Accessibility and Safety of Antipsychotics in the Treatment of Autism Spectrum Disorder in Children and Adolescents

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I dedicate this to my two beautiful mothers, my brother and

all the researchers who would utilise this work in their paths.

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Abstract

Risperidone and aripiprazole (RiAr) are the only approved drugs by the FDA for the treatment of irritability associated with Autism Spectrum Disorder (ASD) in children and adolescents. The regulatory bodies in Europe (European Medicines Agency) and India (The Central Drugs Standard Control Organization) have not approved the drugs for the indication of ASD. Cultural, economic and regulatory variations may impact the approach towards the treatment of ASD in India and Malta.

The objectives of the research are to 1) develop and administer a questionnaire to psychiatrists in India and Malta 2) evaluate and compare the accessibility and affordability of RiAr and 3) detect adverse drug reactions (ADRs) not listed in the approved Summary of Product Characteristics (SmPC) in children and adolescents treated with RiAr for ASD through Eudravigilance.

The methodology included 1) a questionnaire, entitled ASD-Q $_{(IND-MT)}$ which was developed, validated (by 10 experts) and disseminated to psychiatrists (N=47) in India (n=31) and Malta (n=16). ASD-Q$_{(IND-MT)}$ consisted of 6 sections and 28 close ended Likert scale questions ranging from 1 (strongly disagree) to 5 (strongly agree) and gathered opinions on the perception of ASD, influence of culturally developed screening tools, Childhood Autism Rating Scale (CARS) in Malta and the Indian Scale of Assessment (ISAA) in India, prescribing behaviour of RiAr and role of pharmacists in managing ASD, 2) a comparison of the price of RiAr against the Monthly Per Capita Expenditure (MPCE) in India and Malta to obtain an indication of the affordability of the treatment, 3) Eudravigilance signal detection and French causality assessment was carried out and ADRs

received during November 2001 to September 2017 were extracted in the age group 6-17 years (risperidone) and 5-16 years (aripiprazole).

Statistical analysis of the ASD-Q $_{(IND-MT)}$ indicated a significant difference ($p<0.05$) between the prescribing behaviour of RiAr. A significant difference ($p=0.040$) was noted between the psychiatrists when asked about the interpretation of the screening tools (ISAA/CARS) score. Thirteen Indian psychiatrists out of 31 and 2 Maltese psychiatrists out of 16 agreed that they prescribe RiAr to patients with mild to moderate autism. Eighteen Indian psychiatrists out of 31 and 14 Maltese psychiatrists out of 16 agreed that they would prescribe antipsychotics to patients who have severe autism.

A statistically significant difference ($p<0.001$) is noted between psychiatrists when asked about the influence of screening tools (ISAA/CARS) on the prescribing behaviour of antipsychotics. The Likert mean score was 4.45±0.506 by Indian psychiatrists and 2.56±1.153 by Maltese psychiatrists indicating higher agreement by the Indian psychiatrists.

The Cost analysis of RiAr revealed that RiAr would cost €3.5 and €3.9 in India and €26.7 and €28.8 in Malta monthly. The percentage of MPCE required for one month of treatment with RiAr is 11.30% and 12.60% in India and 3.30% and 3.56% in Malta respectively. Five ADR signals were assessed for risperidone and three signals for aripiprazole. The French causality assessment concluded “uncertain” or “unlikely” relation between the ADR signals and the drugs.

Culturally developed screening tools have a different influence on the prescribing behaviour of drugs in India and Malta. The cost of medicines is low in India compared to

Malta but the treatment is more affordable in Malta. The SmPC of RiAr includes all the ADRs indicated through the EudraVigilance signal detection in this study.

Keywords

Accessibility - Aripiprazole - Autism Spectrum Disorder - India and Malta - Risperidone - Safety - Screening tools

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List of Abbreviations

ADDM	Autism And Developmental Disabilities Monitoring
ADHD	Attention-Deficit Hyperactivity Disorder
ADR	Adverse Drug Reaction(S)
AERS	Adverse Event Reporting System
APA	American Psychiatric Association
ASD	Autism Spectrum Disorder
ASDEU	Autism Spectrum Disorder in the European Union
CARS	Childhood Autism Rating Scale
CCI	Commission On Chronic Illness
CDC	Centres For Disease Control And Prevention
CHAT	Checklist For Autism in Toddlers
CHMP	Committee for Medicinal Products for Human Use
CVI	Content Validity Index
DSM	Diagnostic And Statistical Manual Of Mental Disorders
ECG	Electrocardiogram
EMA	European Medicines Agency
EPS	Extrapyramidal Symptoms
EU	European Union
EVDAS	Eudravigilance Data Analysis System

FDA	Food and Drug Administration
ICD	International Classification of Diseases
ICSR	Individual Case Safety Report(S)
IMPs	Investigational Medicinal Products
ISAA	Indian Scale For Assessment Of Autism
ME(S)	Medication Error(S)
MedDRA	The Medical Dictionary for Regulatory Activities
MMWR	Morbidity And Mortality Weekly Report
NSSO	National Sample Survey Office
PDD	Pervasive Developmental Disorder
PRR	The Proportional Reporting Ratio
RiAr	Risperidone and Aripiprazole
SDRs	Signals of Disproportionate Reporting
SmPC	Summary of Product Characteristics
VAERS	Vaccine Adverse Event Reporting System
WHO	World Health Organization

Chapter 1- Introduction

1.1 Autism Spectrum Disorder

Autism spectrum disorder (ASD) is a group of neurodevelopmental disorders that include a wide range, a spectrum of symptoms. Difficulties in communication and social interactions, repetitive behaviour, and delay in developmental skills are the most predictable symptoms (Murphy et al, 2016). ASD encompasses various disorders characterised by a level of severity of symptoms. A Swiss psychiatrist Eugen Bleuler first coined the term “autism” in 1911 to describe the behaviour of social introversion or withdrawal in children as "turning inward” (Manolova and Achkova, 2014).

In 1943, Leo Kanner noticed autistic symptoms in children of less than two years and described the disorder as “early infantile autism”. Kannar described the symptoms as children dealing with “extreme aloneness” due to their lack of interest in other people (Faras et al, 2010). In 1944, Hans Asperger, a paediatrician noticed similar symptoms but in milder forms, which he described as “autistic psychopathy”, the syndrome was named after the paediatrician as Asperger’s Syndrome (Klin, 2003). Until the 1970s, Autism was considered a form of childhood schizophrenia rather than a distinct disorder (Mintz, 2016). Psychiatrists noticed that children with autism were born with developmental difficulties as compared to children with schizophrenia who displayed normal development at least till the age of two (Goldstein, 2002). The symptoms of ASD differ depending on the characteristics of the individual such as their age (Charman et al, 2005). Distinctive characteristics are also noted between male and female phenotypes in different cultures and ethnic groups (Mandy et al, 2015).

ASD is predominantly noticed by caregivers and the society when the individual fails to behave in an acceptable and effective social context, and the behaviour that constitutes as

acceptable is very different in different cultures (Carter et al, 2005). Behaviour that can be normal for children in one culture may be unusual for children in other cultures such as making eye contact with elders, ability to raise questions in conversations and interactions in social gatherings (Norbury and Sparks, 2013). The differences in behaviour that occur due to cultural diversions are important to notice to make a precise identification and diagnosis of a complex neurodevelopmental disorder like ASD (Matson et al, 2017).

The Diagnostic and Statistical Manual of Mental Disorders (DSM) developed by the American Psychiatric Association (APA) define and categorise autism and its related terms. The third edition of the manual saw the inclusion of the term 'Pervasive Developmental Disorder' (PDD), and this was considered the "broader umbrella" under which many subtypes of autism are included for better understanding of the disorder and the associated symptoms (Hyman, 2002). The fifth edition of the manual, DSM-5 and tenth edition of the International Classification of Diseases (ICD-10) by the World Health Organisation (WHO) are predominantly used as an ultimate guide by the clinicians for diagnostic classification of ASD (Volkmar and Reichow, 2013).

The primary purpose of guidelines like DSM or ICD is to make mental healthcare professionals aware and alert them of the 'red flags' in a person to diagnose a disorder like ASD. As the guidelines are developed based on research conducted in Western countries, it is important to consider the variations in behaviour occurring due to cultural diversions in Eastern countries. The fourth version of DSM saw an update and significant changes were observed due to diagnostic criteria not catering to cultural differences, but many professionals across the globe still were not convinced by the classification and diagnostic criteria of ASD in the guidelines (Lord and Jones, 2012). Differences in Eastern and

Western cultures have led to the debate over the criteria. In this study, Malta and India were compared to study the impact of cultural differences on approach towards ASD.

The ideal guidelines, screening, or diagnosis should also be able to consider the cultural variations across the globe as the most critical characteristic of ASD is noted through the social behaviour of a child, which could vary significantly across cultures.[1]

1.1.1 Prevalence of Autism Spectrum Disorder

The WHO defines the prevalence of a condition as "*the number of individuals who have the condition at any moment*".[2] The Autism Developmental Disabilities Monitoring (ADDM) Network by the Centers for Disease Control and Prevention (CDC) in the United States reported that 1 in 59 children are identified with ASD.[3] A steady increase is also observed in the prevalence from 1 in 150 children in 2000 to 1 in 59 children in 2014 (Table 1.1).

A study by Christensen et al (2016) observed ASD was about 4.5 times more common among boys (1 in 42) than among girls (1 in 189). The average percentage of individuals within Asia, Europe, and North America with ASD prevalence are estimated to be in between 1% and 2%.[4]

[1] Sarah C. Bauer S. How Cultural Differences Affect Autism Diagnoses [Internet]. Scientific American Blog Network. 2018 [cited 2018 May 25]. Available from: https://blogs.scientificamerican.com/guest-blog/how-cultural-differences-affect-autism-diagnoses/

[2] WHO. Disease incidence, prevalence and disability [Internet]. Who.int. 2018 [cited 2018 May 25]. Available from: http://www.who.int/healthinfo/global_burden_disease/GBD_report_2004update_part3.pdf

[3] CDC. Data and Statistics | Autism Spectrum Disorder (ASD) | NCBDDD | CDC [Internet]. Centers for Disease Control and Prevention. 2018 [cited 2018 May 25]. Available from: https://www.cdc.gov/ncbddd/autism/data.html

[4] CDC | Data and Statistics | Autism Spectrum Disorder (ASD) | NCBDDD [Internet]. Cdc.gov. 2017 [cited 2018 May 25]. Available from: https://www.cdc.gov/ncbddd/autism/data.html

Table 1.1 Identified Prevalence of Autism Spectrum Disorder in the United States

Surveillance year	Birth year	Number of ADDM sites reporting	Prevalence per 1000 children (range)	1 in X children
2000	1992	6	6.7 (4.5-9.9)	1 in 150
2002	1994	14	6.6 3.3-10.6)	1 in 150
2004	1996	8	8.0 (4.6-9.8)	1 in 125
2006	1998	11	9.0 (4.2-12.1)	1 in 110
2008	2000	14	11.3 (4.8-21.2)	1 in 88
2008	2002	11	14.7 (5.7-21.9)	1 in 68
2012	2004	11	14.6 (8.2-24.6)	1 in 68
2014	2006	11	16.8 (13.1-29.3)	1 in 59

Adapted from CDC | Data and Statistics | Autism Spectrum Disorder (ASD) | NCBDDD [Internet]. Cdc.gov. 2017 [cited 2018 May 25]. Available from: https://www.cdc.gov/ncbddd/autism/data.html

The European Commission published the first-ever report on the prevalence of ASD in the European Union (EU) in 2005. The report suggests that ASD affects approximately 0.62-0.70% of the population. A global prevalence study by Elsabbagh et al (2012) estimated 1% to 2% of prevalence rates. The increase in the prevalence rates of autism has been partially linked to the change in definition and of ASD.[5]

The EU definition of a rare disease is "*the disorder that have lower than 5 per 10 thousand prevalence rates in EU*".[6] The prevalence rates in EU as per the reports were found to be 63

[5] EC. Autistic Spectrum Disorders (ASD) - Public Health - European Commission [Internet]. Public Health. 2018 [cited 2018 May 25] Available from: https://ec.europa.eu/health/non_communicable_diseases/diseases/autistic_en#fragment1

[6] European Commission. Rare diseases - Public Health - European Commission [Internet]. Public Health. 2018 [cited 2018 May 25]. Available from: https://ec.europa.eu/health/non_communicable_diseases/rare_diseases_en

per 10 thousand, which does not make ASD a rare disease in the EU. [7] The EU debates that the reason for increased prevalence rates of ASD is due to the broadening of the definition of ASD as per the DSM-V criteria by the USA, which allows individuals with milder forms of disorder like PDD-NOS to be included in the spectrum.[8] The Autism Spectrum Disorder in the European Union (ASDEU) project was launched in 2015 to establish prevalence rates and definition of subtypes of autism.[9]

The increase in the prevalence of the reports can be linked to broadening the definition of ASD in the recent years, but the actual increase in the number of people being diagnosed cannot be ignored.

In Malta, 213 families are associated with their children being on the spectrum and it is estimated that 1:52 births will be associated with ASD in the future.[10] The statistics in table 1.2 represents data from 2008 to 2014 estimating the number of students identified to have autism in schools. The National School Support Services under the Ministry of Education and Employment was contacted for this research purpose to get an estimate of children identified in Malta with autism. The data is represented in figure 1.1. It is important to note that this data represents the number of children identified with the disorder in schools, which is a limitation, as students suffering from severe autism may not be admitted to schools.

[7]European Commission. Some elements about the prevalence of Autism Spectrum Disorders (ASD) in the European Union [Internet]. Luxembourg: European Commission; 2005 [cited 2018 May 25]. Available from: https://ec.europa.eu/health/sites/health/files/major_chronic_diseases/docs/asds_eu_en.pdf

[8] European Commission. Policy - Public Health - European Commission [Internet]. Public Health. 2017 [cited 2018 May 25]. Available from: https://ec.europa.eu/health/rare_diseases/policy en

[9] ASDEU. Prevalence [Internet]. ASDEU. 2017 [cited 2018 May 25]. Available from: http://asdeu.eu/prevalence/

[10] Parlament.mt. (2016). The Autism Spectrum. [online] Available at: https://www.parlament.mt/media/80620/06851.pdf [Accessed 2018 May 25].

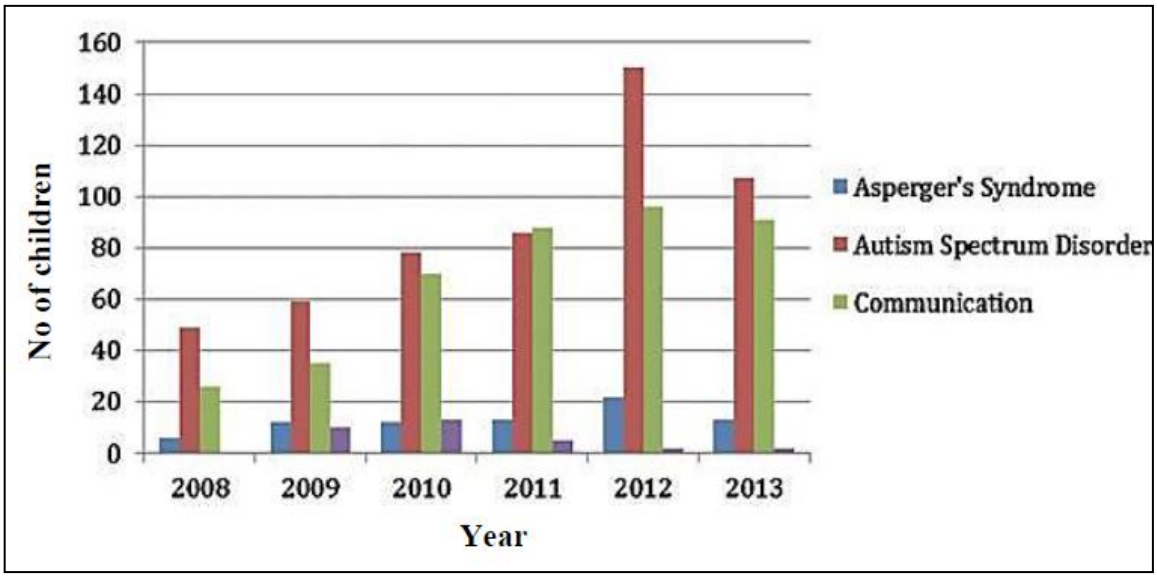

Figure 1.1 Identified School Children with Autism Spectrum Disorder in Malta from 2008-2013

Adopted from Parlament Ta' Malta. P.L 6851, The Autism Spectrum [Internet]. Parlament.mt. 2015 [cited 2018 May 25]. Available from: https://www.parlament.mt/media/80620/06851.pdf

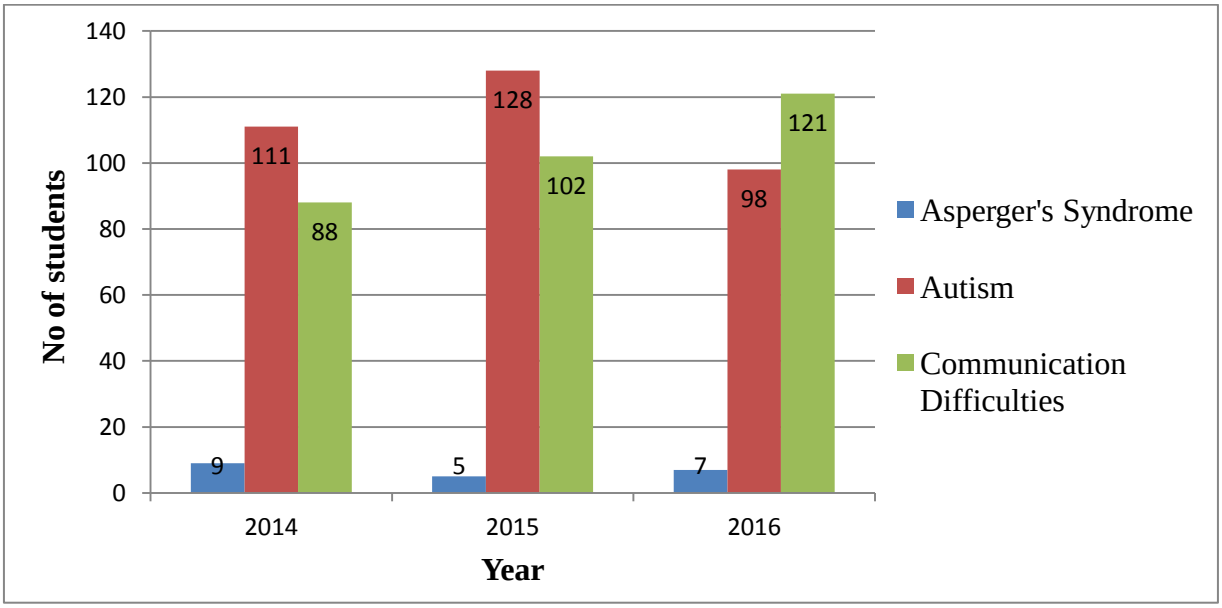

Figure 1.2 Identified School Children with Autism Spectrum Disorder in Malta (2014-2016)

Accurate ASD Prevalence in Malta is not known as a significant mental health survey has not been carried out due to the large expenses and lack of patient data. It is not mandatory

for all the patients to be referred to a government hospital in Malta for the screening of the disorder, which creates significant limitations in a study to be carried out based on the statistics provided by the hospitals.

India is a country with the vast population and the prevalence is estimated to be approximately 1.7-2 million (Deshpande et al, 2015). A prevalence survey by Raina et al (2017) among children aged 1-10 years in the northwest of India diagnosed 43 out of 28,070 children with ASD, yielding a prevalence of 0.15%. The increase in prevalence is not only attributed to a broader definition of ASD but has also been linked to change in screening criteria, availability of different screening and diagnostic tools and better awareness of ASD among people (Fombonne, 2008). The prevalence rates in Asia differ from region to region, which can be a result of various screening tools used across the continent.

A prevalence study conducted by Rudra et al (2017) included children from a broader spectrum of autism using standard screening tools and reported 0.23% prevalence rates, but the data was collected from schools which poses a significant limitation as severely autistic patients are not admitted in regular schools. South Asia represents more than 20% of the world population, and yet the prevalence of ASD is not known in these regions. As the prevalence is linked to change in criteria of screening and diagnosis of ASD, it is essential to have precise tools that can identify, differentiate, and diagnose ASD.

1.1.2 Screening Tools for Autism Spectrum Disorder

The United States Commission on Chronic Illness (CCI) defines screening as "*the presumptive identification of unrecognised disease or defect by the application of tests,*

examinations, or other procedures which can be applied rapidly. Screening tests sort out well persons who probably have a disease from those who probably do not."[11] Screening is a way to alert healthcare professionals that further clinical attention might be required for the patient. This is important in case of ASD as on positive screening, the healthcare professional can refer the patient to a specialist for diagnosis of autism as early as possible (Koegel et al, 2005).

Early and proper screening of autism is crucial because it results in better intervention and positive outcome.[12] Early screening has displayed potential benefits like improvement in core symptoms, IQ, speech, and severity of ASD (Zwaigenbaum et al, 2015). Early screening can help parents and caretakers to understand the child's disorder and plan the management accordingly, in case of misdiagnosis early screening can induce anxiety in patients and financial loss. Early identification has advantages and disadvantages, but the advantages far outweigh the risks associated with early screening (Jin, 2016). The signs and symptoms of ASD can be identified during the first two years of a child's life (Maestro et al, 2001).

ASD displays a range of disruptive behavioural symptoms such as impulsiveness, aggressiveness, self-harm and temper tantrums that may vary significantly from one child to another (Elbe et al, 2012). As ASD spreads across the spectrum, misdiagnosis of children on either end of the spectrum is observed. Children with severe symptoms of autism are diagnosed as suffering from a severe case of intellectual disability, and those with mild

[11] Wilson j, Jungner g. Principles and practice of screening for disease [Internet]. GENEVA: World Health Organisation; 1968 [cited 2018 May 25]. p. 11. Available from: http://apps.who.int/iris/bitstream/handle/10665/37650/WHO_PHP_34.pdf?sequence=17

[12] Burnette C, Trott M, Biswell C. The Importance of Early Screening for Autism Spectrum Disorder [Internet]. Cdd.unm.edu. 2016 [cited 2018 May 25]. Available from: https://www.cdd.unm.edu/ecln/FIT/pdfs/FIT2017/importance-of-early-screening.pdf

symptoms may be misdiagnosed as having a communication disorder or social anxiety (Faras et al, 2010). Children with milder symptoms or other pervasive developmental disorders might go unrecognised or mislabelled until later in childhood or perhaps adulthood (Posey et al, 2008). In case of misdiagnosis, mildly affected children may develop life skills at an early age and be able to function with minimal assistance but severely affected children may not be able to functions in almost any setting and would require constant supervision and care throughout their life (Geier et al, 2013).

Screening tools are used for assessing the presence and severity of autism and ensure that the child is meeting the developmental milestones. Not only is it essential to have a useful screening tool for autism but also the stage at which the evaluation is being done is important. Early screening leads to an early intervention that leads to a better outcome for the child (Johnson and Myers, 2007). Screening individuals with proper tools help to create a tailor-made intervention, which not only helps, in a better prognosis for the child but also improves the quality of life for family members and caretakers (Schreibman et al, 2015).

Screening for autism is a two-tier process and different screening tools are applied at different levels. The level 1 screening, also known as the first stage screening is applied in paediatric population to detect children with potential developmental disorder, the level 2 screening is a selective in-depth screening applied to individuals identified at risk by level 1 tools, to establish and differentiate ASD from other developmental disorder (Matson et al, 2008). The screening tools are used accordingly at different levels of screening.

The level 1 screening tools are administered by a primary health care professional or paediatrician while the level 2 tools are administered by experts such as child psychologists

(Sappok et al, 2015). The screening tools at level 1 should be brief and low-cost tool but the screening tools at level 2 are time-consuming and more expertise is required for the screening (Robins, 2008).

