use cooling wallets (e.g: Frio® pack) when travelling

References

Lantus 100 units/ML solution for injection in a cartridge - summary of product characteristics (SmPC) - (EMC). Available at: https://www.medicines.org.uk/emc/product/2376/smpc#gref (Accessed: 12 July 2024).

Hypoglycaemia Management
- Symptoms of hypoglycaemia:
  - Shaking
  - Sweating
  - Tachycardia
  - Dizziness
  - Hunger
  - Confusion
  - Irritability
- Use fast-acting glucose tablets immediately
- Re-check blood glucose after 15 minutes and repeat treatment if necessary

Hyperglycaemia Management
- Symptoms of hyperglycaemia:
  - Polyuria
  - Polydipsia
  - Dry mouth
  - Blurred vision
  - Fatigue
- Increase insulin dose
- Check urine ketone levels



Injection sites

Rapid-acting
- Upper outer arms
- Abdomen

Long-acting
- Buttocks
- Upper outer thighs

Malta Medicines Authority*
https://medicinesauthority.gov.mt/advanced-search

Drug-Drug Interactions*
https://healthlibrary.brighamandwomens.org/Library/DrugReference/DrugInteraction/