The first attempt to develop a potential screening tool for ASD was made by Baron-Cohen and his colleagues in Europe when they developed the Checklist for Autism in Toddlers (CHAT) (Garcia-Primo et al, 2014). In figure 1.2, screening tools are categorised according to their application at different levels. Some examples of tools used at the level 1 are Checklist for Autism in Toddlers (CHAT), Modified CHAT (M-CHAT), The Early Screening for Autistic Traits (ESAT). Level two screening tools include Childhood Autism Rating Scale (CARS), Gilliam Autism Rating Scale (GARS), and The Screening Test for Autism in Two-Year-Olds (STAT).[13]

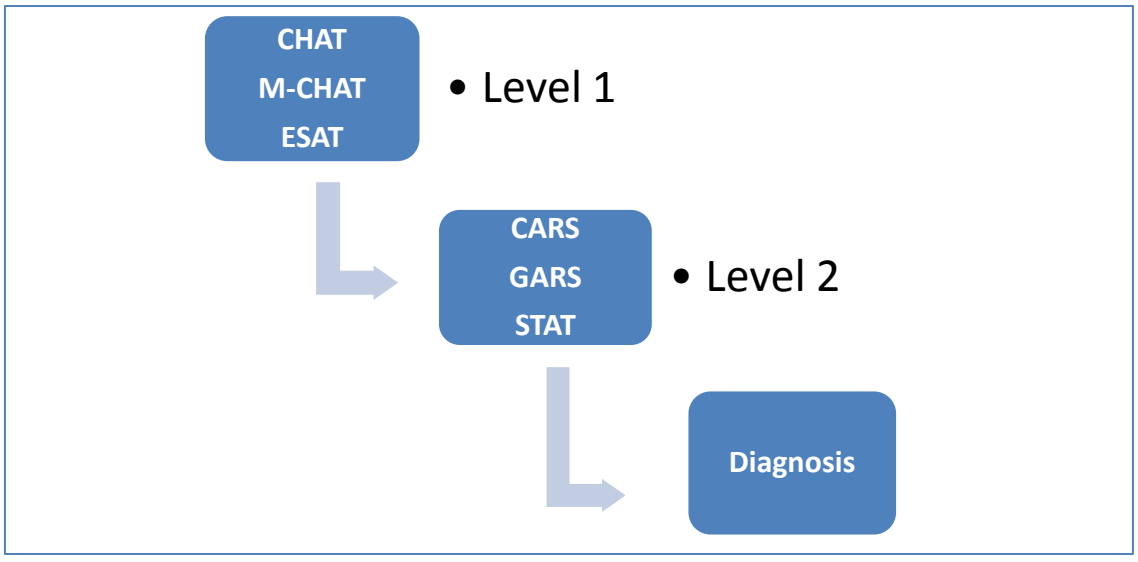

Figure 1.3 Autism Spectrum Disorder Screening Steps and Tools

[13] Lord C, Luyster R. Early Diagnosis and Screening of Autism Spectrum Disorders [Internet]. Medscape. 2005 [cited 2018 May 25]. Available from: https://www.medscape.com/viewarticle/518834_2

The screening tools developed in Europe have been adapted by efficaciously translating and testing the tools in other countries due to ethnocultural factors, for example, M-CHAT was adopted in Spain and Sweden (Garcia-Primo et al, 2014). Out of all the screening tools developed, the best documented and the most reliable rating scale for behaviours associated with autism since its publication in 1980 has been Schopler's Childhood Autism Rating Scale (CARS) (Rapin et al, 2008). CARS is used in many countries including Malta and India and as it is developed in a western country, the tool often requires a license fee to be accessible to patients in different clinical settings such as India. The Indian Scale for Assessment of Autism (ISAA) was developed by the National Institute for Mentally Handicapped, India to overcome the issue and have a culturally appropriate and economic tool (Patra and Arun, 2011). A scale like ISAA was also necessary, as there was no official Indian tool to assess children with ASD and provide them with disability certificate under the Persons with Disability (PWD) Act, which enables children to join schools with special needs (Deshpande et al, 2015).

1.2 Pharmacological Therapies for ASD in Children and Adolescents

ASD is associated with comorbid mental conditions like Attention-Deficit Hyperactivity Disorder (ADHD), epilepsy, anxiety, sleeplessness and learning disabilities (Hsia et al, 2013). The first-line treatment is usually behavioural therapy along with pharmacological therapies added to help patients to function throughout their daily activities, as drugs cannot cure the core symptoms of ASD (LeClerc and Easley, 2015). Drug therapies are targeted towards managing different symptoms associated with ASD, for example, fluoxetine, a selective serotonin reuptake inhibitor (SSRI) is used to manage anxiety or depression in adolescents with ASD (Kolevzon et al, 2006). Methylphenidate is also used to manage

hyperactivity together with behavioural therapy (Kumar et al, 2012). Melatonin has been prescribed in ASD to manage sleep disturbances (Rossignol and Frye 2011). Typical antipsychotics were studied for the irritability associated with autism but their tendency to cause extrapyramidal symptoms (EPS) significantly limited their use. Typical antipsychotics are largely being replaced by atypical antipsychotics to manage irritability associated with autism (Blankenship et al, 2010). The drugs have been prescribed off-label as the only drugs approved by the FDA are risperidone and aripiprazole (RiAr) for the management of irritability associated with ASD in children and adolescents (Posey et al, 2008).

1.2.1 RiAr for Irritability Associated with Autism

In 2006, risperidone was approved by the Food and Drug Administration (FDA) in the USA for the treatment of irritability associated with autistic disorder in 5 to 16-year-olds, including aggression and deliberate self-harm. The approval of risperidone was notable as it was the first antipsychotic to be approved for use in children and adolescents and to be approved for the indication of ASD. Atypical antipsychotics were being used off-label much before the approval by FDA (Posey et al, 2008).

A multisite double blind trial was carried out to measure the safety and efficacy of risperidone in managing severe aggression, tantrums, and self-injurious behaviour in 101 children and adolescents with ASD belonging to the age group 5-17 years. The cohort was randomised to receive 0.5 to 3.5 mg per day of risperidone for 8 weeks or placebo. Significant improvement in behavioural symptoms was noticed in the group receiving risperidone when measured using the Aberrant Behaviour Checklist (ABC) and the Clinical Global Impressions-Improvement scale (CGI-I) scale (McCracken et al, 2002).

The benefits of risperidone for adaptive behaviours were examined in 48 children and adolescents, aged 5 to 16 years and significant improvement was seen in adaptive behaviour in the areas of communication, daily living skills, and socialisation (DeFilippis and Wagner, 2016).

The FDA also approved aripiprazole in 2009 after demonstrating efficacy in the same indication but in 6 to 17-year-olds (Isac et al, 2015). Two large clinical trials and several open studies have been conducted regarding the use of aripiprazole for the indication of ASD. Two large double blind, randomised clinical trials were carried out for 8 weeks to measure the short-term efficacy and safety of aripiprazole in the management of irritability associated with ASD in children and adolescents belonging to age group of 6 to 17 years (Blankenship et al, 2010).

The first study included 218 children and adolescents who were randomised to receive 5, 10, or 15 mg of aripiprazole per day or placebo (Marcus et al, 2009). The second study included 96 children and adolescents who were randomised to receive flexible doses of aripiprazole with a target dose of 5, 10 or 15 mg or placebo. The mean dose was found to be 8.6 mg per day. Significant improvement in irritability was observed in the group receiving aripiprazole when measured using the ABC and the CGI-I scale (Owen et al, 2009). RiAr are the only approved antipsychotics for the indication of ASD due to which it is essential that the drugs are accessible to all.

1.3 Access to RiAr in India and Malta

Access to medicines has become increasingly controversial. The problem of access had been discussed throughout the years with several national policy documents. The first

finalised document was of the World Health Organisation (WHO) in 1977, which included a list of essential medicinal products (Pace et al, 2013). Pharmaceutical policies in a country should be able to balance goals related to the availability, safety, appropriate use of medicines, and affordability of the treatment by the individuals of the country (Morgan et al, 2010).

The National regulatory bodies in India and Malta are responsible for authorisation of drugs in their countries respectively (Figure 1.3). Different procedures are used to provide marketing authorisation to the medicinal product, which affects the accessibility of drugs. The drugs are approved for particular indications, and any use other than indicated is considered off-label.

1.3.1 RiAr Regulations in India

The Central Drugs Standard Control Organisation (CDSCO) is the National Regulatory Authority (NRA) of India. CDSCO is responsible for approval of new drugs by issuing marketing authorisation, conducting clinical trials and maintaining standards and quality of drugs in India. CDSCO works along with the Drugs Control Administration (DCA) to regulate the manufacturing, sales and distribution of approved drugs on a state level.[14] Risperidone is approved by the CDSCO as a maintenance therapy for Bipolar-I disorder.[15] Aripiprazole is approved by the CDSCO only for the treatment of schizophrenia.[16]

[14] CDSCO. CDSCO [Internet]. Cdscoonline.gov.in. 2018 [cited 2018 May 25]. Available from: https://cdscoonline.gov.in/CDSCO/homepage
[15] CDSCO. Risperidone [Internet]. Cdscoonline.gov.in. 2018 [cited 2018 May 25]. Available from: https://cdscoonline.gov.in/CDSCO/Drugs
[16] CDSCO. Aripiprazole [Internet]. Cdscoonline.gov.in. 2018 [cited 2018 May 25]. Available from: https://cdscoonline.gov.in/CDSCO/Drugs

1.3.2 RiAr Regulations in Malta

European Medicines Agency (EMA): **"***The European Medicines Agency (EMA) is a decentralised agency of the European Union (EU)"*. The Agency is responsible for facilitating and developing access to medicine by approving and issuing marketing authorisations. Monitoring safety of drugs and providing the information to the public in the EU. [17] Drugs are approved by various procedures in the EU that affects availability throughout the EU countries.[18]

The originator drug of aripiprazole is Abilify by Otsuka Pharmaceutical. The drug is centrally authorised in the EU, which makes the drug available throughout with a single marketing authorisation. Abilify is approved only for schizophrenia in adults and adolescents and bipolar 1 in children and adolescents.[19] Risperdal (risperidone) is the originator drug manufactured by Janssen Pharmaceuticals.

[17] EMA. European Medicines Agency - About Us - About us [Internet]. Ema.europa.eu. 2018 [cited 2018 May 25]. Available from: http://www.ema.europa.eu/ema/index.jsp?curl=pages/about_us/document_listing/document_listing_000426.jsp&mid=

[18] MA. European Medicines Agency - What we do - Authorisation of medicines [Internet]. Ema.europa.eu. 2018 [cited 2018 May 28]. Available from: http://www.ema.europa.eu/ema/index.jsp?curl=pages/about_us/general/general_content_000109.jsp&mid=WC0b01ac0580028a47

[19] EMA. European Medicines Agency - Find medicine - Abilify [Internet]. Ema.europa.eu. 2018 [cited 2018 May 28]. Available from: http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/000471/human_med_000619.jsp&mid=WC0b01ac058001d124

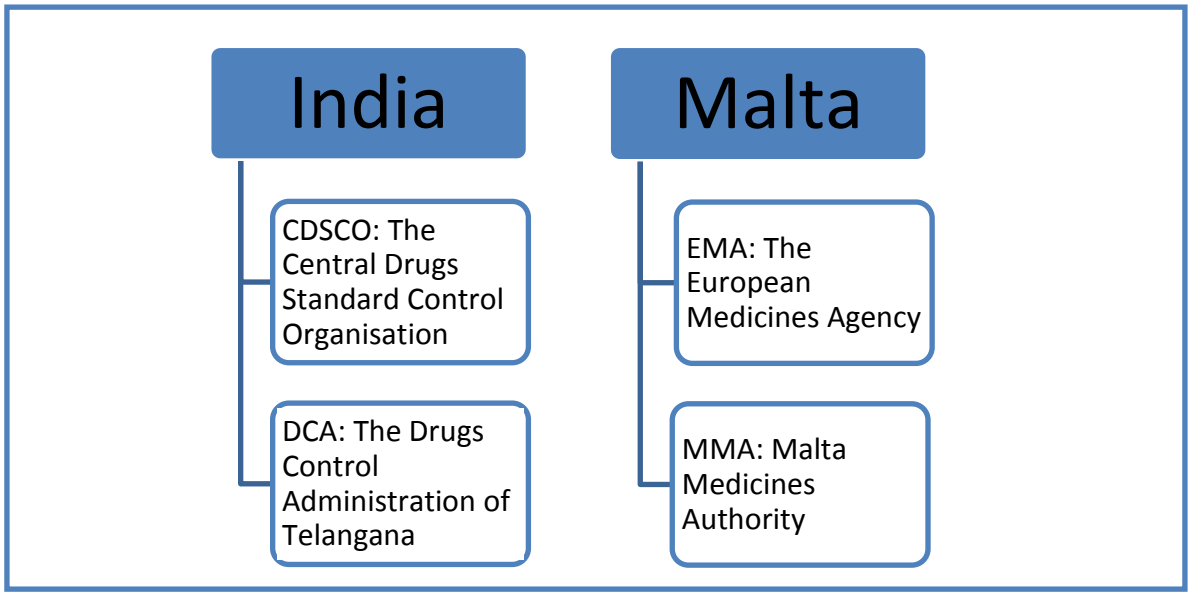

Figure 1.4 National Regulatory Authorisations in India And Malta

The national procedure authorises Risperdal in Malta. It is approved for the schizophrenia and bipolar disorder. RiAr are not indicated for irritability associated with ASD in India[20] and Malta.[21] On 24th July 2007, an article 30 referral was presented to the EMEA to harmonise the SmPC of risperidone in all the countries in EU due to divergence in the text available. The Committee for Medicinal Products for Human Use (CHMP) did not consider the indication of ASD due to lack of specificity and due to risperidone not being able to treat the core symptoms of ASD.[22] The inclusion of ASD indication for Abilify was

[20]CDSCO [Internet]. Cdscoonline.gov.in. 2018 [cited 2018 May 28]. Available from: https://cdscoonline.gov.in/CDSCO/Drugs

[21] EMA. European Medicines Agency - - Risperdal [Internet]. Ema.europa.eu. 2018 [cited 2018 May 28]. Available from: http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/referrals/Risperdal/human_referral_000022.jsp

[22]EMA. [Internet]. Ema.europa.eu. 2018 [cited 2018 May 28]. Available from: http://www.ema.europa.eu/docs/en_GB/document_library/Referrals_document/Risperdal_30/WC500007979

rejected due to the clinical relevance not being established and the lack of robust data presented to the EMA.[23]

1.4 RiAr on National Formularies in India and Malta

The national formularies in India and Malta are National List of Essential Medicine (NLEM) and Schedule V respectively. The NLEM was developed inspired by the WHO list of essential medicine list under the Drug and Cosmetic Act in 1996.[24] The Schedule V was developed under the Act 1 and the fifth schedule of the Social Security (2012) originated under National Assistance act.[25]

The drugs in the NLEM are categorised by therapeutic area and requirement of the drug divided into P (Primary), S (Secondary) and T (Tertiary) level. The essential list is supposed to include the most cost-effective drug options for any indication. It is developed in accordance with the standard treatment guidelines focussing on the healthcare needs of the majority of the population.[26] The drugs included in the list are supposed to be available all year round ensuring access to everyone. Medicines can be bought from a pharmacy by an individual whose prices are fixed by National Pharmaceutical Pricing Authority (NPPA). Risperidone (tablet, syrup) is included under "Psychotic disorders", aripiprazole is not included in the list (Narula 2015).

[23] EMA. [Internet]. Ema.europa.eu. 2018 [cited 2018 May 25]. Available from: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Procedural_steps_taken_and_scientific_information_after_authorisation/human/000471/WC500020172.pdf
[24] WHO. National List of Essential Medicines (NLEM) 2015 - India [Internet]. Apps.who.int. 2018 [cited 2018 May 25]. Available from: http://apps.who.int/medicinedocs/en/d/Js23088en/
[25] Schedule V [Internet]. Deputyprimeminister.gov.mt. 2018 [cited 2018 May 25]. Available from: https://deputyprimeminister.gov.mt/en/poyc/Pages/360%C2%B0-One-Stop-Shop-Service-Concept/Medicines-Approval/Schedule-V.aspx
[26] CDSCO. National List of Essential Medicines 2015 [Internet]. Cdsco.nic.in. 2018 [cited 18 June 2018]. Available from: http://cdsco.nic.in/WriteReadData/NLEM-2015/NLEM,%202015.pdf

The Schedule V in Malta is divided into hospital and outpatient formulary. The list includes seventy-nine chronic conditions and its medications. Risperidone (injection, syrup, tablets) is included under "Chronic psychiatric disorder starting in early childhood", and the list does not include aripiprazole.[27] Social Security Act entitles patients suffering from any of the seventy-nine chronic conditions listed free medications with the help of a yellow card. People are entitled to free medication for a specific disease and entitlement is based upon the presence of disease irrespective of means, income, or age.[28]

1.5 Safety Profile of RiAr

Risperidone is associated with frequent mild and tolerable adverse effects, but weight gain is observed as one of the significant adverse effects (Boon-yashid et al, 2014). Research conducted to study efficacy and secondary effects of RiAr concluded similar safety concerns regarding both the drugs (Cohen et al, 2013).

A controlled trial by Aman et al (2005) to study the safety and tolerability of risperidone in children and adolescents with ASD noticed several ADRs such as enuresis, sleeplessness, weight gain, and drooling.

The most common adverse event was sleeplessness and two experience seizures, which are very serious adverse events to happen in children. Review of safety and efficacy of aripiprazole in children concluded that the main adverse event was sedation and agitation (Kirino 2012).

[27] Ministry for Health. Hospital Formulary List [Internet]. Deputyprimeminister.gov.mt. 2018 [cited 2018 May 25]. Available from: https://deputyprimeminister.gov.mt/en/pharmaceutical/Documents/GFL/hosp_gfl_may_2018.pdf
[28] Ministry for Health. Out-Patients Formulary List [Internet]. Deputyprimeminister.gov.mt. 2018 [cited 2018 May 25]. Available from: https://deputyprimeminister.gov.mt/en/pharmaceutical/Documents/GFL/out_patients_gfl_may_2018.

As the Autism patients may have other underlying conditions such as congenital heart diseases, the risk of adverse effect significantly increases. It has been observed that people treated with antipsychotics have a higher Electrocardiogram (ECG) changes and QT prolongation, which may lead to sudden deaths (Abdelmawla and Mitchell, 2006).

Drug induced adverse events are the reason for discontinuation of the drug for the treatment of the disorder. As RiAr are the only approved drugs, their safety profile should be updated frequently so that consultants are aware of all the risks and take precautions before prescribing.

1.6 Postmarketing Surveillance of Drugs

Postmarketing surveillance is the systematic monitoring of the drugs to ensure quality, safety and efficacy of the drugs post the approval of the drugs. The post-marketing safety surveillance is designed to detect new as well as the safety concerns observed during the pre-approval phase I, II, and III of the drug.[29] The detection of adverse drugs reaction (ADR) in post-marketing safety surveillance is vital due to limitations of pre-marketing drug safety evaluations such as limited cohort in a clinical trial, limited duration if time and bias in selection criteria of cohort resulting in limited heterogeneity (Sultana et al, 2013). The detection of ADRs leads to reasonable regulatory decisions that will affect significant therapeutic advances outcomes.

Pharmacovigilance (PV) is defined as *"the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other drug-related*

[29] Muñoz M. Introduction to Post-Marketing Drug Safety Surveillance: Pharmacovigilance in FDA/CDER [Internet]. Fda.gov. 2018 [cited 2018 May 28]. Available from: https://www.fda.gov/ucm/groups/fdagov-public/@fdagov-afda-gen/documents/document/ucm487405.pdf

problem".[30] Pharmacovigilance plays an essential role in providing updated safety information regarding a drug that would help doctors to decide the prescription of the drug based on risk-benefit evaluation and would create awareness regarding ADRs in patients (Härmark and Van-Grootheest, 2008). The WHO established a programme for international drug monitoring after the thalidomide disaster in 1961. The centre is based in Uppsala monitoring centre in Sweden, and by the end of 2010, 134 countries were part of the WHO PV Programme (Edwards, 2012).

There are two types of data collection in pharmacovigilance, passive data collection and active data collection. The passive data collection depends on voluntary spontaneous reporting method of ADR and medication errors. The active data collection depends on detecting ADR by the use of triggered tools such as laboratory tests.[31] The spontaneous reporting method provides "Signals" concerning suspected ADR for a drug. A signal is defined as the *"Information on a new or known adverse event that may be caused by medicine and requires further investigation".*[32]

1.6.1 Signal Detection

Signal detection is defined as "*the process of looking for and/or identifying signals using data from any source."*[33] Signal detection follows a qualitative or a quantitative methodology to detect signals, which involve a review of individual case safety reports,

[30] WHO. Post market surveillance [Internet]. World Health Organization. 2018 [cited 29 May 2018]. Available from: http://www.who.int/medicines/regulation/ssffc/pms/en/
[31] WHO. Pharmacovigilance [Internet]. Apps.who.int. 2018 [cited 2018 May 29]. Available from: http://apps.who.int/medicinedocs/documents/s19612en/s19612en.pdf
[32] EMA. European Medicines Agency - Pharmacovigilance - Signal management [Internet]. Ema.europa.eu. 2018 [cited 2018 May 25]. Available from: http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000587.jsp
[33] EMA. Guideline on good pharmacovigilance practices (GVP) Module IX – Signal management (Rev 1) [Internet]. Ema.europa.eu. 2017 [cited 2018 May 25]. Available from: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2017/10/WC500236408

statistical analysis or both. Signal detection involves qualitative data mining methods from the spontaneous reporting systems of a country.

Signal detection by various statistical methods generates Signals of Disproportionate Reporting (SDRs). "*SDRs refer to statistical associations between medicinal products and adverse events, i.e. drug-event pairs."*[34] One of the important qualitative methods to measure the disproportionality is Proportional Reporting Ratio (PRR). A PRR makes an assumption that *"when an SDRs (involving a particular adverse event) is identified for a medicinal product (P), this adverse event is reported relatively more frequently in association with this medicinal product P than with other medicinal products".*[35]

A signal does not signify that the reported ADR was caused by the drug being evaluated. A comorbid condition or concomitant medication can cause the ADR in the patients along with other risk factors that could be involved. A causality assessment is essential to establish the relationship between the drug and the ADR.[36]

1.6.2 Causality Assessment of Signals

Causality assessment is defined as a method of *"determination of whether there is a reasonable possibility that the product is causally related to the adverse event".*[37] Systems have been developed around the globe and followed, and many have their interpretation of

[34] EMA. Guideline on the use of statistical signal detection methods in the Eudravigilance data analysis system [Internet]. Ema.europa.eu. 2018 [cited 2018 May 25]. Available from: http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/20
[35] EMA. EudraVigilance and Risk Management [Internet]. Ema.europa.eu. 2018 [cited 2018 May 29]. Available from: http://www.ema.europa.eu/docs/en_GB/document_library/Presentation/2010/12/WC500100020.pd
[36] European Medicines Agency - Pharmacovigilance - Signal management [Internet]. Ema.europa.eu. 2017 [cited 2018 May 25]. Available from: http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000587.jsp
[37] Cobert B. Causality Assessment [Internet]. 2018 [cited 2018 May 25]. Available from: https://www.health.gov.il/UnitsOffice/HD/MTI/Drugs/risk/Conferences/Documents/First-Causality-Israel-2013.pdf

the causality scores. Assessment tools, algorithms decision-making tables have been developed to assess the causality and to have a validated method as the assessment before the development of tools was done by experts who often had disagreements (Kramer, 1986). The World Health Organisation–Uppsala Monitoring centre (WHO–UMC) scale is very commonly used for assessment, which classifies the relationship between the ADR and the drug as ‘Certain’, ‘Likely’, ‘Possible’, ‘Unlikely’ or ‘Unclassified’ (Pande, 2018).

1.6.3 Pharmacovigilance Programme of India

An official ADR monitoring system was initiated in 1986 in India. India became a member of WHO Programme for International Drug Monitoring in the year 1997, managed by the Uppsala Monitoring Centre (UMC), Sweden. A limited number of active centres across India resulted in low spontaneous reports. To overcome the issue, The Government of India has launched National Pharmacovigilance Programme (NPP) in November 2004 with grants from the World Bank. The grants ended in 2009 and the programme was suspended (Lihite and Lahkar, 2015).

The Pharmacovigilance Programme of India (PvPI) was initiated by the Government of India in 2010 together with the All India Institute of Medical Sciences (AIIMS), New Delhi as the National Coordination Centre (NCC) for monitoring Adverse Drug Reactions (ADRs) in the country realising the need for a stronger ADR monitoring programme. The PvPI runs in collaboration with the WHO Programme for International Drug Monitoring

(PIDM).[38] In 2011, the NCC was shifted to CDSCO under the legislation of Ministry of health and family welfare (Biswas, 2013). The PvPI is still in its infancy in India.

The electronic database in India for the management system of Individual Case Safety Report (ICSR) is "VigiFlow" which is specifically designed to be used by national centres in the WHO PIDM (Chandel et al, 2014). Pharmaceutical companies or clinical research organisations can also use it for monitoring of their ICSR. The WHO global ICSR database is known as "Vigibase" and is managed by the UMC (Kumar and Khan 2015). The programme communication and flow of ADR in the PvPI are described in figure 1.4 adopted by Lihite and Lahkar (2015).

1.6.4 Pharmacovigilance Programme in Malta

EudraVigilance is "*the system for managing and analysing information on suspected adverse reactions to medicines which have been authorised or being studied in clinical trials in the European Economic Area (EEA). The European Medicines Agency (EMA) operates the system on behalf of the European Union (EU) medicines regulatory network"*.[39]

[38] WHO. Collaborating Centre for Pharmacovigilance in Public Health Programmes and Regulatory Services [Internet]. World Health Organization. 2018 [cited 2018 May 25]. Available from: http://www.who.int/medicines/regulation/medicines-safety/about/collab-

[39] European Medicines Agency - Pharmacovigilance - EudraVigilance [Internet]. Ema.europa.eu. 2017 [cited 2018 May 25]. Available from: http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000679.jsp&mid=WC0b01ac05800250b5

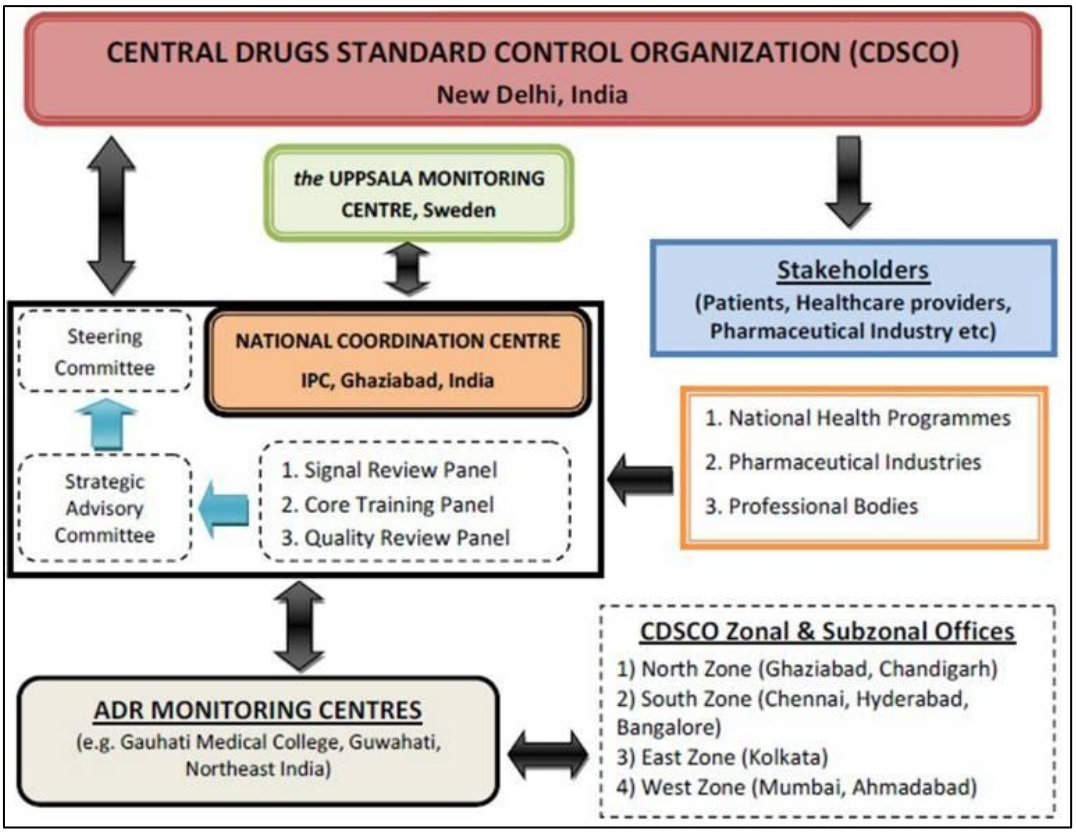

Figure 1.5 Indian Programme Communication and Flow of Adverse Drug Reaction Reports

Adopted from Lihite R, Lahkar M. An update on the Pharmacovigilance Programme of India. Frontiers in Pharmacology. 2015;6

In 2010, the new pharmacovigilance legislation under the Directive 2010/84/EU and regulation 1235/2010 amended the existing legislation the European Union (EU). The aim of the legislation was to promote and protect public health by enhancing the safety monitoring system in the EU (Tanti et al, 2017).

The changes were made to improve patient safety and public health through better prevention, detection, and assessment of adverse reactions to medicines. It also allowed patients to report adverse drug reactions directly to the competent authorities.[40]

[40] European Commission. Public Health. *Pharmacovigilance - Public Health - European Commission*.2017 [online] Available at: https://ec.europa.eu/health/human-use/pharmacovigilance_en [cited 2018 May 28].

The database management system in the EU for the management of ICSR is the Eudravigilance Database Management System (EDBMS) and the system for detection and analysis of ICSR EudraVigilance data analysis system (EVDAS)[41]. Figure 1.5 describes the Eudravigilance system overview.[42]

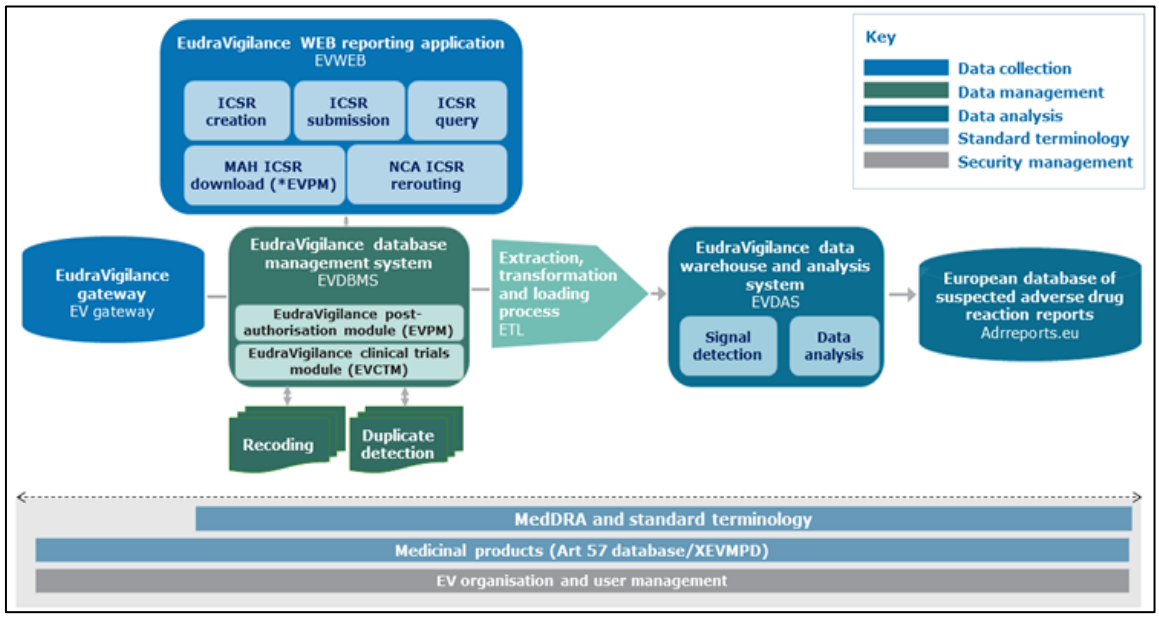

Figure 1.6 Eudravigilance System Overview

Adopted from EMA. European Medicines Agency - EudraVigilance - EudraVigilance system overview [Internet]. Ema.europa.eu. 2018 [cited 2018 May 25]. Available from: http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/q_and_a/q_and_a_detail_000166.jsp

1.7 Rationale of the Study

The prevalence rates of ASD are on the rise worldwide, but the healthcare professionals, patients and caregivers are still not sufficiently educated regarding the underlying symptoms of autism. RiAr are the only approved drugs for the management of ASD and the

[41] EMA. European Medicines Agency - EudraVigilance - EudraVigilance system overview [Internet]. Ema.europa.eu. 2018 [cited 2018 May 25]. Available from: http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/q_and_a/q_and_a_detail_000166.jsp&mid=WC0b01ac0580a68f78

[42] EMA. European Medicines Agency - EudraVigilance - EudraVigilance system overview [Internet]. Ema.europa.eu. 2018 [cited 2018 May 25]. Available from: http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/q_and_a/q_and_a_detail_000166.jsp

accessibility, affordability and safety of RiAr is crucial. The primary step in identifying ASD is screening, which involves a screening tool. The rationale of the study is to evaluate if cultural and economic differences affect the approach towards treatment of ASD in India and Malta.

1.8 Research Questions

The review of the state-of-the-art regarding ASD and its treatment in India and Malta gave rise to research questions that will lead to filling the research gaps identified while reviewing the literature.

1. Does the cultural difference affect the approach towards autism in India and Malta?
2. Do the culturally developed screening tools (ISAA/ CARS) have a different influence on the prescribing behaviour of drugs?
3. How will the regulation of RiAr in India and Malta affect the accessibility and affordability of the drugs?
4. Are all the RiAr induced ADRs generated by Eudravigilance reflected in the SmPC?

1.9 Aims and Objectives

The research aims to study the accessibility, prescribing behaviour and safety of RiAr in children and adolescents. The objectives of the study are

1. To develop and administer a questionnaire to psychiatrists to measure the impact of cultural, economic and regulatory differences on approach towards ASD (Part I).
2. To measure the accessibility and affordability of RiAr in India and Malta (Part II).
3. To conduct Eudravigilance signal detection and assessment to detect potential ADR to be included in the SmPC of RiAr (Part III).

Chapter 2 Methodology

2.1 Part I-Autism Spectrum Disorder Comparative Questionnaire: India-Malta [ASD-Q $_{(IND-MT)}$]

The section explains the steps involved in development, validation and dissemination of the ASD-Q $_{(IND-MT)}$ in India and Malta.

2.1.1 Design of ASD-Q $_{(IND-MT)}$

Autism Spectrum Disorder Comparative Questionnaire India-Malta [ASD-Q $_{(IND-MT)}$] was designed to collect and compare opinions from psychiatrists in India and Malta on autism to measure if cultural, economic and regulatory differences would affect the approach towards treatment and prescribing behaviour of antipsychotics in children and adolescents with ASD. The questionnaire measures the level of agreement or disagreement on statements referring to autism spectrum disorder (ASD), its screening tools, medication and their accessibility.

The ASD-Q $_{(IND-MT)}$ was intended for psychiatrists as the antipsychotics can be prescribed only by psychiatrists in India and Malta. Two versions of the questionnaire were developed, one with Indian specific details [ASD-QI $_{(IND-MT)}$] and other with Malta specific details (ASD-QM $_{(IND-MT)}$] to remove any bias. The Indian version of the questionnaire was designed to collect information on an Indian autism screening tool, Indian Scale of Assessment of Autism (ISAA), Indian national formulary and regulations (Appendix 1). The Maltese version of the questionnaire was designed to collect information on a western autism screening tool used in Malta, Childhood Autism Rating Scale (CARS), Maltese national formulary and regulations (Appendix 2).

2.1.2 Structure of ASD-Q (IND-MT)

The developed ASD questionnaire is divided into six sections and has 28 questions in total. The questions are close-ended questions and a 5-point Likert scale is used to collect answers ranging from 1-5, where 1 is the lowest score and 5 is the highest score. The Likert scale markers differ in sections as explained below. The sections are divided were as follows and evaluate:

- Section 1: Demographics
- Section 2: Importance of early detection of ASD
- Section 3: Role of pharmacists in detection and management of ASD
- Section 4: Accessibility of antipsychotics
- Section 5: Influence of screening tool based on scores obtained
- Section 6: Interpretation of final scores obtained through CARS/ ISAA

- **Section 1:** Collects data relating to the participants of the questionnaire for example age, sex, years of practice and amount of new and repeat autism cases dealt within a month.
- **Section 2:** This section contains a set of 12 different statements. The questions focus on the opinions regarding ASD and its screening tools detection of ASD and the CARS/ ISAA. The Likert scale marker in this section ranges from 1- 5 where 1 was ‘strongly disagree’ and 5 was ‘strongly agree’.
- **Section 3:** This section focuses on the role of pharmacists in detection and treatment of ASD by being a part of multidisciplinary team. It consists of 9 questions mentioning pharmacists who are experts in different practice areas like community, hospital and clinical pharmacy, which may efficiently lead to the better intervention of the disorder.

The Likert scale marker is similar to previous section ranging from 1-strongly agree to 5- strongly disagree.

- **Section 4:** This section contains four questions focusing on the importance of accessibility of the antipsychotics and the importance of studying the safety of these drugs post-marketing. This section also has similar Likert scale marker as previous sections.
- **Section 5:** This section obtains an opinion on the influence of screening tool's score on the prescribing behaviour of RiAr in children and adolescents. The section contains only one question, and the Likert scale in this section ranges from 1 being 'not at all influential' to 5 being 'extremely influential'.
- **Section 6:** This section examines the interpretation of the final score obtained by the screening tools (ISAA/CARS). The section contains two questions, and the Likert scale markers range from no autism to severe autism depending on the screening tool being evaluated.

2.1.3 Validation of ASD-Q $_{(IND-MT)}$

Validation of the ASD-Q $_{(IND-MT)}$] was performed to calculate the relevance of the content in the questionnaire by a panel of experts from different fields following the Content Validity Index (CVI) adapted from Lynn, M (1986).

2.1.3.1 Characteristics of Content Validity Index (CVI) Method

Content validity has been defined as '*the degree to which an instrument has an appropriate sample of items for the construct being measured'*. The CVI measures content validity of each item individually (I-CVI) and content validity of the whole scale (S-CVI) (Polit and

Beck, 2006). The CVI method as described by Lynn M (1986) focuses on evaluating the relevance of the content through expert assessment involved in a panel and also recommends the number of experts required to validate the questionnaire positively.

The content validity determination required five steps and two stages:

- **Stage 1: Developmental stage:**

Stage 1 consisted of three main steps that were:

1. Identification of full content domain for the questionnaire intended for validation
2. Item generation and
3. Formation of instrument/ ASD questionnaire

The stage one involves identification and development of the ASD-Q $_{(IND-MT)}$ questionnaire to be validated in stage two.

Stage 2: Judgment- quantification stage:

This stage contained two final steps as noted by Lynn (1986), the first step involves validating the individual items (I–CVI), and the second step involves content validating the entire scale (S-CVI).

4. Quantification of content validity of each item in the questionnaire (I-CVI)
5. Quantification of content validity of instrument / the whole questionnaire (S-CVI)

The two steps of validation require the development of a validation tool to be disseminated to the panel members to validate the questionnaire.

2.1.3.2 Selection of Experts for CVI Method

The selection of the number of experts was determined by the CVI method, 10 members were invited to participate in the validation phase, and all the panel members were from Malta. The panel included:

- 4 psychologists
- 2 community pharmacists
- 3 hospital / clinical pharmacists
- 1 paediatrician

All the participants had been working with the state general hospitals with patients who have ASD. The pharmacists were selected from different institutions.

The experts were invited to participate in the research through personal contacts via e-mail. A content validity index tool was developed and (CVI-T) disseminated to all the panel members. The application of the CVI-T was explained to each member. The validation procedure took approximately 10 – 15 minutes for completion. All the responses were collected and analysed.

2.1.3.3 Content Validity Index Tool (CVI-T)

A tool was developed following recommendations mentioned by Lynn, M (1986). The CVI-T (Appendix 3) evaluates the relevance of individual items and the scale. The tool was generated by using a 4 –point rating scale, where 1 signifies an irrelevant item and four an extremely relevant item. A table (Table 2.1) was developed representing the relevance

interpretation, which the experts had to follow to measure the relevance of each question. Steps involved in validating and disseminating the questionnaire is described in figure 2.1

Table 2.1 Relevance Interpretation Table for Validation of the Questionnaire

Numbers	Relevance interpretation
1	Not relevant
2	Unable to access relevance without item revision
3	Relevant but needs minor alterations
4	Very relevant and succinct

Adopted from Lynn, M. Determination and Quantification of Content Validity. Nursing Research, 1986; 35(6):382-386.

2.1.4 Dissemination of ASD-Q $_{(IND-MT)}$

The ASD-Q $_{(IND-MT)}$ was disseminated to forty-seven psychiatrists (N=47) via Google forms. The ASD-QI $_{(IND-MT)}$ was disseminated to 31 psychiatrists in India, Hyderabad (n=31) and the ASD-QM $_{(IND-MT)}$ was disseminated to 16 psychiatrists in Malta (n=16). Junior psychiatrists were also included in the study due to less number of specialised child psychiatrists in Malta.

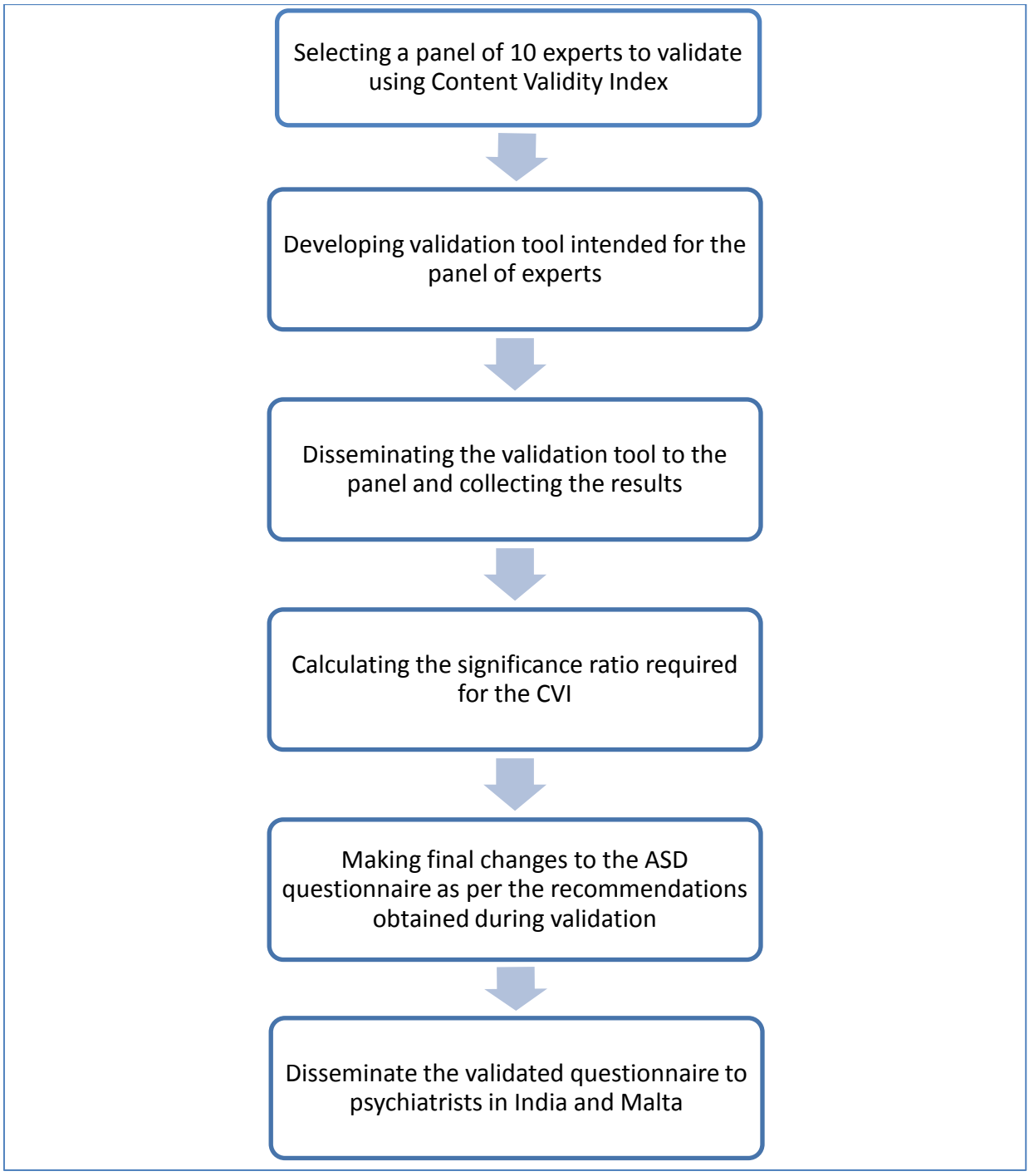

Figure 2.1 Steps Involved In Validating and Disseminating the ASD-Q (IND-MT)

2.1.5 Statistical Analysis of ASD-Q (IND-MT)

The data were coded and analysed using Statistical Package for the Social Sciences (SPSS) version 24 (IBM SPSS Statistics). Twenty-six questions were evaluated using Mann-Whitney U test, and two questions were analysed using the Chi-square test.

The Mann-Whitney U test will compare the mean score obtained through a statement between two independent groups (India and Malta). The mean score ranges from 1-5 where one corresponds to 'strongly disagree' or 'not influential at all' and five corresponds to 'strongly agree' or 'extremely influential'.

The null hypothesis specifies that the mean score provided to a statement vary marginally between the two groups and is accepted if the p-value exceeds 0.05 level of significance ($p>0.05$). The alternate hypothesis specifies that the mean score was statistically significant between two groups and is accepted if the p-value if less than 0.05 ($p<0.05$) criterion.

The Chi-square test was used to access the relation between two categorical variables. One of these variables will describe the nationality of the psychiatrists (India and Malta) where the other categorical variable describes the level of severity of autism based on the scores from the screening tools (ISAA/ CARS).

The null hypothesis specifies that there is no association between the two categorical variables and is accepted if the p-value exceeds the 0.05 level of significance ($P>0.05$). The alternative hypothesis specifies that there is a significant association between the two categorical variables and is accepted if the p-value is less than the 0.05 criterion ($P<0.05$).

2.1.6 Ethics Approval

Ethics approval was obtained from the Faculty of Ethics Committee at the University of Malta (Appendix 4).

2.2 Part II- Accessibility of RiAr in India and Malta

The accessibility of RiAr in India and Malta is measured by analysing and comparing the price of available RiAr in two countries and the affordability of the treatment in ASD. The methodology is adapted from the WHO model of measuring and comparing accessibility of drugs in two different counties.[43]

2.2.1 Comparison of Prices of Individual Medicine

The WHO methodology to compare the price of drugs in two countries is to compare the price of either originator drugs or the cheapest generics available. The originator drugs are Risperdal (Risperidone) by Janssen Pharmaceutical and Abilify (Aripiprazole) by Otsuka Pharmaceuticals. Originator prices of risperidone were compared in both countries, and generic brand prices of aripiprazole were compared due to unavailability of stock of Abilify in Malta as per March 2018 (Figure 2.2).

Dispensing price of Risperdal 1mg tablet was collected from the Medicines Authority database in Malta and National Pharmaceutical Pricing Authority (NPPA) in India. Prices were also confirmed by a chain of pharmacies in Malta and India respectively. The Price of the cheapest available generic brand of aripiprazole was collected from pharmacies in

[43] WHO. Measuring medicine prices, availability, affordability and price components [Internet]. Who.int. 2018 [cited 2018 May 25]. Available from: http://www.who.int/medicines/areas/access/OMS_Medicine_prices.pdf

Malta and India, Hyderabad. The prices obtained from India were converted to euro using nominal exchange rate during March 2018.

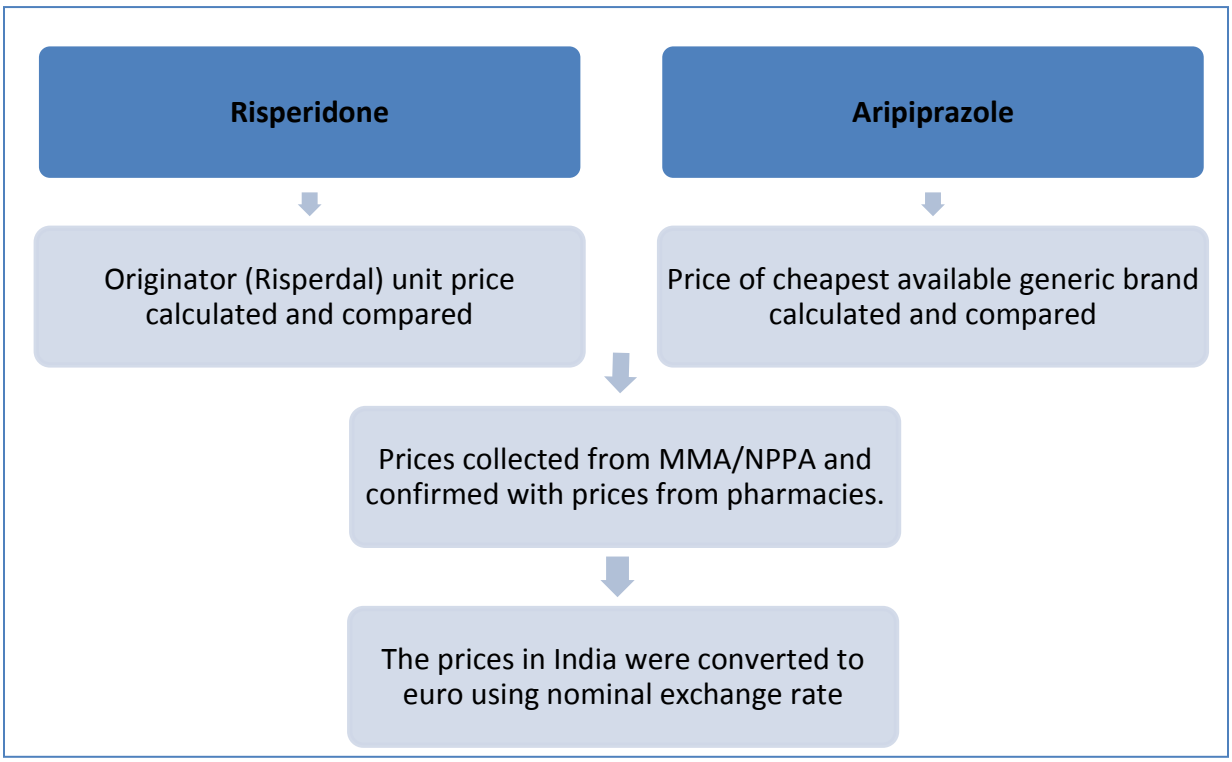

Figure 2.2 Methodology to Calculate the Unit Price of Risperidone and Aripiprazole

2.2.2 Comparison of Affordability of the Treatment

This methodology includes evaluating and comparing the affordability of one month of treatment for ASD patients with RiAr. Cost of one month of treatment was calculated using the recommended daily effective dose by the FDA for the treatment of ASD. Cost variation percentage was calculated between India and Malta. The cost of treatment was compared against the Monthly Per Capita Expenditure (MPCE) of households in India and Malta to obtain an indication of the affordability of the treatment (Figure 2.3).

The MPCE is defined as the household consumer expenditure on each item for a reference period.[44] MPCE is used as a universally applicable indicator of the level of living of the population of a country. Average MPCE was calculated based on the Household budgetary survey conducted in Malta (2015).[45] In India, an average MPCE was calculated for both urban and rural areas based on the National statistical survey conducted in India (2012). [46]

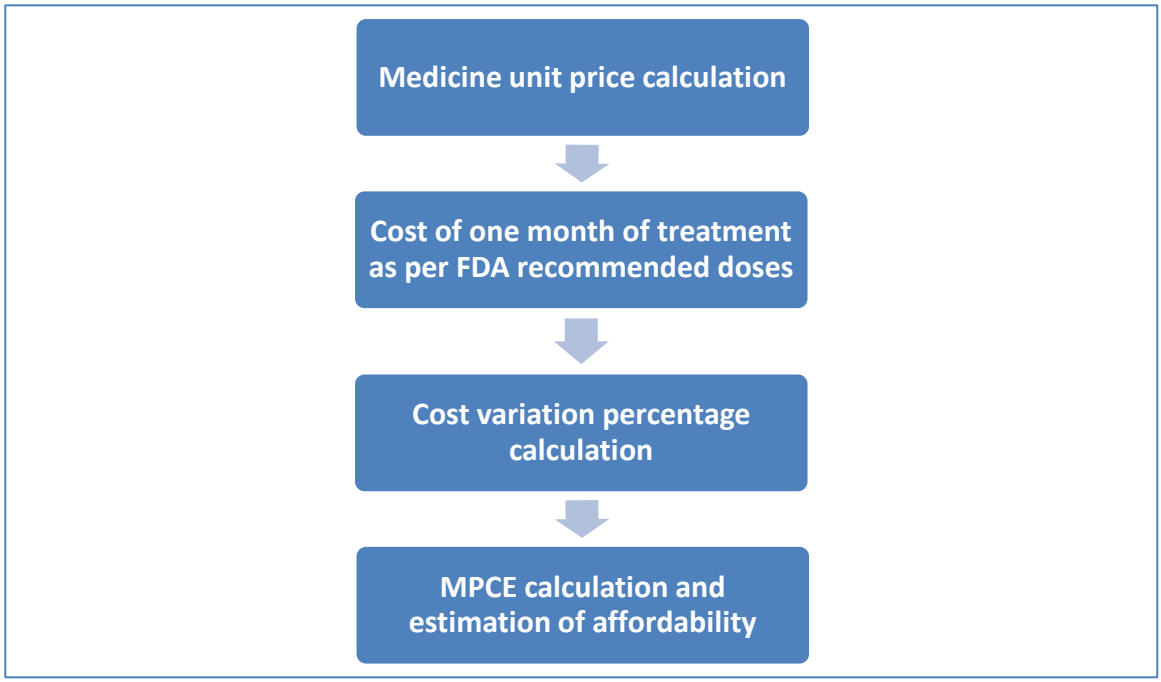

Figure 2.3 Steps Involved In Measuring Affordability of the Treatment

[44] OGD. Monthly Per Capita Expenditure [Internet]. Open Government Data (OGD) Platform India. 2018 [cited 2018 May 25]. Available from: https://data.gov.in/keywords/monthly-capita-expenditure
[45] NSO. Household Budgetary Survey 2015 [Internet]. Nso.gov.mt. 2018 [cited 25 May 2018]. Available from:https://nso.gov.mt/en/publicatons/Publications_by_Unit/Documents/C1_Living_Conditions_and_Culture_Statistics/HBS%20Publication%202015.pdf
[46] MOSPI. India - Household Consumer Expenditure, NSS 68th Round Sch1.0 Type 2: July 2011 - June 2012, Type - 2 - Overview [Internet]. Mail.mospi.gov.in. 2018 [cited 2018 May 25]. Available from: http://mail.mospi.gov.in/index.php/catalog/145

2.3 Part III- Eudravigilance Signal Detection and Analysis

This methodology includes detecting ADRs not listed in the European approved SmPC of RiAr in children and adolescents and assessing the signals using the French causality assessment. The steps involved are summarised in figure 2.4.

The PRR report including the signals was extracted from EVDAS applying an age filter of 5-16 years for risperidone and 6-17 years for aripiprazole as per the FDA recommendations. Valid signals from November 2001 to September 2017 were extracted and the cut of date for the extraction of signals was 25th September 2017.

A PRR report is calculated based on the 2x2 contingency table (table 2.2) for the computation of the PRR.

Table 2.2 Data Mining Algorithm- Proportional Rate Ratio

	Events (E)	**All other events**	**Total**
Medicinal Product (P)	A	B	A+B
All other medicinal products	C	D	C+D
Total	A+C	B+D	N = A+B+C+D

A=Individual cases for P involving adverse event E

B= Individual cases for P involving another adverse event than E

C=Individual cases involving E but for other medicinal product than P

D= Individual cases involving other events than E and for other medicinal product than P

The PRR for the event is computed using the formula[47]:

$$PRR = \frac{A/(A+B)}{C/(C+D)}$$

The PRR report can be extracted using different criteria for spontaneous reports, and the SDRs are highlighted if

- Number of ICSRs $\geq$ 3 and
- Lower bound of 95% Confidence Interval of PRR $\geq$ 1

A PRR (+) and PRR (-) indicate the upper and the lower bounds of the 95% confidence interval of the PRR.

The SDRs (in red) from the PRR report were extracted to check the expectedness of the signals by reviewing the approved European SmPC. The filtered signals were checked for the indication of ASD by searching the medical dictionary for regulatory activities (MedDRA) terminologies. Individual Case Safety Reports (ICSR) was extracted and causality assessment was carried out.

The French causality assessment (Imputability method) was conducted which includes evaluation of case chronologically as described in table 2.3 and semiologically as described in table 2.4. The causal relationship is determined based on the final decision-making table of the assessment (Table 2.5).

[47] EMA. Guideline on the use of statistical signal detection methods in the Eudravigilance data analysis system [Internet]. Ema.europa.eu. 2018 [cited 2018 May 29]. Available from: http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/20

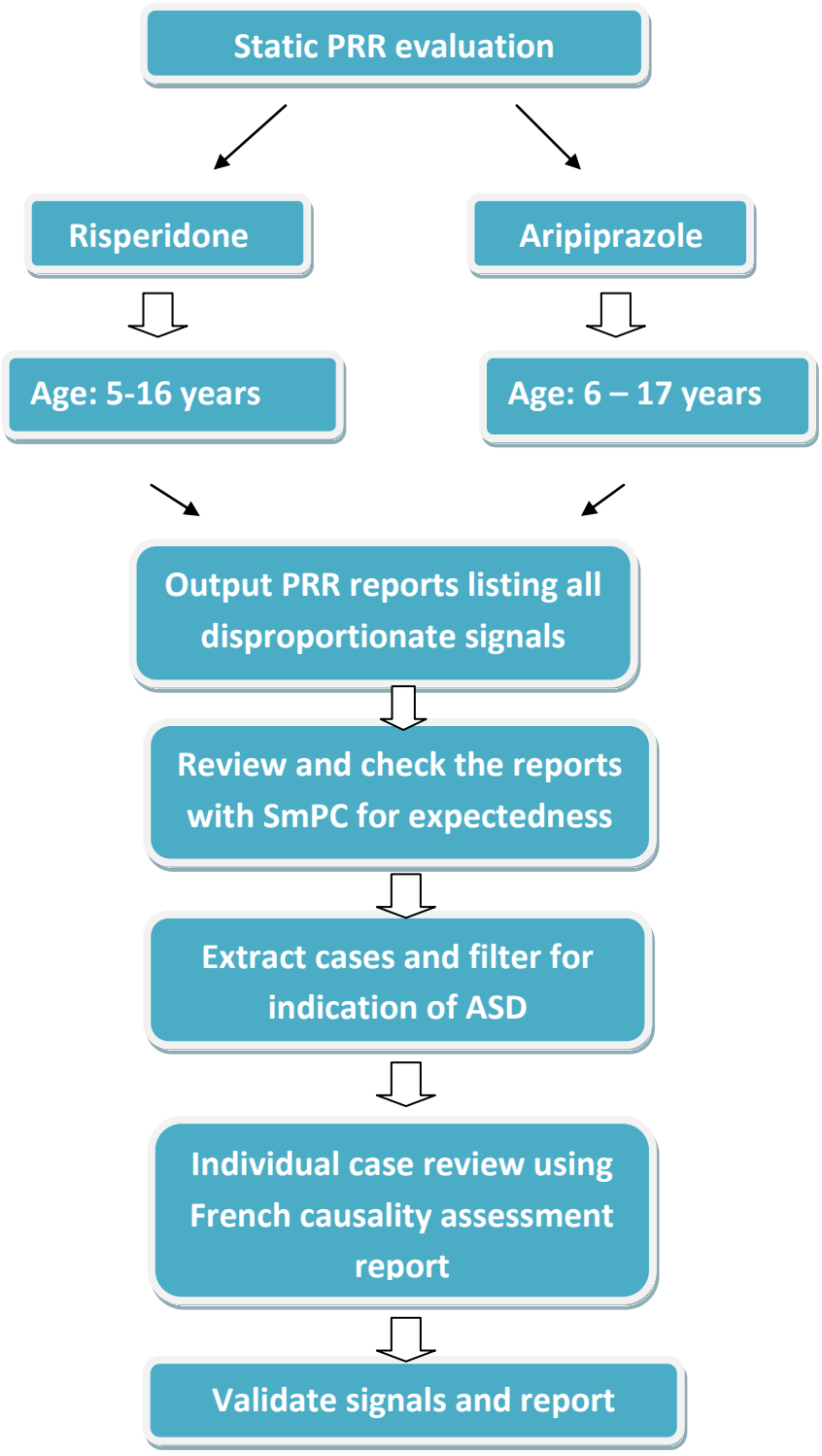

Figure 2.4 Developmental Steps Involved in the Methodology of Studying Safety Using Eudravigilance

Table 2.3 Chronological Imputability

	Rechallenge (R)						
	Challenge Very Suggestive			Challenge Compatible			
Dechallenge	R+	R0	R–	R+	R0	R–	Challenge Incompatible
Suggestive: event regression seems linked to drug withdrawal	C3	C3	C1	C3	C2	C1	C0
Inconclusive: regression of the event seems spontaneous or induced by nonspecific treatment known to be effective or unknown evolution or too short follow-up or irreversible lesions (or drug not withdrawn)	C3	C2	C1	C3	C1	C1	C0
Unsuggestive: no regression of reversible event (or complete regression without drug withdrawal)	C1	C1	C1	C1	C1	C1	C0

Abbreviations: C0, incompatible chronology; C1, dubious chronology; C2, possible chronology; C3, suggestive chronology; R+, rechallenge positive; R–, rechallenge negative; R0, rechallenge not performed.

Adopted from Benahmed S, Picot M, Dumas F, Demoly P. Accuracy of a Pharmacovigilance Algorithm in Diagnosing Drug Hypersensitivity Reactions. Archives of Internal Medicine. 2005;165(13):1500.

Table 2.4 Semiological Imputability

Variable	Reliable and Specific Laboratory (L) Test					
	Suggestive of the Drug and/or Favoring Factor			Other Cases		
Alternative non–drug-related explanation	L+	L0	L–	L+	L0	L–
None after an appropriate search	S3	S3	S1	S3	S2	S1
Possible or present	S3	S2	S1	S3	S1	S1

Abbreviations: L+, test result positive; L–, test result negative; L0, test not performed; S1, dubious; S2, possible; S3, suggestive history.

Adopted from Benahmed S, Picot M, Dumas F, Demoly P. Accuracy of a Pharmacovigilance Algorithm in Diagnosing Drug Hypersensitivity Reactions. Archives of Internal Medicine. 2005;165(13):150

Table 2.5 Final Decision-Making Table-French Causality (Imputability) Assessment

Chronology (C)	Symptom (S) Score		
	S1	S2	S3
C0	I0	I0	I0
C1	I1	I1	I2
C2	I1	I2	I3
C3	I3	I3	I4

Abbreviations: I0, unlikely imputability; I1, dubious imputability; I2, possible imputability; I3, likely imputability; I4, very likely imputability.

Adopted from Benahmed S, Picot M, Dumas F, Demoly P. Accuracy of a Pharmacovigilance Algorithm in Diagnosing Drug Hypersensitivity Reactions.Archives of Internal Medicine. 2005;165(13):1500

2.4 Publications

Two abstracts entitled "*Accessibility and safety of antipsychotics in the treatment of Autism Spectrum Disorder in children and adolescents"* and "*Affordability of Risperidone and Aripiprazole for the Treatment Of Autism Spectrum Disorder"* were submitted for the American College of Clinical Pharmacy (ACCP) Global Conference on Clinical Pharmacy held in Seattle, Washington from 20 to 23rd October, 2018 (Appendix 6) and the 78th International Pharmaceutical Federation (FIP) World Congress of Pharmacy and Pharmaceutical Sciences held it Glasgow, UK from 2 - 6 September 2018 (Appendix 7) for a poster presentation.

Chapter 3 Results

3.1 Part I- Analysis of Validation of ASD-Q $_{(IND\text{-}MT)}$ Using Content Validity Index Tool

The results were analysed based on the method described in the CVI determination. After collecting all the responses from the experts, the significance of each item was calculated by taking the proportion of some experts endorsing the item as content valid (a rating of 3 or 4 on the content validity index tool) by a number of total experts in the panel. The formula used to calculate the CVI is mentioned in the equation below.

$$CVI\left(\frac{A}{B}\right) = \frac{(\mathrm{A})\text{Number of experts endorsing the item as content valid}}{(B)\text{Number of total experts in the panel}}$$

The significance of the results as compared to the cut of the mean score of 0.70 as explained by the author Lynn as mentioned in table 3.1. The calculated statistics are described in table 3.2.

Table 3.1 Proportions of Experts Required to Establish Significant Level of Content Validity

Number of Experts	Number of Experts Endorsing Item or Instrument as Content Valid								
	2	3	4	5	6	7	8	9	10
2	1.00								
3	.67	1.00							
4	.50	.75	1.00						
5	.40	.60	.80	1.00					
6	.33	.50	.67	.83	1.00				
7	.29	.43	.57	.71	.86	1.00			
8	.25	.38	.50	.63	.75	.88	1.00		
9	.22	.33	.44	.56	.67	.78	.89	1.00	
10	.20	.30	.40	.50	.60	.70	.80	.90	1.00

Note: The caution over using the standard error of the proportion when $n \leq 10$ (Downie & Heath, 1974) does not apply in this situation because only when $p > q$ is there significance, and any nonunique p [×] q solutions are irrelevant.

Adopted from Lynn, M. Determination and Quantification of Content Validity. Nursing Research. 1986; 35(6) 382-86.

Table 3.2 Statistics of Content Validity Index

Questions	No of experts endorsing item as content valid (a rating of 3/4) (a)	No of experts in the panel (b)	CVI (a/b)
Section I			
A	10	10	1.00
B	10		1.00
C	10		1.00
D	10		1.00
E	10		1.00
F	10		1.00
Section II			
1	10	10	1.00
2	10		1.00
3	9		0.9
4	10		1.00
5	9		0.9
6	10		1.00
7	10		1.00
8	10		1.00
9	9		0.9
10	10		1.00
11	10		1.00
12	9		0.9
Section III			
13	10	10	1.00
14	8		0.8
15	8		0.8
16	9		0.9
17	8		0.8
18	10		1.00
19	7		0.7
20	9		0.9
21	10		1.00
Section IV			
22	10	10	1.00
23	10		1.00
24	10		1.00
25	10		1.00
Section V			
26	7	10	0.7
Section VI			
27	10	10	1.00
28	10		1.00

The final version of the questionnaire was amended according to the recommendations by the panel of experts during the validation. The summary of changes has been explained in table 3.3.

Table 3.3 Summary of Changes to the ASD-Q $_{(IND-MT)}$ After Validation

1. A new question was added in section 1 which determines the number of repeat patients that psychiatrists deal within a month
2. Question 17 and 19 were reworded for a better understanding of the questions
3. Questions in section V were separated, and a new section was created
4. A new question was added in section V measuring the influence of screening tool (CARS/ ISAA)
5. Question 25 and 26 were reworded according to the suggestions provided by experts in the panel.

3.2 Descriptive Statistics of ASD-Q $_{(IND-MT)}$

The section of the chapter explains the descriptive statistics by the analysis of responses received after dissemination of ASD-Q $_{(IND-MT)}$ in India and Malta. Forty-seven psychiatrists participated in the study out of which 31 were Indian and 16 were Maltese psychiatrists.

In India, 18 psychiatrists were of age group 31-40 years, 7 were 41-50 years old, and 3 were 51-60 years old. In Malta, 3 psychiatrists were less than 30 years old, 7 were 31-40 years old, 4 were 41-50 years old, and 2 were 51-60 years old (Figure 3.1).

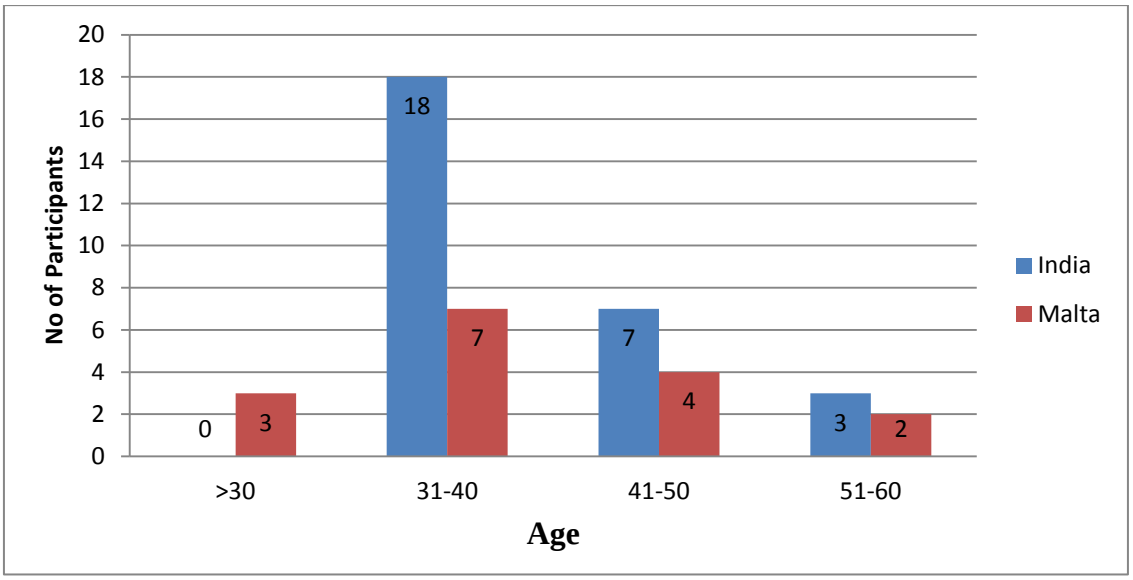

Figure 3.1 Age of the Participants in India and Malta

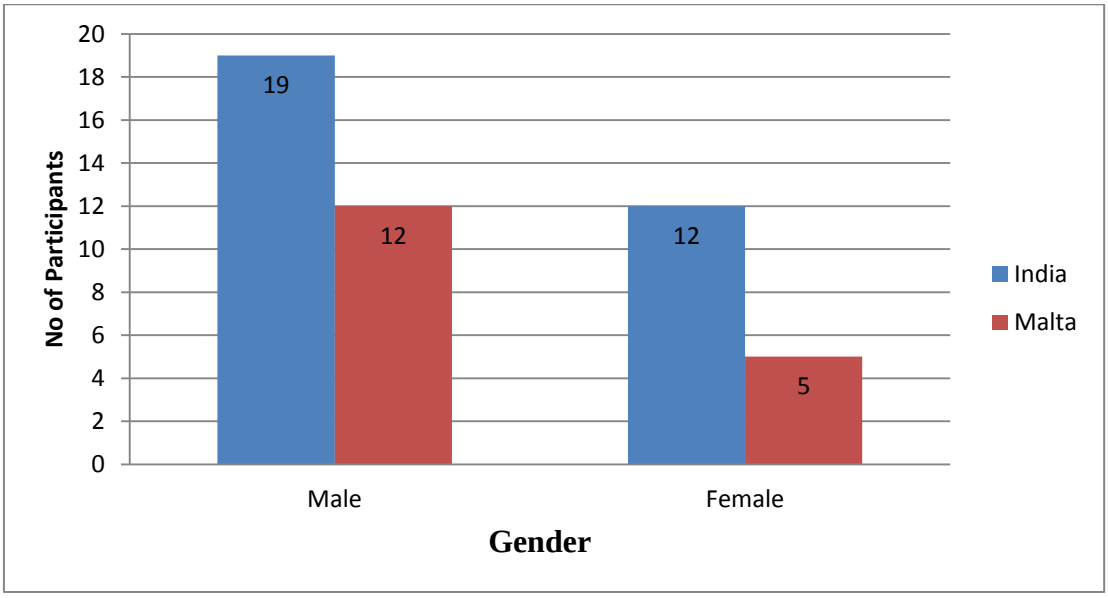

Figure 3.2 Gender of the Participants

In India, 19 psychiatrists were male and 12 female. In Malta, 12 psychiatrists were male, and 4 were female (Figure 3.2).

In India, 8 psychiatrists have been practising psychiatry for 2-4 years, 11 for 5-7 years, 9 for 8-10 years and 2 more than ten years. In Malta, 3 psychiatrists have been practising for

less than or equal to 1 year, 7 for 5-7 years, 4 for 8-10 years, and 2 more than 10 years (Figure 3.3).

In India, 5 psychiatrists diagnose 0-1 child every month with ASD, 17 diagnose 2-4 children, 5 diagnose 5-7 children, and 4 diagnose 8-10 children with ASD. In Malta, 12 psychiatrists diagnose 0-1 child and 4 diagnose 2-4 children every month with ASD (Figure 3.4).

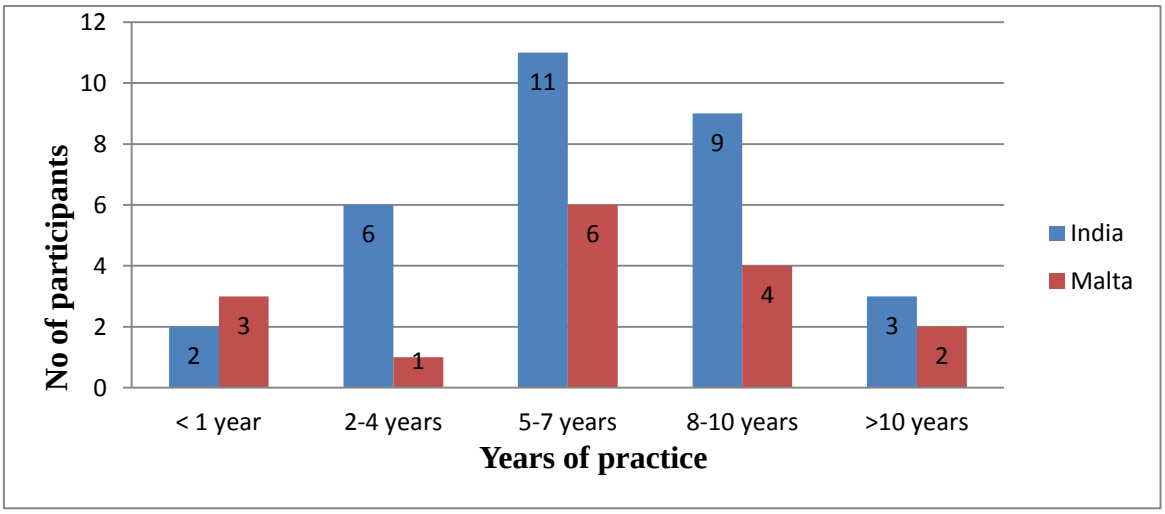

Figure 3.3 Psychiatrists Total Years in Practice

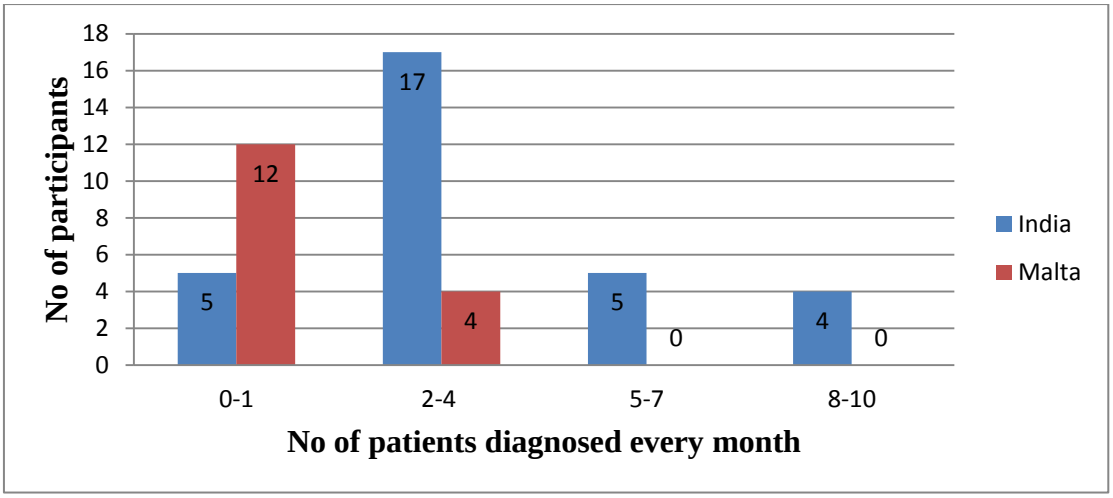

Figure 3.4 Number of People Newly Diagnosed with Autism Spectrum Disorder Every Month

In India, 19 psychiatrists deal with 2-4 follow up cases of ASD every month, 6 with 5-7 and 5 with 8-10 follow up cases. In Malta, 13 psychiatrists deal with 0-1 follow up cases of ASD and 3 deal with 2-4 follow up cases (Figure 3.5).

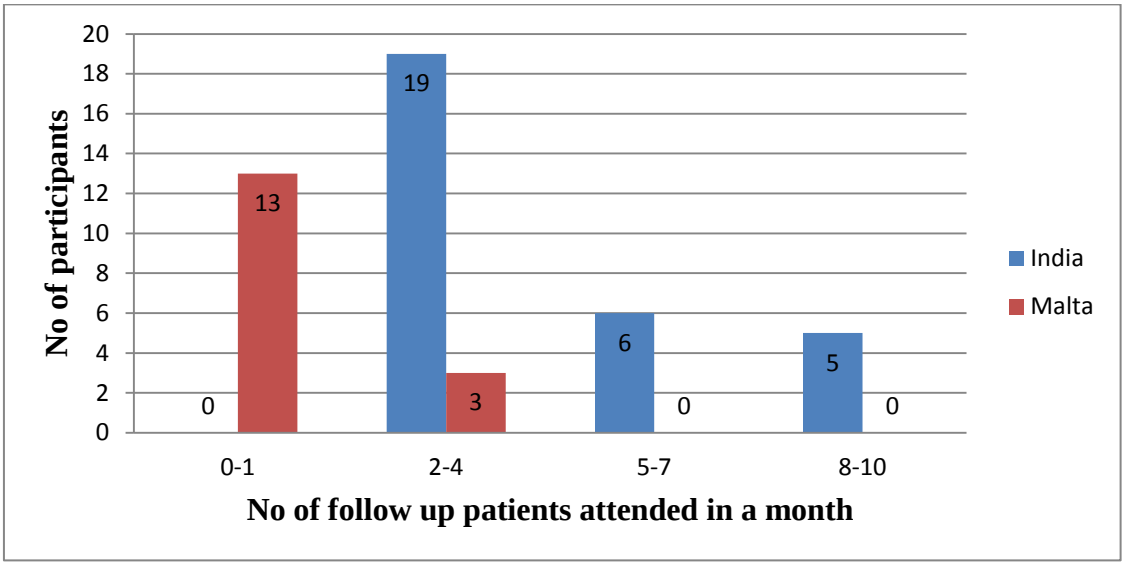

Figure 3.5 Number of Follow Up Patients Attended by the Psychiatrists Every Month

The above-presented demographics of the participants represent the analysis of section 1 of the questionnaire. Section two to section six contains 28 questions. A five-point Likert scale ranging from one to five is used, where one is the lowest score and five is the highest score. In section two, one represents strong disagreement towards the statement by the psychiatrists and five represents a firm agreement by the psychiatrists towards the statement. Descriptive statistics of section two, containing 12 questions were analysed in table 3.4.

Table 3.4 Descriptive Statistics of Section Two of ASD-Q $_{(IND-MT)}$ (N=47)

Statements	Group	Mean	Std.Dev	P. Value (<0.05)
1. The DSM-V manual accurately defines and classifies ASD.	Malta	4.50	0.894	0.001
	India	5.00	0.000	
2. Early detection of ASD is pivotal for better intervention and outcome	Malta	4.56	0.629	<0.001
	India	5.00	0.000	
3. Differentiating between ASD and other developmental disorders is crucial	Malta	5.00	0.000	1.000
	India	5.00	0.000	
4. Screening tools (ISAA/CARS) play an essential role in achieving the above	Malta	2.56	1.153	<0.001
	India	4.45	0.506	
5. The complete treatment of ASD should be government funded due to its increasing prevalence	Malta	5.00	0.000	<0.001
	India	2.71	0.461	
6. ISAA/CARS as a screening tool is always accurate in identifying the ASD	Malta	2.38	0.500	<0.001
	India	3.58	0.502	
7. ISAA/CARS determines all the symptoms indicating ASD	Malta	1.94	0.574	<0.001
	India	3.52	0.508	
8. Including questions on genetic factors and birth, conditions can increase the efficacy of ISAA/CARS	Malta	4.31	0.479	0.014
	India	3.65	0.950	
9. Pictorial assessment tools could be more user-friendly and accurate than ISAA/CARS	Malta	3.44	0.512	0.061
	India	2.97	0.836	
10. IQ scores should be a parameter in the screening tools to determine ASD	Malta	4.50	0.516	<0.001
	India	2.23	0.425	
11. ISAA/CARS precisely indicates The presence and severity of ASD	Malta	1.75	0.447	<0.001
	India	3.42	0.502	
12. ISAA/CARS scores can help to determine the need to prescribe antipsychotics	Malta	2.06	0.854	<0.001
	India	4.55	0.506	

Forty-seven psychiatrists, 31 in India and 16 in Malta have answered this section of the questionnaire.

A statistically significant difference (p=0.001) was noted between the psychiatrists when asked if the DSM-V manual accurately defines and classifies ASD. The mean score was 5.00 ±0.00 by Indian psychiatrists and was 4.50±0.894 by Maltese psychiatrists indicating higher agreement to the statement by Indian psychiatrists.

A statistically significant difference (p<0.001) was noted on when asked if early detection of ASD is pivotal for better intervention. The mean score was 5.00±0.000 by Indian psychiatrists and was 4.56±0.629 by Maltese psychiatrists indicating higher agreement by Indian psychiatrists.

No statistically significant difference (p=1.000) was noted between psychiatrists when asked if differentiating between ASD and other developmental disorders is crucial. The mean score by an Indian and Maltese psychiatrist was comparable 5.00±0.000 indicating similar opinions by both groups.

A statistically significant difference (p<0.001) was noted between psychiatrists when asked if screening tools (ISAA/CARS) could detect and differentiate between ASD and other developmental disorders. The mean score was 4.45±0.506 by Indian psychiatrists and 2.56±1.153 by Maltese psychiatrists indicating a higher level of agreement by the Indian psychiatrists.

A statistically significant difference (p<0.001) was noted between psychiatrists when asked if the complete treatment of ASD should be government funded due to its increasing

prevalence. The mean score was 2.71±0.461 by Indian psychiatrists and 5.00±0.000 by Maltese psychiatrists indicating a higher level of agreement by the Maltese psychiatrists.

No statistically significant difference (p=0.061) was a noted between the psychiatrists when asked if pictorial assessment tools could be more user-friendly and accurate than the current screening tools. The mean score was 3.44±0.512 by Indian psychiatrists and 2.97±0.836 by Maltese psychiatrists indicating similar opinions on the statements.

A statistically significant difference (p<0.001) was noted between psychiatrists when asked if screening tools ISAA/CARS precisely indicates the presence and severity of ASD. The mean score was 3.42±0.502 by the Indian psychiatrists and 1.75±0.447 by the Maltese psychiatrists indicating a higher level of agreement by the Indian psychiatrists. The section two ends at question 12 and the next section will be represented in table 3.5.

Forty-seven psychiatrists participated in the study, 31 Indian and 16 Maltese and all the participants answered this section.

A statistically significant difference (P<0.001) was noted between psychiatrists in India and Malta when asked if pharmacists are an essential part of the healthcare system in suggesting medical interventions specifically in patients with ASD. The mean score was 2.29±0.824 by Indian psychiatrists and 4.13±0.342 by Maltese psychiatrists indicating a higher level of agreement by the Maltese psychiatrists.

A statistically significant difference (p<0.001) was noted when asked if clinical pharmacists could play an important role in dosage adjustments for patients with ASD. The mean score was 2.84 ±0.824 by Indian psychiatrists and 4.44±0.342 by Maltese psychiatrists indicating

a higher level of agreement by the Maltese psychiatrists. The section three ends at question 21 and the next section will be represented in table 3.6

Table 3.5 Descriptive Statistics of Section Three of ASD-Q $_{(IND-MT)}$ (N=47)

Statements	Group	Mean	Std.Dev	P. Value (<0.05)
13. Pharmacists are an essential part of the healthcare system in suggesting medical interventions.	Malta	4.13	0.342	<0.001
	India	2.29	0.824	
14. Pharmacist's knowledge of ASD is sufficient for suggesting interventions.	Malta	4.13	0.342	0.004
	India	3.13	0.824	
15. Pharmacists are aware of EMA/CDSCO approved drugs for ASD	Malta	3.44	0.342	0.116
	India	2.94	0.824	
16. Pharmacists are aware of FDA approved drugs for ASD	Malta	3.44	0.342	0.001
	India	3.03	0.824	
17. Clinical pharmacists can play an essential role in dosage adjustments for patients with ASD	Malta	4.44	0.342	<0.001
	India	2.84	0.824	
18. Clinical pharmacists role in designing individual therapies for ASD patients	Malta	4.50	0.342	<0.001
	India	2.39	0.824	
19. Clinical pharmacists can play a crucial role in reporting abnormalities detected during birth.	Malta	3.56	0.342	<0.001
	India	2.19	0.824	
20. Community pharmacists can play a vital role in providing counselling to patients & caregivers	Malta	4.44	0.342	<0.001
	India	3.00	0.824	
21. Pharmacists should be an active member of a multidisciplinary team to treat ASD	Malta	5.00	0.342	<0.001
	India	2.35	0.824	

Table 3.6 Descriptive Statistics of Section Four and Five of ASD-Q (IND-MT) (N=47)

Statements	Group	Mean	Std.Dev	P. Value (<0.05)
22. Accessibility of risperidone is a matter of concern in India/Malta	Malta	2.50	0.516	0.232
	India	2.68	0.909	
23. Accessibility of aripiprazole is a matter of concern in India/Malta	Malta	3.56	0.512	<0.001
	India	2.55	0.768	
24. Including risperidone and aripiprazole on the National formulary will significantly increase the accessibility	Malta	4.50	0.516	0.463
	India	4.61	0.495	
25. Evaluating the post-marketing safety of the drugs in this cohort is essential	Malta	4.38	0.500	<0.001
	India	3.87	0.341	
26. How influential is the ISAA/CARS score while deciding to prescribe risperidone /aripiprazole after the final diagnosis?	Malta	2.56	1.153	<0.001
	India	4.45	0.506	

Forty-seven psychiatrists participated in the study, 31 Indian and 16 Maltese and all the participants answered this section.

No statistically significant difference (p=0.232) was noted between psychiatrists when asked if the accessibility of risperidone is a matter of concern. The mean score was 2.68±0.909 by Indian psychiatrists and 2.50±0.516 by Maltese psychiatrists indicating similar opinions regarding the statement.

No statistically significant difference (p=0.463) was noted between Indian and Maltese psychiatrists when asked if including RiAr on the national formulary will significantly increase the accessibility of the drugs. The mean score was 4.61±0.495 by Indian psychiatrists and 4.50±0.516 by Maltese psychiatrists indicating similar opinions regarding the statement.

A statistically significant difference ($p<0.001$) is noted between psychiatrists when asked about the influence of screening tools (ISAA/CARS) on the prescribing behaviour of antipsychotics. The mean score was 4.45±0.506 by Indian psychiatrists and 2.56±1.153 by Maltese psychiatrists indicating higher agreement by the Indian psychiatrists.

The section five ends here and the statistics from the section six are described in table 3.7 and 3.8. This section was analysed using chi-square method and the Likert scale markers ranged from “No autism” to “Severe autism”.

A statistically significant difference ($p=0.040$) is noted between the psychiatrists when asked about the interpretation of the screening tools (ISAA/CARS) score. Thirteen Indian psychiatrists out of 31 and 2 Maltese psychiatrists out of 16 agreed that they prescribe RiAr to patients with mild to moderate autism. Eighteen Indian psychiatrists out of 31 and 14 Maltese psychiatrists out of 16 agreed that they would prescribe antipsychotics to patients who have severe autism.

No statistically significant difference ($p=0.260$) was noted between Indian and Maltese psychiatrists when asked about the score that would make a child eligible to attend a regular educational institution. Fifteen Indian psychiatrists out of 31 and 5 Maltese psychiatrists out of 16 agreed that a child with even mild to moderate autism should be allowed in a regular educational institution.

Table 3.7 Descriptive Statistics of Section six (Q27) of ASD-Q $_{(IND-MT)}$ (N=47)

Question	Score		Malta	India	Total
27. The score which would have a positive influence while deciding the prescription of antipsychotics risperidone /aripiprazole	Mild to moderate autism	Count	2	13	15
		Percentage	12.5%	41.9%	31.9%
	Severe autism	Count	14	18	32
		Percentage	87.5%	58.1%	68.1%
Total		Count	16	31	47
		Percentage	100.0%	100.0%	100.0%

$X^2(1) = 4.208$, $p = 0.040$

Table 3.8 Descriptive Statistics of Section six (Q28) of ASD-Q $_{(IND-MT)}$ (N=47)

Question	Score		Malta	India	Total
28. The score which would make a child eligible to join a regular educational institution with frequent monitoring	No autism	Count	5	15	20
		Percentage	31.3%	48.4%	42.6%
	Mild to moderate autism	Count	11	16	27
		Percentage	68.8%	51.6%	57.4%
Total		Count	16	31	47
		Percentage	100.0%	100.0%	100.0%

$X^2(1) = 1.268$, $p = 0.260$

3.3 Part III- Comparative Analysis of Accessibility of RiAr in India and Malta

This section deals with the results of the comparison of price and affordability of RiAr in India and Malta.

3.3.1 Cost Analysis for Comparison of Unit Price of RiAr in India and Malta

Unit Price of risperidone (Risperdal) and aripiprazole (branded generic) was measured using the available drug in similar strength in India and Malta. The Indian rupee (INR) (₹) was converted using the nominal exchange rate during March 2018. The collected price in Euro (€) is described in table 3.9. The price of RiAr per tablet in India and Malta is described in table 3.10. The price of drugs in Indian rupees is

- Risperidone = 96.30 ₹
- Aripiprazole= 105.50₹

$$Nominal\ Exchange\ Rate = 1\ Euro = 80\ INR$$

Table 3.9 Price of Risperidone and Aripiprazole in India and Malta in Euro

Name	India	Malta
Risperidone (Originator)	1mg x10 tablets= €1.20	1mg x 20 tablets= €17.84
Aripiprazole (Generic)	10mg x 10 tablets=€1.32	10mg x 30 tablets=€28.92

Table 3.10 Price per Tablet of Risperidone and Aripiprazole in India and Malta in Euro

Name	India	Malta
Risperidone (Originator)	€1.17 /10 tablets=**€0.12**	€17.84/20 tablets=**€0.89**
Aripiprazole (Generic)	1.32 /10 tablets= **€0.13**	28.92/30 tablets=**€0.96**

3.3.2 Cost Analysis for Comparison of Affordability of RiAr in India and Malta

The first step to measure the affordability is to estimate the cost of treatment for one month. Cost of one month of treatment is estimated based on FDA recommended doses of risperidone[48] and aripiprazole[49] for ASD as mentioned in table 3.11

The cost of 30 days of treatment is calculated in table 3.12 with 1 mg of risperidone and 10 mg of aripiprazole, which is within the recommended range of daily dose for the management of irritability associated with ASD in children and adolescents.

Table 3.11 FDA Recommended Daily Dose of Risperidone and Aripiprazole for Autism Spectrum Disorder

Drug	Dose
Risperidone	0.5-3 mg /day
Aripiprazole	5-10 mg/day

Table 3.12 Cost of Monthly Treatment with Risperidone and Aripiprazole in Euro

Name (strength)	India	Malta
Risperidone (1mg)	€0.12x 30 days= **€3.50**	€0.89 x 30 days= €**26.70**
Aripiprazole (10mg)	€0.13 x 30 days= **€ 3.90**	€0.96 x 30days=**€28.80**

a) The cost variation percentage is calculated to measure the difference between monthly costs of treatment in India and Malta.

[48] FDA. Label of Risperdal. [Internet]. Accessdata.fda.gov. 2018 [cited 2018 May 25]. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2009/020272s056,020588s044,021346s033,0
[49] FDA. Label of Abilify. [Internet]. Accessdata.fda.gov. 2018 [cited 2018 May 25]. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2014/021436s038,021713s030,021729s022,0

$$Cost\ Variation\ (\%) = \frac{Max.cost - Min.cost}{Min.cost} \times 100$$

i. The percentage cost variation between India and Malta for one month of treatment with risperidone is

€ 26.7- €3.5/ €3.5 x 100 = ***662%***

ii. The percentage cost variation between India and Malta for one month of treatment with aripiprazole is

€ 28.8- €3.9/€3.9 x100= ***638%***

b) The cost of one month of treatment is compared against the Monthly Per Capita Expenditure (MPCE) in India and Malta. The average MPCE in India was taken from the National Sample Survey Office (NSSO) report of the 68th national survey conducted and published in 2012 and converted to euro in table 3.13[50]

Table 3.13 Average Monthly Per Capita Expenditure in India in Euro

India	Rural	Urban
Rupee(₹)	₹ 1287.17	₹ 2477.02
Euro(€)	€16.90	€30.96

The Average MPCE in Malta was calculated based on the household budgetary survey conducted in 2015. [51]

- *The annual average household expenditure - € 22,346*

[50] NSSO. [Internet]. Admin.indiaenvironmentportal.org.in. 2018 [cited 2018 May 24]. Available from: http://admin.indiaenvironmentportal.org.in/files/file/State-wise%20estimates%20of%20Average%20Monthly%20Per%20Capita%20Expenditure.pdf

[51] Nso.gov.mt. 2018 [cited 2018 MAY 23]. Available from: https://nso.gov.mt/en/publicatons/Publications_by_Unit/Documents/C1_Living_Conditions_and_Culture_Statistics

- *Monthly average household expenditure - € 22346/12 months =* ***€ 1,862/month***

The data available was converted into MPCE by applying a formula to calculate the average monthly expenditure using the household expenditure.[52]

$$\text{Average expenditure per person} = \frac{\text{Average expenditure per household}}{\text{The average size of the household}}$$

Eurostat household estimated the average size of the household in Malta composition survey published in 2016.[53] The average household size in Malta is 2.6 members per household

- *Average expenditure per person per month- €1862 / 2.3 =* ***€ 809.58***

All the results of cost analysis are summarised in the table 3.14. The unit price of RiAr is less in India as compared to Malta but when compared against the MPCE, the cost of treatment for one month with risperidone is more affordable in Malta (3.30%) as compared to India (Urban-11.30%). Monthly treatment with RiAr is most expensive in the rural areas of India, which would require an individual to spend 20.71% of their monthly expenses to get the treatment with risperidone or 23.08% of the expenses for treatment with aripiprazole. The cost does not include travel charges, prescription charges and other expenses. Adding additional costs will make the treatment even more expensive in India.

[52] Minister responsible for Statistics Canada. User Guide for the Survey of Household Spending, [Internet]. Statcan.gc.ca. 2018 [cited 2018 May 23]. Available from: http://www.statcan.gc.ca/pub/62f0026m/62f0026m2017002-eng.pdf

[53] Eurostat. Household composition statistics - Statistics Explained [Internet]. Ec.europa.eu. 2018 [cited 2018 May 23]. Available from: http://ec.europa.eu/eurostat/statistics-explained/index.php/Household_composition_statistics

Table 3.14 Summary of Cost Analysis of Risperidone and Aripiprazole in India and Malta

Drug	Unit Price per tablet (€)		Cost of Treatment for a Month (€)		Percentage cost variation	Average MPCE (€)			Percentage of MPCE for a Month of Treatment		
						India		Malta	India		Malta
	India	Malta	India	Malta		Urban	Rural		Urban	Rural	
Risperidone	€0.12	€0.89	€3.50	€26.70	662%	€30.96	€16.90	€809.50	11.30%	20.71%	3.30%
Aripiprazole	€0.13	€0.96	€3.90	€28.80	638%				12.60%	23.08%	3.56%

3.4 Part III- Causality Assessment of the Signals- The French Method (Imputability)

The PRR report included 1226 ADRs for risperidone and 876 ADRs for aripiprazole. SDRs (in red) with more than 95% of significance interval were filtered from the list to be reviewed and checked with the latest approved SmPC for the expectedness of the ADRs. The list included 170 signals corresponding to risperidone and 134 signals corresponding to aripiprazole (Appendix 5). The signals not included in the SmPC were extracted from the list to check the indication of ASD by accessing EVDAS and searching for the signal (MedDRA term) to check the indication of ASD for risperidone (Table 3.15) and aripiprazole (Table 3.16).

The signals with an indication of ASD are represented in table 3.17 (risperidone) and table 3.18 (aripiprazole). The signals assessed using the French causality assessment method also known as the French Imputability method. The interpretation of the score was done as described in table 3.17. All the Individual Case Safety Reports (ICSR) was extracted from Eudravigilance Data Analysis System (EVDAS) intact and was chronologically edited to carry out the French causality assessment.

Table 3.15 List of Adverse Drug Reactions Not Included in the SmPC- Risperidone

Reaction PT	PRR (-)	PRR	PRR (+)	CHI^2	Cases
Stereotypy	3.78	8.44	18.85	38.9165	1
Disturbance in social behavior	2.18	4.32	8.54	21.0200	2
Arachnoid cyst	2.90	10.07	35.04	20.1925	3
Breast cyst	5.21	20.15	77.88	38.2135	3
Breast discomfort	6.74	28.20	117.98	49.2026	3
Bundle branch block	3.09	10.85	38.05	21.7935	3
Bundle branch block left	3.88	14.10	51.22	28.0942	3
Conduct disorder	1.04	3.36	10.83	4.6366	3
Dependence	2.43	8.30	28.30	16.3627	3
Echolalia	3.88	14.10	51.22	28.0942	3
Glossodynia	1.59	5.22	17.21	9.2207	3
Grimacing	1.44	4.70	15.40	7.9473	3
Homicide	1.24	4.03	13.10	6.2941	3
Immobile	1.84	6.13	20.41	11.3986	3
Impulse-control disorder	1.39	4.55	14.87	7.5753	3
Metabolic disorder	1.04	3.36	10.83	4.6366	3
Serum ferritin decreased	2.43	8.30	28.30	16.3627	3
Spontaneous penile erection	3.32	11.75	41.63	23.6109	3
Suspiciousness	5.21	20.15	77.88	38.2135	3
Anticholinergic syndrome	1.41	3.92	10.86	8.0240	4
Energy increased	3.37	9.90	29.08	26.4295	4
Excessive eye blinking	1.20	3.30	9.09	5.9894	4

Hyperlipidaemia	0.99	2.73	7.46	4.1304	4
Left ventricular hypertrophy	1.05	2.89	7.94	4.6684	4
Mononucleosis syndrome	3.72	11.06	32.86	29.6354	4
Mutism	1.64	4.59	12.80	10.2220	4
Nipple disorder	7.87	26.86	91.73	63.3828	4
Pituitary tumour	2.53	7.23	20.71	18.6198	4
Rabbit syndrome	11.76	47.01	187.90	90.0625	4
Therapy cessation	2.21	6.27	17.78	15.6284	4
Cerebral atrophy	1.25	3.09	7.64	6.6456	5
Compulsions	4.41	11.75	31.30	39.3534	5
Diet refusal	4.22	11.19	29.67	37.4889	5
Negativism	2.12	5.34	13.46	15.8485	5
Obsessive thoughts	1.60	3.98	9.92	10.3041	5
Delusion	1.30	2.45	4.62	8.1517	10
Homicidal ideation	2.87	4.79	8.01	43.5886	16
Anal incontinence	3.83	6.34	10.51	67.4534	17
Glucose tolerance impaired	8.90	15.37	26.55	172.1579	17
Hyperphagia	9.58	16.65	28.92	184.7107	17

Table 3.16 List of Adverse Drug Reactions Not Included in the SmPC- Aripiprazole

Reaction PT	**PRR (-)**	**PRR**	**PRR (+)**	**CHI^2**	**Cases**
Homicidal ideation	2.98	6.04	12.24	32.1425	1
Apathy	2.87	4.98	8.64	39.8427	1
Insulin resistance	5.28	14.83	41.68	46.3067	2
Posture abnormal	1.15	3.60	11.34	5.4961	3
Post-traumatic stress disorder	4.09	13.42	44.02	31.2653	3

Psychotic behaviour	1.88	5.99	19.04	11.9217	3
Rabbit syndrome	18.62	77.86	325.52	142.2615	3
Tension headache	2.34	7.49	23.95	15.9440	3
Acanthosis nigricans	8.00	27.81	96.67	63.8502	3
Binge eating	7.52	25.95	89.56	59.9823	3
Breast pain	1.88	5.99	19.04	11.9217	3
Bulbar palsy	11.72	43.25	159.63	92.8786	3
Complex regional pain syndrome	1.07	3.36	10.55	4.8393	3
Disinhibition	1.78	5.64	17.91	10.9835	3
Flat affect	1.83	5.81	18.45	11.4388	3
Tension headache	2.34	7.49	23.95	15.9440	3
Acanthosis nigricans	8.00	27.81	96.67	63.8502	3
Breast pain	1.88	5.99	19.04	11.9217	3
Psychiatric symptom	1.39	4.37	13.81	7.5565	4
Insulin resistance	5.28	14.83	41.68	46.3067	4
Psychiatric symptom	1.39	4.37	13.81	7.5565	4
Acute myeloid leukaemia	1.18	3.16	8.52	5.7871	4
Akinesia	5.09	16.93	56.32	39.7715	4
Autonomic nervous system imbalance	1.07	2.87	7.71	4.7645	4
Bipolar I disorder	6.30	17.90	50.85	56.0896	4
Bradykinesia	6.51	18.54	52.79	58.0785	4
Acute myeloid leukaemia	1.18	3.16	8.52	5.7871	4
Akinesia	5.09	16.93	56.32	39.7715	4
Autonomic nervous system imbalance	1.07	2.87	7.71	4.7645	4

Table 3.17 Adverse Drug Reactions Observed in Autism Spectrum Disorder - Risperidone

Reaction PT	PRR (-)	PRR	PRR (+)	CHI^2	Cases
Disturbance in social behavior	2.18	4.32	8.54	21.0200	2
Stereotypy	3.78	8.44	18.85	38.9165	1
Pituitary tumour benign	6.14	12.82	26.78	77.0832	1
Motor dysfunction	1.30	2.53	4.95	7.9326	1
Delusion	1.30	2.45	4.62	8.1517	1

Table 3.18 Adverse Drug Reactions Observed in Autism Spectrum Disorder – Aripiprazole

Reaction PT	PRR (-)	PRR	PRR (+)	CHI^2	Cases
Homicidal ideation	2.98	6.04	12.24	32.1425	1
Insulin resistance	5.28	14.83	41.68	46.3067	2
Apathy	2.87	4.98	8.64	39.8427	1

Table 3.19 Interpretation of the French Imputability score

Imputability Score	
I0	Unlikely
I1	Uncertain
I2	Possible
I3	Probable
I4-	Highly Probable

3.4.1 Signals-Risperidone

The Individual Case Safety Reports relating to extracted signals of aripiprazole are assessed in this section.

3.4.1.1 Case 1- Disturbance in Social Behaviour

Reaction PT	PRR (-)	PRR	PRR (+)	CHI^2	Cases
Disturbance in social behavior	2.18	4.32	8.54	21.0200	2

Description of the case:

(a) "*The case concerns an 8-year-old male patient. The patient's height and weight were not reported. The patient's medical history and concurrent conditions included: attention deficit hyperactivity disorder ADHD, aggression disorder, autism, bipolar, and obsessive-compulsive disorder. The patient abstained from alcohol use and was a non-smoker. The patient had no known allergies, drug allergies, drug abuse/illicit drug use.*

2000: *The patient was treated with risperidone (2-8 mg), once a day, initiated in for autism and then later years was on generic risperidone (2-8 mg), once a day, initiated on an unspecified date for autism. Concomitant medications were not reported.*

2001: *The patient experienced erratic behaviour since early age-related that persisted and that became more destructive with age (destructive behaviour).*

2009: *The patient's behaviour was out of control. Treatment with risperidone was discontinued on an unspecified date, and generic risperidone was also discontinued. The*

patient was treated with another antipsychotic. The patient had not recovered from erratic behaviour and was not recovering from uncontrollable behaviour and destructive social behaviour."

- **Causality Assessment**

Table 3.20 The French Imputability Assessment - Disturbance in Social Behaviour (a)

Chronological criteria		**Semiological criteria**	
Challenge	Compatible	Symptoms	Compatible
Rechallenge	R0	Lab Test	L0
Dechallenge	C1	Alternate	S1
Result	I0	Unlikely	

- **Comments:** Destructive and erratic behaviour is a symptom of severe autism.[54] In this case, the child has been experiencing the symptoms from early childhood. It is also important to note that the patient failed to recover even after the risperidone was discontinued due to which another antipsychotic was prescribed.
- **Description of the case**

(b) "*The case concerns a 15-year-old male. The patient's weight was 64 kilograms and height was 170 centimetres. The patient's concurrent conditions included autism, behaviour disorder, and gluten intolerance. The patient was treated with risperidone tablets 0.5 mg*

[54] Boelter E. Disruptive Behavior and Autism Spectrum Disorder [Internet]. The Autism Blog. 2011 [cited 2018 May 21]. Available from: http://theautismblog.seattlechildrens.org/whats-the-function/

once a day, initiated in June 2008 and 0.5 mg twice a day, initiated on 14th October 2008 for behaviour disorder and autism. Concomitant medications included fish oil.

2008: *The patient experienced insomnia, weight gain (about 2 kilograms), behaviour disorder related to food intake, off-label use and patient also experienced generalised erythema following risperidone intake at two separate occasions on 14th October 2008 and 17th October 2008 and decreased to recovery each time. The dose of risperidone was increased. The patient outcome was unknown for insomnia, weight gain, behaviour disorder, off-label use and generalised erythema.*

2009: *Patient had a weight gain of 12 kilograms in six months and the case was reassessed. The patient was still treated with risperidone 0.5mg twice a day for a behaviour disorder. He experienced a weight gain of 12 kg in the six last months. The patient experienced anxiety and unruly behaviour which was characterised by violence. The patient received treatment with fluoxetine for anxiety. At the time of reporting, the treatment with risperidone was still ongoing. The patient has not yet recovered from anxiety, uncontrollable behaviour and violence. On 16th October 2009 patient demographics were updated.*

The patient's weight was 80 kilograms. The patient's medical history and concurrent conditions included autism, hyperactivity, insomnia (between 3 months and ten years old), and pervasive developmental disorder beginning 2nd April 1991. It was reported that the patient was a non-verbal child. The patient was treated with risperidone and fluoxetine hydrochloride for autism and nocturnal anxiety. When the treatment with fluoxetine hydrochloride was initiated, an improvement was observed. The patient experienced

behaviour disorder related to the food intake resulting in a marked weight gain (2 kilograms).

In August 2009, treatment with fluoxetine hydrochloride was discontinued due to the occurrence of aggression, excessive weight gains and hyperexcitation. The dose of risperidone was reduced to 0.5mg per day. The patient had recovered with sequelae from weight gain and uncontrollable behaviour in October 2009, was recovering from aggression, had recovered from increased insomnia in March 2009 and outcome was unknown for anguish crisis and anxiety."

- **Causality Assessment**

Table 3.21 The French Imputability Assessment - Disturbance in Social Behaviour (b)

Chronological criteria		**Semiological criteria**	
Challenge	Compatible	Symptoms	Compatible
Rechallenge	R0	Lab Test	L0
Dechallenge	C1	Alternate	S1
Result	I0	unlikely	

- **Comments**: Weight gain is a prevalent side effect of risperidone, which is also mentioned in the SmPC. Anxiety, sleep disorder, restlessness, are common side effects

of fluoxetine.[55]The behaviour was under control ones the fluoxetine was discontinued. The disturbance is behaviour is a common symptom of ASD.

- **Conclusion:** The relationship between the ADR and the drug is unlikely.

3.4.1.2 Case 2- Stereotypy

Reaction PT	PRR (-)	PRR	PRR (+)	CHI^2	Cases
Stereotypy	3.78	8.44	18.85	38.9165	1

- **Description of the case**

"The case concerns the 8-year-old child. The patient's height was 152 centimetres, and weight was 49 kilograms. The patient's concurrent conditions included autism. The patient's history of drug allergies, non-drug allergies, alcohol use and smoking, diagnostic data were not reported. The patient did not use the drug for the first time.

2009: *The patient was treated with risperidone 6mL oral solution initiated on an unspecified date, and the dose was reduced to 4 mL initiated on an unspecified date, and to 1.5 mL initiated on an unspecified date in for autism. The physician reduced the dose. Concomitant medications included aripiprazole (prescribed since four months ago) for hyperactivity and aggressiveness. It was manifested that, when the patient did not take the drug, he presented with aggressiveness and loss of control. On an unspecified date, the patient experienced weight gain and missed a dose.*

[55] eMC.Fluoxetine 20mg Capsules - Summary of Product Characteristics (SmPC) - (eMC) [Internet]. Medicines.org.uk. 2018 [cited2018 May 21]. Available from: https://www.medicines.org.uk/emc/product/540/smpc

2013: *Treatment with risperidone was withdrawn in July. The reporter wanted to know when the drug would be back again to the pharmacy stock. It was also reported that so far, the patient had not presented with any adverse event or reaction since the drug was finished. On 24th July 2013 it was reported that since 20th July 2013, the patient did not take risperidone because the drug was not available due to this situation the patient experienced stereotypic movement disorder and aggressiveness."*

- **Causality Assessment**

Table 3.22 The French Imputability Assessment - Stereotypy

Chronological criteria		**Semiological criteria**	
Challenge	Compatible	Symptoms	Compatible
Rechallenge	R0	Lab Test	L0
Dechallenge	C1	Alternate	S1
Result	I0	unlikely	

- **Comment:** Stereotyped behaviour is one of the three core symptoms of ASD (Cunningham and Schreibman 2008). The patient had a history of increased symptoms when missed a dose. The increased aggressiveness and stereotypic movement are likely to be caused due to missing dose rather than as an adverse event of risperidone.
- **Conclusion:** The relationship between the ADR and the drug is unlikely.

3.4.1.3 Case 3- Pituitary Benign Tumour

Reaction PT	PRR (-)	PRR	PRR (+)	CHI^2	Cases
Pituitary benign tumour	6.14	12.82	26.78	77.0832	1

- **Description of the case**

"The case concerns a 13-year-old boy. The patient's height was 66 inches, and weight was 145 pounds at the time of risperidone ingestion. The patient's medical history and concurrent conditions included: autism (approximately in 1994). The patient was a non-smoker and abstained from alcohol. Family history noted the patient's grandmother and grandfather with alcoholism. The patient had no history of illegal/illicit drug use.

2005: *The patient was prescribed risperidone in doses of 0.5 mg and 1mg from 24th January 2005 to 20th April 2006 for autism and risperidone long-acting injection in varying doses of 25 mg, 37.5 mg and 50 mg respectively. The patient was treated with quetiapine 25 mg from approximately September to November 2005 for autism. The patient stopped taking the medication as it was wrong medicine as the symptoms that were supposed to be treated become worse. The patient was treated with clozapine in varying doses of 25 mg and 100 mg.*

2006: *The patient experienced inferior right pituitary cyst (coded as pituitary cyst), Craniofacial disproportion with apparent hypoplasia of the frontal and parietal lobes (coded as hypoplasia of the frontal and parietal lobes), hypogonadotropic hypogonadism, gait disorder, kyphosis, abnormal posture, eye blinking, eye rolling, problem with speech (coded as speech problems), lethargy and psychological and emotional distress (emotional*

distress). The patient became aware of the condition by observation and abnormal test results. The patient was diagnosed with diabetes mellitus and tardive dyskinesia or other movement disorder approximately in 2013 and gynecomastia approximately in 2012. Treatment with risperidone and quetiapine was withdrawn. Action taken with risperidone LAI and clozapine was not reported. The patient's outcome was not reported for pituitary cyst, hypoplasia of frontal and parietal lobes, hypogonadotropic hypogonadism, gait disorder, kyphosis, abnormal posture, eye blinking, eye rolling speech problems, lethargy and emotional distress."

- **Causality Assessment**

Table 3.23 The French Imputability Assessment - Pituitary Benign Tumour

Chronological criteria		**Semiological criteria**	
Challenge	Compatible	Symptoms	Compatible
Rechallenge	R0	Lab Test	L0
Dechallenge	C1	Alternate	S1
Result	I1	uncertain	

- **Comment:** The patient shows a lot of adverse reactions caused by risperidone that are already mentioned in the SmPC. The case was not followed up, and many details are missing and further information required. There are suggestions on antipsychotics producing a risk of acquiring pituitary tumours, but more extensive studies are required (Szarfman et al, 2006).
- **Conclusion:** The relationship between the ADR and the drug is uncertain.

3.4.1.4 Case 4- Motor Dysfunction

Reaction PT	PRR (-)	PRR	PRR (+)	CHI^2	Cases
Motor dysfunction	1.30	2.53	4.95	7.9326	1

- **Description of the case:**

"The case concerns her 6-year-old girl. The patient's height was 125 centimetres, and weight was 24 kilograms. The patient's medical history included autism. The patient abstained from alcohol and smoking use. The patient's concurrent condition included ADHD (attention deficit/hyperactivity disorder) and Asperger's syndrome.

2011: *The patient was treated with risperidone (solution, oral) 1 mg twice a day initiated, on an unspecified date in August 2011 for ADHD and autism. The patient's mother had avoided medications for a long time. The patient was previously treated with clonidine and imipramine as an antipsychotic and then risperidone was used a third option. The patient was treated with risperidone 1.5 mg twice a day, (morning and night, at the beginning and continued up to one year), initiated on an unspecified date in 2010, as an antipsychotic for ADHD.*

The patient was also treated with methylphenidate hydrochloride dose and frequency unspecified, initiated on an unspecified date for ADHD, together with risperidone. Concomitant medications were not reported. Medication review was done every six months and wanted her child off the medication a year ago, to evaluate or see the need to use it. The dose of risperidone was dropped gradually to 1 mg (in morning and night), 0.75 mg (in morning and night), dropped it in increments, 0.25 mg (in morning and night, for several

months) and treatment with risperidone was stopped entirely on an unspecified date. On an unspecified date, the patient's limb started twitching and jerking. She started to cross her big toes over little toes and dragged them over until they ulcerated and she looked like a toddler who needed to go to the toilet, jumping up and down.

2013: *The patient experienced dyskinesia. The patient was noticed with strange movements; when a pen was given, she would draw back to giant letters. She could not slow down or use the fine motor skills. It was like going to pre-school. She had a level of anger that was quite disturbing, but not self-harming or threatening;*

she was just very angry. She never had an issue pre-med sleeping at night, but on the day of reporting, she was mentally going in and out of fiery and tears. Then she was hitting the wall, smashing the bed, was furious and was half asleep. Her mother managed to calm her down and settle her, and half an hour later it happened again.

She was bashing around without waking up, and this was all night long. The action taken with risperidone was not applicable, and a dose of methylphenidate hydrochloride was not changed. The patient had not recovered from symptoms, very angry, abnormal behaviour and impaired motor skills and outcome dyskinesia and only slept for one hour. The patient's mother believed that ceasing risperidone had caused withdrawal symptoms.

- **Causality Assessment**

Table 3.24 The French Imputability Assessment - Motor Dysfunction

Chronological criteria		**Semiological criteria**	
Challenge	Compatible	Symptoms	Compatible
Rechallenge	R0	Lab Test	L0
Dechallenge	C1	Alternate	S1
Result	I0	Unlikely	

- **Comments:** Dyskinesia, insomnia, spontaneous involuntary moments and recurrence of psychotic behaviour are withdrawal symptoms of risperidone as per the SmPC. Motor dysfunction is caused by the withdrawal of the drug and not as a side effect of the drug during the treatment.
- **Conclusion:** The relationship between the drug and the ADR is unlikely.

3.4.1.5 Case 5- Delusion

Reaction PT	**PRR (-)**	**PRR**	**PRR (+)**	**CHI^2**	**Cases**
Delusion	1.30	2.45	4.62	8.1517	1

- **Description of the case**

"A 12-year-old boy (weight and history unspecified), was treated with risperidone.

2003- 2004 *Tablets (oral) 0.5 mg twice daily initiated in and then reduced to 0.5 mg daily in Jun-04 for the treatment of autism. Concomitant medications include paroxetine hydrochloride and suspected schizophrenia. The patient experienced a 30-pound weight gain over a period of one month. The patient developed delusions which were worsening. Risperidone therapy is ongoing. No laboratory findings reported.*"

- **Causality Assessment**

Table 3.25 The French Imputability Assessment - Delusion

Chronological criteria		**Semiological criteria**	
Challenge	Compatible	Symptoms	Compatible
Rechallenge	R0	Lab Test	L0
Dechallenge	C1	Alternate	S1
Result	I1	Uncertain	

- **Comments:** Delusion can be part of ASD in patients. It is also possible that the patient had underlying schizophrenia as Woodbury-Smith et al, (2010) explained that the symptoms of ASD and schizophrenia might overlap due to genetic concerns and there may be diagnosis confusion. The weight gain can be related to risperidone, and it is one of the most common side effects mentioned in the SmPC.
- **Conclusion:** The relationship between the ADR and the drugs is uncertain.

3.4.2 Signals-Aripiprazole

The Individual Case Safety Reports relating to extracted signals of aripiprazole are assessed in this section.

3.4.2.1 Case 1- Homicidal Ideation

Reaction PT	PRR (-)	PRR	PRR (+)	CHI^2	Cases
Homicidal ideation	2.98	6.04	12.24	32.1425	1

- **Description of the case**

"The case concerns a 16-year-old male patient, height: 64 inches; weight: 97 pounds. Relevant history included hospitalisation at a mental facility. Concomitant medications included clomipramine and aripiprazole. On an unknown date, the patient started receiving generic methylphenidate (methylphenidate), 36 milligrams with unknown frequency. The patient was first given oral quetiapine fumarate samples for his Autism - Asperger (preferred term: off-label use) and was started off at the 50 mg dosage, however, was increased in increments of 50 mg until he reached 200 mg at night.

2011: *In June, methylphenidate was stopped. The patient was then prescribed the generic Quetiapine 200 mg tablets at night for Autism - Asperger. On unspecified dates, the patient became suicidal (preferred term: suicidal ideation), homicidal (preferred term: homicidal ideation) - pulled a gun on father and punched mother in the mouth, delusional (preferred term: delusional disorder, unspecified type), psychotic (preferred term: psychotic disorder), very angry (preferred term: anger), and irrational (preferred term: thinking abnormal). He woke up early - ate - and went back to bed, developed an increase in appetite (preferred term: increased appetite). The patient could not eat on generic of Methylphenidate, had a tremor with Abilify (preferred term: drug intolerance). The action taken with generic Quetiapine and generic of methylphenidate was unknown*."

- **Causality Assessment**

Table 3.26 The French Imputability Assessment - Homicidal Ideation

Chronological criteria		**Semiological criteria**	
Challenge	Compatible	Symptoms	Compatible
Rechallenge	R0	Lab Test	L0
Dechallenge	C1	Alternate	S1
Result	I1	Uncertain	

- **Comments:** Suicidal/homicidal ideation, delusional disorder unspecified type, psychotic disorder, anger and thinking abnormal is not listed in the SmPC of Quetiapine fumarate. The concomitant medication of clomipramine could cause suicidal ideation according to the summary of product characteristics and patient's relevant history of hospitalisation at a mental facility with Autism - Asperger's syndrome may provide an alternative explanation for the events of homicidal ideation.
- **Conclusion:** The relationship between the drugs and the ADR is unlikely.

3.4.2.2 Case 2- Insulin Resistance

Reaction PT	**PRR (-)**	**PRR**	**PRR (+)**	**CHI^2**	**Cases**
Insulin resistance	5.28	14.83	41.68	46.3067	2

- **Description of the case**

a*) "The case concerns a 14-year-old male patient who developed keto-acidosis and insulin resistance with a latency of year after initiation of treatment with aripiprazole 10mg once daily. The patient was diagnosed with behaviour disturbances, tics and signs of autism. He was treated with olanzapine until a year ago but gained weight and was decided to switch to aripiprazole. The patient was admitted very recently to the hospital with ketoacidosis and high blood sugars (more than 20). Even after treatment with insulin (up to 200 Units/day), the patient's blood sugars remained high (between 12 and 15). After the night in the morning, the ketones were still measurable. So the patient was diagnosed with keto-acidosis and insulin resistance following treatment with aripiprazole. Therapy with aripiprazole was stopped and further analysis of diabetes would take place. The physician reported that the patient had been receiving aripiprazole tablet 10 mg/day for oppositional defiant disorder since Jan-2012.*

2013: *in February, the patient developed ketoacidosis and diabetes mellitus. These events developed with a latency of 13 months after starting aripiprazole in January 2012. Laboratory results showed insulin resistance (first-week insulin > 220 E/day). A panel of five auto-antibodies (against GAD, IA2, ICA, insulin and ZnT8) were inconclusive. Only IA2 was weak positive at 1.3 U/ml (normal value < 1.1 U/ml). The laboratory test showed:*

Base Excess	*17 mmol/L*
blood glucose	*23.2 mmol/L,*
Blood insulin	*2 mmol/L,*
Insulin C-peptide	*0.74 nmol/L*
pCO2	*3.3 kPa*
pH	*7.23.*

On 15-Feb-2013, therapy with aripiprazole was discontinued. At the time of this report, the patient had not recovered from the events. The seriousness criteria of ketoacidosis and diabetes mellitus were reported as life-threatening and hospitalization. The reporter offers possible other explanations for these events suggesting that the patient could have had a pre-existing type 2 diabetes mellitus (DM), or MODY (Maturity onset diabetes of the young) or type I DM aroused by aripiprazole. Concomitant medication was methylphenidate."

- **Causality Assessment**

Table 3.27 The French Imputability Assessment-Insulin Resistance (a)

Chronological criteria		**Semiological criteria**	
Challenge	Compatible	Symptoms	Compatible
Rechallenge	R0	Lab Test	L0
Dechallenge	C1	Alternate	S1
Result	I1	Uncertain	

- **Comments:** As suggested by the physician diabetes could have been a pre-existing condition in this patient. Aripiprazole therapy can cause an increase in insulin levels in the body as per the SmPC. Ketoacidosis is common in patients with diabetes and insulin resistance. Aripiprazole has been studied to affect insulin resistance (Teff et al, 2013) but it is noted very clear in this case. Laboratory results after stopping the aripiprazole are not available so it is not clear if resistance was caused due to aripiprazole. More data is needed.

- **Description of the case**

b) "*The case concerns a 10-year-old female. The patient had developed polycystic ovaries.* ***2003:*** *Laboratory tests suggested early polycystic ovary syndrome (PCOS) and that the child's weight gain was associated with the use of psychotropic drugs. Endocrinology lab tests conducted on 30-May-2003 indicated insulin resistance and glucose intolerance Therapy with aripiprazole (15 mg, once per day orally) was administered from 16-Dec-2002 to 07-Jan-2004 for the indication of Autism and Asperger's Syndrome. Therapy with escitalopram (20 mg/day orally) was administered from 10-May-2003 to 07-Jan-2004 for the indication of anxiety. The child suffered from severe weight gain - approximately 40 pounds' overweight - since the introduction of psychotropic drugs. The child had suffered from skin acne, severe constipation and had exhibited unusual mouth movements. Mentally the child suffered from irrational fears and talked frequently about being dead or death in general. In addition, the child had sleep problems and had reported that her dreams were scary.*

2004: *Supplemental information from the child's physician revealed she is involved in an awful divorce of her parents and she is seriously disturbed. He reported the child was showing signs of childhood schizoaffective disorder in addition to her diagnosis of Asperger's syndrome. She was experiencing bizarre ideations and interpersonal problems towards the end of the school year. The child's father does not want her on any psychoactive drug; therefore, he blames everything she experiences on her medication(s). She has experienced some symptoms associated with Type II diabetes, although she has not been diagnosed with Type II diabetes. The physician stated that all of her symptoms are part of PCOS and was ongoing long before the start of aripiprazole. Furthermore, he*

stated that Type II diabetes runs in the mother's family and none of her symptoms worsened after the start of aripiprazole therapy."

- **Causality Assessment**

Table 3.28 The French Imputability Assessment-Insulin Resistance (b)

Chronological criteria		**Semiological criteria**	
Challenge	Compatible	Symptoms	Compatible
Rechallenge	R0	Lab Test	L0
Dechallenge	C1	Alternate	S1
Result	I0	Unlikely	

- **Comments:** Obesity and insulin resistance are common symptoms of PCOS and insulin resistance affects 65-75% of women with PCOS (Marshall and Dunaif, 2012). Aripiprazole has been studied to cause insulin resistance (Teff et al, 2013) but in this case, it is clear that the insulin resistance is caused by PCOS as the symptoms appeared before the patient was prescribed aripiprazole.
- **Conclusion:** The relationship between the ADR and the drugs is 'unlikely'.

3.4.2.3 Case 3- Apathy

Reaction PT	**PRR (-)**	**PRR**	**PRR (+)**	**CHI^2**	**Cases**
Apathy	2.87	4.98	8.64	39.8427	1

- **Description of the case**

"The case concerns a 12-year-old male patient had aripiprazole for delusions and hallucinations and autistic symptoms (drug use for unapproved indication). The patient's medical history included generalised anxiety disorder, obsessive-compulsive disorder, visual and auditory hallucination, prior to starting aripiprazole. Within 2 to 3 weeks of starting escitalopram oxalate, he experienced fatigue, lower motivation. He experienced weight gain, broken leg (traumatic), walking difficulty, handshaking, fatigue worsened, lower motivation worsened (lack of motivation) and weight loss while on therapy with aripiprazole.

2016: *The patient started receiving therapy with aripiprazole tablets 15 mg at a dose of 7.5 mg daily. He did not have a diagnosis of schizophrenia because the delusions and hallucinations occurred off and on and were not frequent enough for him to be diagnosed with it. The dose of aripiprazole 7.5 mg was achieved by splitting aripiprazole 15 mg tablets in half to save cost. Soon after starting aripiprazole therapy in 2016, he began gaining weight. Within 2 weeks of starting aripiprazole, his hallucinations and irritability were fading. About 1.5 months after starting aripiprazole, he jumped from a rock on a hike and broke his leg. He was not able to participate in swimming due to the broken leg and gained 65 pounds of weight. The dose of aripiprazole was increased to 10 mg and he started walking very stiff like Frankenstein and developed handshaking. The therapy with aripiprazole dose was decreased back to 7.5 mg daily. Benzatropine mesylate 0.25 mg was added and the tremors in hand were resolved. On an unknown date after starting aripiprazole, his fatigue and lower motivation worsened.*

2017: *As of June, he was still taking aripiprazole 7.5 mg for delusions and hallucinations and irritation. He was no longer gaining weight or losing weight. The broken leg had healed. He was still experiencing worsened fatigue and worsened lower motivation."*

- **Causality Assessment**

Table 3.29 The French Imputability Assessment - Apathy

Chronological criteria		**Semiological criteria**	
Challenge	Compatible	Symptoms	Compatible
Rechallenge	R0	Lab Test	L0
Dechallenge	C1	Alternate	S1
Result	I0	Unlikely	

- **Comments:**

The patient's underlying psychiatric illness as indicated by the use of aripiprazole was a significant risk factor for apathy. Apathy is also observed in patients with autism (Ang et al, 2017). Considering that the antipsychotics, including aripiprazole, can be associated with weight fluctuation, its role in weight gain and weight loss leading to fatigue and gait disturbance were possible. Extrapyramidal symptoms including tremors can be associated with antipsychotics including aripiprazole as per the SmPC.

- **Conclusion:** The relationship between the ADR and the drugs is 'unlikely'.

Chapter 4 Discussion

4.1 Implications of Cultural, Economic and Regulatory Differences in Approach towards ASD in India and Malta

Autism Spectrum Disorder is a group of neurodevelopmental disorders with different levels of severity. No treatment options are available for the core symptoms, and the primary identification of disorder depends on keen observation of symptoms by parents and clinicians. Cultural and economic differences affect the perception towards autism in children in different countries (Samadi and McConkey, 2011). The conceptualisation of ASD is through the manuals like DSM-V and ICD-10, which are used worldwide by clinicians. The manuals have been updated to incorporate the precise concept of ASD (Mandy et el, 2013). Behaviour which is considered 'normal' in a European-American culture might be avoided in other cultures, for example avoiding eye contact is considered one of the possible "Red Flags" for ASD [56] in the Western culture, but it is completely normal not to make eye contact with elders in other cultures. In some cultures, making direct eye contact is considered a sign of disrespect so children are taught not to do so and applying the Western criteria of evaluation in these children for ASD might lead to misdiagnosis. The diversions occurring due to cultural differences have led countries to adapt the screening and diagnostic tools from the West to meet the linguistic, cultural and economic requirements (DeWeerdt, 2012). One such example is the Indian Scale of Assessment of Autism (ISAA) which was designed and developed in India inspired by the Western screening tool "Childhood Autism Rating Scale" (CARS). It was developed to have a more culturally and economically suitable tool for the Indian population (Deshpande et al, 2015).

[56] CDC.Signs & Symptoms | Autism Spectrum Disorder (ASD) | NCBDDD | CDC [Internet]. Centres for Disease Control and Prevention. 2018 [cited 2018 May 15]. Available from: https://www.cdc.gov/ncbddd/autism/signs.html

The study aimed to understand the effect of the cultural, economic and regulatory differences in approach towards autism in India and Malta using a questionnaire ASD-Q $_{(IND-MT)}$ for Indian and Maltese psychiatrists. On analysis of ASD-Q $_{(IND-MT)}$, it was observed that psychiatrists in India and Malta strongly agreed with the definition of ASD provided by the DSM-V manual. Psychiatrists believe that the classification as per the current knowledge includes all the prominent behavioural symptoms that are observed in a patient with ASD ($p=0.001$). The DSM-V is a significantly revised edition of the manual since its previous version DSM-IV published in 1994. The DSM-V was reviewed by more than 400 experts from over 13 countries to standardise the manual and upgrade it as per a research that concluded the significant effects of cultural difference on the diagnosis of ASD. One of the significant changes in the DSM-V was the inclusion of the term Autism Spectrum Disorder for a group of neurodevelopmental disorders that were earlier individually assessed such as the PDD-NOS (Regier et al, 2013). Psychiatrists in India and Malta might have agreed with the DSM-V classification despite different perceptions of autism because of the standardisation of manual. Psychiatrists in India and Malta strongly agreed that differentiating between ASD and other developmental disorders at a proper age is pivotal ($p=1.000$). Early identification of ASD is essential as the influence of the behavioural therapy is greater at a younger age when the brain is still developing which will result in a better intervention and also provide parents and caregivers precise knowledge of the disorder and the proper way to manage the patient (Kope et al, 2001).

A significant difference ($p<0.001$) was noted between Maltese and Indian psychiatrists over the screening tools being able to play an essential role in early detection and differentiation of ASD. Indian psychiatrists strongly agreed (mean 4.45 ± 0.506) that ISAA can differentiate

between ASD and other developmental disorders, but Maltese psychiatrists disagreed (mean 2.56±1.153) that CARS plays an essential role in distinguishing between disorders. Indian psychiatrists agreed (mean 3.58±0.050) that screening tool ISAA is accurate in identifying the ASD but Maltese psychiatrists disagreed (mean 2.38±0.500) with the statement ($p<0.001$) taking into consideration the CARS. Possible reasoning behind this could be the inclusion of questions related to cognitive symptoms like memory abilities or other savant abilities in the ISAA that are not part of CARS tool which makes ISAA more accurate in identifying and differentiating ASD with other neurodevelopmental disorders. A study conducted by Chakraborty et al (2015) on assessing ISAA with other tools concluded that the ISAA was able to differentiate between patients with autism and four other groups with other developmental disorders. Psychiatrists in India and Malta agreed that current screening tools (ISAA/ CARS) should collect information on genetic factors and birth conditions to increase the accuracy and efficacy of the tool towards assessing ASD ($p=0.014$). A possible postulation about this finding could be that ASD has been associated to be caused by multiple genetic and environmental factors. Advanced paternal and maternal age has been associated with increased risk of having an offspring with ASD (Johnson and Myers, 2007). The sibling of a single child who has autism can be found to be at increased risk of having ASD by 3-10% which could increase significantly to 33-50% if two or more siblings have ASD (Cop et al, 2015). Observing congenital disabilities can be significant as studies have shown that increased head circumference in infants can be a predictor of ASD and it might alert paediatricians to request for a screening of the child (Courchesne, 2003), (Elder et al, 2007), (Fidler et al, 2007). A population-based study by Dawson et al (2009) has also listed out the possible congenital disabilities that could warn the healthcare professionals of the risk such as parent's age, mothers race and child's

gender. A significant difference was observed between Indian and Maltese psychiatrists ($p<0.001$) when asked about inclusion of Intelligence Quotient (IQ) score as a parameter for ASD in the screening tools. Maltese psychiatrists strongly agreed (mean 4.50±0.516) with the statement but Indian psychiatrists disagreed (mean 2.23±0.425). In studies, IQ has been considered as a moderator of ASD symptoms and cognitive abilities and IQ level below 70 is associated with high rates of severe ASD (DiGuiseppi et al, 2010); (Kamio et al, 2012); (Ryland et al, 2014). A study conducted by Rommelse et al (2015) on the effect of IQ cognitive abilities in patients concluded that cognitive symptoms were more severe in ASD patients who had an IQ above average as compared to patients with a below average IQ. It is interesting to note that Indian psychiatrists disagree with the inclusion of IQ score as a parameter for ASD in the screening tool. The possible reason can be the difficulties in determining IQ in the Indian population. A study conducted by Ashok et al (2015) focused on difficulties faced in determining IQ in the Indian autistic population and concluded that absence of a standardised global intelligence measuring tools was a major limitation and the available tools were not feasible. Overestimation of the IQ score was also noted within the patient group due to limitations in the tools. Psychiatrists were also asked about their opinion on having pictorial assessment tools or upgrading the current tools (ISAA/ CARS) with pictorial forms to make the tools more user-friendly and both the groups agreed ($p=0.061$) that including pictorial forms might be a great way to increase the efficacy of the tool and make it more user friendly. A tool, Pictorial Autism Assessment Schedule (PAAS) has already been adapted in India and has been proved to be useful in assessing ASD. The feasibility of the tool to use within the community is being established (Perera et al, 2017). On the role of pharmacists in the treatment of ASD, a significant difference was noted between Indian and Maltese psychiatrists. Maltese psychiatrists strongly believe

(mean 4.44±0.512) that clinical pharmacists can play a crucial role in designing individual therapies for ASD patients and Indian psychiatrists disagreed (mean 2.39±0.558) with the statement. A possible reason behind this is attributed to the fact that clinical pharmacy is an infant subject in India and caregivers and parents insist on getting first-hand information from the specialist consultants as compared to a pharmacist but psychiatrists in both the countries agreed that pharmacists possess enough knowledge on ASD drugs to suggest interventions ($p=0.004$). Psychiatrists also agreed that pharmacists are aware not only of the FDA approved drugs but also of the nationally authorised medications for autism in the respective countries ($p=0.116$). A significant difference was also noticed regarding the role of community pharmacists in providing counselling to patients and caregivers about the drugs used in ASD ($p<0.001$). Wongpakaran et al (2017) studied the impact of pharmacist intervention in reducing the drug-related problems occurring in patients with ASD and significant results were observed with reduced drug-related problems which resulted in the better effectiveness of the drug and better outcome for the patient.

Psychiatrists were also questioned regarding the accessibility of the only FDA approved drugs for ASD, RiAr. Psychiatrists, in India and Malta, agreed that accessibility of RiAr is a matter of concern ($p=0.232$). One of the objectives of the research is to study and compare the accessibility of the RiAr in India and Malta. The accessibility of the drugs was investigated by measuring the price of the drug and the affordability of the treatment in both countries. The study was designed as per the WHO methodology of measuring and comparing the cost of treatment in two countries. The price of risperidone in India and Malta was €1.16 and €17.84 respectively. The price of aripiprazole was found to be €1.30 in India and €28.92 in Malta. A difference between the prices of RiAr is noted. A study

conducted by Shukla and Agnihotri (2017) in India also concluded similar results where variations were observed in the price of different generic brands of the same antipsychotic and risperidone 2mg had the highest cost ratio and percentage cost variation.

The cost of treatment was calculated as per the FDA recommended daily effective dose for one month. The cost of one month of treatment with risperidone in India and Malta was €3.50 and €26.70 respectively. The cost of treatment with aripiprazole was €3.90 in India and €28.80 in Malta. The percentage variation in the cost of treatment with RiAr in India and Malta is observed to be 662% and 638% respectively. The prices obtained reflect that the cost of the drugs is much higher in Malta as compared to India but this price cannot be taken as a true expression of affordability as it may vary depending on the amount of expenditure by the population of the country. The WHO recommends measuring the affordability of the drugs by considering the minimum wage of an unskilled employee in a country. In this study, the affordability is measured by comparing the price against the Monthly Per Capita Expenditure (MPCE). The drug prices from India are converted according to the nominal exchange rate, which does not include any inflation rates or the Purchasing Power Parity (PPP). The cost of medication in India could have been different with the inclusion of the rates.

The recommended method of calculating affordability by the minimum wage of an unskilled labour was not considered because 1) the wage system in India is more complicated as compared to Malta. The wage differs across the states in India, and it would be challenging to calculate an average wage of an unskilled employee across India, 2) the daily wage provided to the labourer might be less than the lowest wage as approved by the government, 3) members of a household might be unemployed or dependant on one family

member for expenditure, 4) jobs might be seasonal in India and wages may also vary across the seasons. MPCE was considered to avoid such limitations.

Comparison of the cost of treatment against the MPCE in India revealed that the treatment is more expensive in India as compared to Malta despite the low prices of the drug. The percentage of MPCE required to attain one month's treatment with risperidone is 11.30% in urban and 20.71% in rural India but only 3.30% in Malta. The percentage of MPCE required for treatment with aripiprazole is 12.60% in urban and 23.08% in rural India and only 3.56% in Malta. There is a vast difference between the percentage of expenditure required by the people in India for just one month of treatment. Despite the medication being expensive in Malta as compared to India, the treatment in Malta is still more affordable. Psychiatrists in India and Malta agreed ($p=0.463$) that including RiAr on the national formulary will increase the accessibility of the drugs. It is observed that the accessibility and the cost are crucially affected by the inclusion of the drugs on the national formularies. Unlike in Malta, where the drugs included in the schedule V are available for free, people in India have to pay for their medications. The NLEM includes only risperidone for psychotic disorders, which will significantly affect the availability and the price of the drug. [57] The National Pharmaceutical Pricing Authority (NPPA) regulates the prices of essential medicines in India by setting fixed ceiling prices for drugs on the list regulating the price to make the drug more affordable. The higher cost of aripiprazole may be explained by the fact that the drug is not present on the NLEM, which gives an authority to the manufacturers to increase the price to obtain profitable margins. The higher cost of

[57] Ministry of health and family welfare. National List of Essential Medicines (NLEM-2015) [Internet]. Cdsco.nic.in. 2015 [cited 2018 May 25]. Available from: http://www.cdsco.nic.in/writereaddata/National%20List%20of%20Essential%20Medicine-%20final%20copy.pdf

medicines in India can be related to the market-based pricing (MBP) mechanism adopted by the NPPA which has been criticised as it is based on average price of competitor brands prevailing in a specific therapeutic category than the actual cost of the drug (Narula, 2015). Analysis of antipsychotics on the Indian market by Tondare and Bhave (2014) concluded that an increase in manufacturers resulted in increased percentage variation between the prices of the drug. To tackle the high cost of medicines and to increase the accessibility, the government of India has come out with schemes and policies supporting the use of generic medications. The Jan Aushadhi [58] campaign has been launched to increase access to low-cost generic medicines claimed to be bioequivalent as the branded drugs by the government.

The Medical Council of India (MCI) launched guidelines for physicians to prescribe a drug with generic names rather than brand names to promote the generic industry[59] and the Jan Aushadhi campaign. Under the campaign, a Jan Aushadhi pharmacy is established in each state for people to buy the generics. Competition of drugs in India is between branded generics and unbranded generics (Jan Aushadhi scheme), unlike other countries where the competition is between the originator and the generic brands of the drugs. It is also important to note that Jan Aushadhi caters for the drugs, which are on the NLEM which excludes aripiprazole. RiAr are indicated for irritability associated with autism spectrum disorder in children and adolescents only by the FDA and not by the EMA or the CDSCO, which implies that the drugs cannot be included in the national formularies in both

[58] Bureau of Pharma PSU of India (BPPI). Jan Aushadhi: An Initiative of Government of India | Generic Medicine Campaign Improving Access to Medicines [Internet]. Janaushadhi.gov.in. 2018 [cited 2018 May 25]. Available from: http://janaushadhi.gov.in/about_jan_aushadhi.html

[59] Medical Council of India. MCI notification regarding use of generic names 2017 [Internet]. Ipgmer.gov.in. 2017 [cited 2018 May 25]. Available from: http://www.ipgmer.gov.in/PharmacovigilanceCommittee/MCI_CircularUseofGenericNames20170421.pdf

countries and will be used off-label when prescribed. The Committee for Medicinal Products for Human Use (CHMP) recommended against an autism indication for aripiprazole due to not having robust clinical data to approve the indication.[60] A request to include the posology in the Summary of Product Characteristics (SmPC) was requested to the EMA but was rejected due to not having long-term study no follow up. Recommendation on posology was not made. The comment provided was *'Irritability associated with autistic disorder: the safety and efficacy of ABILIFY in children and adolescents below 18 years of age have not yet been established. Currently available data are described in section 5.1, but no recommendation on a posology can be made'.* [61]

The CHMP also rejected the request the approval of risperidone for the indication of ASD and the comment provided was '*The CHMP further discussed efficacy in Children and Adolescents with Autistic Disorder, a Pervasive Developmental Disorder that is different from Conduct Disorder which is a Disruptive Behaviour Disorder. As a consequence, children with autistic disorders are not included in the proposed indication. This exclusion is supported by the fact that the primary symptoms of the autism disorder cannot successfully be treated with Risperdal because the target symptoms in autism for which Risperdal has demonstrated its most robust efficacy are associated symptoms rather than a broad spectrum of symptoms of the disease. Because of the lack of specificity and the availability of other treatment options, the CHMP did not consider the indication in Autistic Disorder as supported. In conclusion, the CHMP adopted the following*

[60] EMA. Abilify- EPAR- Procedural steps [Internet]. Ema.europa.eu. 2018 [cited 2018 May 25]. Available from: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Procedural_steps_taken_and_scientific_information_after_authorisation/human/000471/WC500020

[61] EMA. Abilify – EPAR assessment report [Internet]. Ema.europa.eu. 2018 [cited2018 May 25]. Available from: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Assessment_Report_-_Variation/human/000471/WC500151731.pdf

indication'.[62] The approval of the indication might significantly affect the accessibility and price of RiAr. One of the questions asked in the questionnaire was about the post-marketing safety study for any potential ADR's and psychiatrists in India (mean 3.87±0.341) and Malta (mean 4.30± 0.500) agreed that it is crucial to monitor drugs post-marketing scenario. One of the objectives was to perform signal detection and validation o Eudravigilance to detect any potential ADRs. It was observed in the results that the most common ADR of risperidone was gynaecomastia with 1,427 cases in children and adolescents followed by weight increase with risperidone with 512 cases. The most common ADR is for aripiprazole were weight gain with 150 cases and then dystonia with 101 reported cases. According to the SmPC of risperidone weight gain is more common than gynaecomastia and for aripiprazole, the frequency of weight gain is still unknown.

4.2 Limitations

The questionnaire, ASD-Q $_{(IND-MT)}$ developed in the study used close-ended questions, which might have created bias in selecting responses, as the answers are limited. The questionnaire was also designed using a five-point Likert scale, which again limits the options of responses, by providing just five choices to select from. The Likert scale responses are also likely to be influenced by previous responses from the questionnaire. The responses obtained might not reflect the real scenario as not all psychiatrists who participated in the study were specialised in child psychiatry. Some of the reported findings in the study might have been biased due to the difference in a number of participants from India and Malta.

[62] EMA. Risperdal- Article 30 referral. [Internet]. Ema.europa.eu. 2018 [cited2018 May 25]. Available from: http://www.ema.europa.eu/docs/en_GB/document_library/Referrals_document/Risperdal_30/WC500007979.pdf

An updated version of CARS, CARS-2 was not available at the hospital due to which the original version of CARS was studied. A limitation was noted as, during the period of collecting data for the research, Abilify, the originator brand of aripiprazole was out of stock and not available in Malta due to which generic brands had to be compared. Another limitation of the study was that the data collection was cross-sectional where longitudinal perspective was lacking.

4.3 Recommendations for Future Work

The recommendation for future work suggests reviewing and comparing culturally adapted diagnostic tools to measure the impact and interpretation of the tool in different countries. Similar studies using the updated CARS-2 should be compared in different countries to measure the efficacy of the tool. Future studies should also involve studying SSRI for example fluoxetine which is being prescribed (off-label) in the patients with autism. Pharmacist's intervention should also be evaluated within the psychiatric wards in hospital concerning patients with ASD. The intervention of pharmacists should also be evaluated in specialised multidisciplinary teams to manage ASD in children such as the Team for Assessment of Attention and Social Communication (TAASC), a newly set up team in Malta to offer individuals with ASD tailor-made assessment pathways for a better outcome. The TAASC consists of psychologists, psychiatrists, therapists and pharmacists are not included. Pharmacist intervention as part of such a multidisciplinary team would be beneficial for patients especially when drugs with prominent ADR profile are used such as antipsychotics.

4.4 Conclusion

The study represents the first comparison of differences in culture, economy and regulations in India and Malta and its impact on the management of ASD by RiAr. The results presented in the study helps to conclude that screening tools also have an influence on the prescribing behaviour of RiAr. It was also observed that culturally developed screening tools (ISAA and CARS) have a different influence on the prescribing behaviour of RiAr in India and Malta. Screening tools in India (ISAA) and Malta (CARS) aim at assessing the severity of ASD, but the interpretation of scoring is very different in both countries. This study also suggests the need to improve and update the screening tools or develop a standard tool that can be efficaciously applied in different countries to assess ASD irrespective of cultural divergences. The study noted that the price of the drug cannot be taken as a sole factor to estimate the affordability of treatment in a country. The price of the drug is observed to be expensive in Malta as compared to India but the treatment with RiAr is much more affordable in Malta than in India. It was also observed that regulatory laws in India not only affect the availability of drugs but also the affordability. The approval of RiAr for the indication of ASD by national regulatory authorities in India and Malta will significantly affect the accessibility of the drugs by inclusion on national formularies in both the countries. Robust data should be provided by companies to support the approval of RiAr. The Eudravigilance signal detection report revealed that gynaecomastia was the most reported ADR observed in 5-16 years treated with risperidone for ASD and weight gain was the most reported ADR observed in 6-17 years treated with aripiprazole for ASD. The assessment of eight safety signals concluded “unlikely” and “uncertain” relationship between the drugs and the ADR indicating that the SmPC of RiAr includes all the indicated ADRs observed in this study that might impact treatment

adherence and could have a detrimental effect on the underlying conditions. In conclusion, this study has set the foundation for future studies to be conducted on ASD.

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Appendices

Appendix 1

Autism Spectrum Disorder Questionnaire India (India- Malta) [ASD-QI (IND-MT)]

Date:

Dear Participants,

My name is Shaista Sadaf, and I am a Doctorate student at the University of Malta. I am conducting my research on "Accessibility and Safety of antipsychotics in the treatment of Autism Spectrum Disorder in children and adolescents." As your specialisation is Psychiatry and dealing with the autism patients, I am inviting you to participate in this research study by completing the attached questionnaire.

The following questionnaire will require approximately 10-15 minutes to complete. The enclosed questionnaire has been designed to collect information specific to autism and the screening tools used to help diagnose children with autism.

There is no compensation for responding nor is there any known risk. In order to ensure that all information will remain confidential, please do not include your name. Copies of the dissertation will be provided to the University of Malta –Department of Pharmacy and will be used for research purposes only.

I would be very grateful if you choose to participate in this project. Participation is strictly voluntary, and you may refuse to participate at any time.

Thank you for taking the time to assist me in my educational endeavours. Yours sincerely,
Shaista Sadaf

Contact details:

Email: shaista.sadaf.15@um.edu.mt
Email (supervisor): anthony.serracino-inglott@um.edu.mt

Directions/ Instructions

- Encircle the option that best represents your answer on the basis of agreement and disagreement for that particular statement/ question.

- Write a comment in the space provided representing the basis for selecting a particular answer.

Section I: Demographics

A. Age

- ☐ <30
- ☐ 31-40
- ☐ 41-50
- ☐ 51-60
- ☐ 61-70

B. Gender:

- ☐ Male
- ☐ Female

C. Total years of practice as a psychiatrist:

- ☐ ≤ 1 year
- ☐ 2-4 years
- ☐ 5-7 years
- ☐ 8-10years
- ☐ >10 years

D. On average how many *new* Autism Spectrum Disorder patients do you deal with in a month?

- ☐ 0-1
- ☐ 2-4
- ☐ 5-7
- ☐ 8-10
- ☐ >10

E. On average how many *follow-up* Autism Spectrum Disorder patients do you deal with in a month?

- ☐ 0-1
- ☐ 2-4
- ☐ 5-7
- ☐ 8-10
- ☐ >10

Section II: Answer the questions based on the level of agreement with the following statements.

A. The questions represent the importance of ASD and its screening tools.	**Strongly disagree**	**Disagree**	**Neither agrees/disagree**	**Agree**	**Strongly agree**	**Comments**
1. The DSM-V manual accurately defines and classifies ASD	1	2	3	4	5	
2. Early detection of ASD is pivotal for better intervention and outcome	1	2	3	4	5	
3. Differentiating between ASD and other developmental disorders, e.g. OCD (obsessive-compulsive disorder) is crucial	1	2	3	4	5	
4. The screening tool Indian scale of assessment of autism (ISAA) plays an essential role in achieving the above goals	1	2	3	4	5	

5. The complete treatment of ASD should be government funded due to its increasing prevalence	1	2	3	4	5	
6. ISAA as a screening tool is always accurate in identifying the ASD	1	2	3	4	5	
7. The information obtained over the range of questions from the ISAA is sufficient or always satisfactory in determining all the aspects of the ASD	1	2	3	4	5	
8. Including questions on genetic factors and birth, conditions can increase the efficiency of the tool (ISAA)	1	2	3	4	5	
9. Pictorial assessment tools such as Pictorial Autism Assessment Schedule (PAAS) could be more accurate than ISAA	1	2	3	4	5	

10. IQ scores should be a parameter in deciding the presence of ASD and should be included in the screening tools.	1	2	3	4	5	
11. The final score of ISAA always leads to an unbiased decision making regarding the presence and severity of ASD	1	2	3	4	5	
12. The final score of ISAA along with other diagnosis and observation can help to determine the need to prescribe antipsychotics	1	2	3	4	5	

Section III: Answer the questions based on the level of agreement with the following statements.

B. The following questions Represent Pharmacists and their role in treating ASD.	Strongly disagree	Disagree	Neither agrees/disagree	Agree	Strongly agree	Comments
13. Pharmacists are an essential part of the healthcare system in suggesting medical interventions.	1	2	3	4	5	
14. Knowledge among pharmacists about ASD, its classification and latest guidelines is sufficient for suggesting interventions.	1	2	3	4	5	
15. Pharmacists have the knowledge to access CDSCO approved drugs indicated for autism and know their target doses.	1	2	3	4	5	
16. Pharmacists have the knowledge to access FDA approved drugs indicated for autism and know	1	2	3	4	5	

their target doses.						
17. Clinical pharmacists can play an important role in dosage adjustments for patients with ASD during periodic reassessments and also recommend the drugs commercially available	1	2	3	4	5	
18. Clinical pharmacists can play an important role in designing individual therapies for patients with ASD to reduce Drug-related problems (DRP's)	1	2	3	4	5	
19. Clinical pharmacists can play a crucial role in reporting abnormalities detected during birth, e.g., abnormal head circumference, which could be an indicator of ASD.	1	2	3	4	5	

20. Community pharmacists can play a vital role in providing counselling to patients & caregivers, which can have a significant impact on their quality of life, e.g. Dietary restrictions and allergens.	1	2	3	4	5	
21. Pharmacists should be an active part of the multidisciplinary team under a protocol to treat ASD as this would lead to better selection of medicine and safety which will finally lead to better outcome	1	2	3	4	5	

Section IV: Answer the questions based on the level of agreement

C. The following questions will represent the ASD drugs and their accessibility	Strongly disagree	Disagree	Neither agrees/disagree	Agree	Strongly agree	Comments

22. Accessibility of risperidone is a matter of concern in India	1	2	3	4	5	
23. Accessibility of aripiprazole is a matter of concern in India	1	2	3	4	5	
24. Including risperidone and aripiprazole on National List of Essential Medicines (NLEM) for indications of autism would significantly increase their accessibility	1	2	3	4	5	
25. Evaluating post-marketing safety of RiAr specifically in children and adolescents is essential	1	2	3	4	5	

Section V: Select one answer based on the influence of ISAA score.

D. Answer the following considering the final scores obtained in ISAA	Not at all influential	Slightly Influential	Somewhat influential	Very influential	Extremely influential	Comments
26. How influential is the ISAA score while deciding to prescribe antipsychotics to the patient(risperidone /aripiprazole) after the final diagnosis and observation	1	2	3	4	5	

Note: If your answer is 1, then kindly skip to question 28

Section VI: Select one answer based on interpretation of final scores of ISAA.

E. Answer the following considering the final scores obtained in ISAA	No autism <30	Mild Autism 71-106	Moderate autism 107-153	Severe Autism 153	N/A	**Comments**
27. The score which would have a positive influence while deciding the prescription of antipsychotics risperidone /aripiprazole	1	2	3	4	5	
28. The score which would make a child eligible to join a regular educational institution with frequent monitoring	1	2	3	4	5	

Remarks:

Appendix 2
Autism Spectrum Disorder Questionnaire Malta (India- Malta) [ASD-QM (IND-MT)

Date:

Dear Participants,

My name is Shaista Sadaf, and I am a Doctorate student at the University of Malta. I am conducting my research on "Accessibility and Safety of antipsychotics in the treatment of Autism Spectrum Disorder in children and adolescents." As your specialisation is Psychiatry and dealing with the autism patients, I am inviting you to participate in this research study by completing the attached questionnaire.

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There is no compensation for responding nor is there any known risk. In order to ensure that all information will remain confidential, please do not include your name. Copies of the dissertation will be provided to the University of Malta –Department of Pharmacy and will be used for research purposes only.

I would be very grateful if you choose to participate in this project. Participation is strictly voluntary, and you may refuse to participate at any time.

Thank you for taking the time to assist me in my educational endeavours. Yours sincerely,
Shaista Sadaf

Contact details:

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Email (supervisor): anthony.serracino-inglott@um.edu.mt

University Of Malta

Directions/ Instructions

- Encircle the option that best represents your answer on the basis of agreement and disagreement for that particular statement/ question.

- Write a comment in the space provided representing the basis for selecting a particular answer.

Section I: Demographics

F. Age

- ☐ <30
- ☐ 31-40
- ☐ 41-50
- ☐ 51-60
- ☐ 61-70

G. Gender:

- ☐ Male
- ☐ Female

H. Total years of practice as a psychiatrist:

- ☐ ≤ 1 year
- ☐ 2-4 years
- ☐ 5-7 years
- ☐ 8-10years
- ☐ >10 years

I. On average how many *new* Autism Spectrum Disorder patients do you deal with in a month?

- ☐ 0-1
- ☐ 2-4
- ☐ 5-7
- ☐ 8-10
- ☐ >10

J. On average how many *follow-up* Autism Spectrum Disorder patients do you deal with in a month?

- ☐ 0-1
- ☐ 2-4
- ☐ 5-7
- ☐ 8-10
- ☐ >10

Section II: Answer the questions based on the level of agreement with the following statements.

A. The questions represent the importance of ASD and its screening tools.	**Strongly disagree**	**Disagree**	**Neither agrees/disagree**	**Agree**	**Strongly agree**	**Comments**
1. The DSM-V manual accurately defines and classifies ASD	1	2	3	4	5	
2. Early detection of ASD is pivotal for better intervention and outcome	1	2	3	4	5	
3. Differentiating between ASD and other developmental disorders, e.g. OCD (obsessive-compulsive disorder) is crucial	1	2	3	4	5	
4. The screening tool Childhood Autism Rating Scale (CARS) plays an essential role in achieving the above goals	1	2	3	4	5	

5. The complete treatment of ASD should be government funded due to its increasing prevalence	1	2	3	4	5	
6. CARS as a screening tool is always accurate in identifying the ASD	1	2	3	4	5	
7. The information obtained over the range of questions from the CARS is sufficient or always satisfactory in determining all the aspects of the ASD	1	2	3	4	5	
8. Including questions on genetic factors and birth, conditions can increase the efficiency of the tool (CARS)	1	2	3	4	5	
9. Pictorial assessment tools such as Pictorial Autism Assessment Schedule (PAAS) could be more accurate than CARS	1	2	3	4	5	

10. IQ scores should be a parameter in deciding the presence of ASD and should be included in the screening tools.	1	2	3	4	5	
11. The final score of CARS always leads to an unbiased decision making regarding the presence and severity of ASD	1	2	3	4	5	
12. The final score of CARS along with other diagnosis and observation can help to determine the need to prescribe antipsychotics	1	2	3	4	5	

Remarks:

Section III: Answer the questions based on the level of agreement with the following statements.

B. The following questions represent pharmacists and their role in treating ASD.	Strongly disagree	Disagree	Neither agrees/disagree	Agree	Strongly agree	Comments
13. Pharmacists are an essential part of the healthcare system in suggesting medical interventions.	1	2	3	4	5	
14. Knowledge among pharmacists about ASD, its classification and latest guidelines is sufficient for suggesting interventions.	1	2	3	4	5	
15. Pharmacists have the knowledge to access EMA approved drugs indicated for autism and know their target doses.	1	2	3	4	5	

16. Pharmacists have the knowledge to access FDA approved drugs indicated for autism and know their target doses.	1	2	3	4	5	
17. Clinical pharmacists can play an important role in dosage adjustments for patients with ASD during periodic reassessments and also recommend the drugs commercially available	1	2	3	4	5	
18. Clinical pharmacists can play an important role in designing individual therapies for patients with ASD to reduce Drug-related problems (DRP's)	1	2	3	4	5	
19. Clinical pharmacists can play a crucial role in reporting abnormalities detected during birth, e.g., abnormal head circumference, which could be an indicator of ASD.	1	2	3	4	5	

20. Community pharmacists can play a vital role in providing counselling to patients & caregivers, which can have a significant impact on their quality of life, e.g. Dietary restrictions and allergens.	1	2	3	4	5	
21. Pharmacists should be an active part of the multidisciplinary team under a protocol to treat ASD as this would lead to better selection of medicine and safety which will finally lead to better outcome	1	2	3	4	5	

Section IV: Answer the questions based on the level of agreement

C. The following questions will represent the ASD drugs and their accessibility	Strongly disagree	Disagree	Neither agrees/disagree	Agree	Strongly agree	Comments
22. Accessibility of risperidone is a matter of concern in Malta	1	2	3	4	5	
23. Accessibility of aripiprazole is a matter of concern in Malta	1	2	3	4	5	
24. Including risperidone and aripiprazole on National Formulary under Schedule V scheme for indications for ASD would significantly increase their accessibility	1	2	3	4	5	

25. Evaluating post – marketing safety of RiAr specifically in children and adolescents is essential.	1	2	3	4	5	

Section V: Select one answer based on the influence of CARS score.

D. Answer the following considering the final scores obtained in CARS	Not at all influential	Slightly Influential	Somewhat influential	Very influential	Extremely influential	Comments
26. How influential is the CARS score while deciding to prescribe antipsychotics to the patient(risperidone /aripiprazole) after the final diagnosis and observation	1	2	3	4	5	

Note: If your answer is 1, then kindly skip to question 28.

Section VI: Select one answer based on interpretation of final scores of CARS.

E. Answer the following considering the final scores obtained in CARS	Non autistics 15-30	Mildly – Moderately autistic 30-37	Severely autistics 37-60	N/A	N/A	**Comments**
27. The score which would have a positive influence while deciding the prescription of antipsychotics risperidone /aripiprazole	1	2	3	4	5	
28. The score which would make a child eligible to join a regular educational institution with frequent monitoring	1	2	3	4	5	

Remarks:

Appendix 3

Content Validity Index Tool (CVI-T)

Dear Experts,

My name is Shaista Sadaf and I am a Doctorate student at University of Malta. As part of my course I am conducting a research entitled "Accessibility and Safety of antipsychotics in the treatment of Autism Spectrum Disorder in children and adolescents- A comparative study in India and Malta " Under one of my objectives I have prepared a questionnaire intended for psychiatrist who deal with patients suffering from ASD. The questionnaire contains details about the ASD and its screening tools.

Every questionnaire that has been developed should be validated by a panel of experts. For this task you have been invited to participate in the validation process as you are experts that deal with autism patients. The validation method being used is content validation index which will calculate the relecance of each question in the actual questionnaire.

Copies of the project will be provided to the University of Malta –Department of Pharmacy and will be used for research purpose only.

Participation is strictly voluntary and you may refuse to participate at any time.

Thank you for taking the time to assist me in my educational endeavors.

Yours sincerely,

Shaista Sadaf

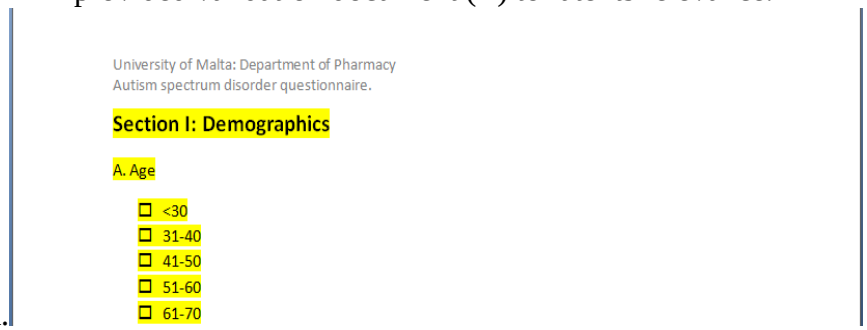
Pharm D student

University Of Malta.

Instructions/directions

1. The following task will take approximately 10 to 15 min to complete
2. Kindly use the below table provided to refer for each answer / number to be selected.
3. Example: If you find the question A (age group distribution) valid and relevant to the context of my research then you would select one option/ number from the provided validation document (B) to rate its relevance.

A.

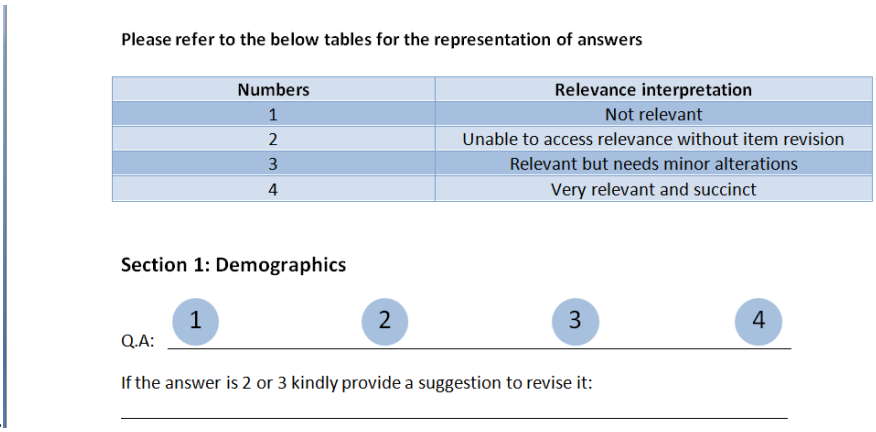

University of Malta: Department of Pharmacy
Autism spectrum disorder questionnaire.

Section I: Demographics

A. Age

- ☐ <30
- ☐ 31-40
- ☐ 41-50
- ☐ 51-60
- ☐ 61-70

B.


Please refer to the below tables for the representation of answers

Numbers	Relevance interpretation
1	Not relevant
2	Unable to access relevance without item revision
3	Relevant but needs minor alterations
4	Very relevant and succinct

Section 1: Demographics

Q.A: 1 2 3 4

If the answer is 2 or 3 kindly provide a suggestion to revise it:

4. If 1 is selected then the question will be considered irrelevant and will be removed from the questionnaire
5. IF 2 or 3 is selected then those questions will be changed according to your suggestions provided below that particular question
6. If 4 is selected then the question will be considered valid and relevant to my research and will be part of the questionnaire without any changes.

Please select one answer / number based on the relevance of the questions provided in the questionnaire:

Please refer to the below tables for the representation of answers

Numbers	Relevance interpretation
1	Not relevant
2	Unable to access relevance without item revision
3	Relevant but needs minor alterations
4	Very relevant and succinct

Section 1: Demographics

Q.A: 1 2 3 4

If the answer is 2 or 3 kindly provide a suggestion to revise it: _____

Q.B: 1 2 3 4

If the answer is 2 or 3 kindly provide a suggestion to revise it: _____

Q.C: 1 2 3 4

If the answer is 2 or 3 kindly provide a suggestion to revise it: _____

Q.D: 1 2 3 4

If the answer is 2 or 3 kindly provide a suggestion to revise it: _____

Section II- A. The questions represent the importance of ASD and its screening tools.

Q.1: 1 2 3 4

If the answer is 2 or 3 kindly provide a suggestion to revise it: _____

Q.2: 1 2 3 4

If the answer is 2 or 3 kindly provide a suggestion to revise it: _____

Q.3: 1 2 3 4

If the answer is 2 or 3 kindly provide a suggestion to revise it: _____

Q.4: 1 2 3 4

If the answer is 2 or 3 kindly provide a suggestion to revise it: _____

Q.5: 1 2 3 4

If the answer is 2 or 3 kindly provide a suggestion to revise it: _____

Q.6: 1 2 3 4

If the answer is 2 or 3 kindly provide a suggestion to revise it: _____

Q.7: 1 2 3 4

If the answer is 2 or 3 kindly provide a suggestion to revise it: _____

Q.8: 1 2 3 4

If the answer is 2 or 3 kindly provide a suggestion to revise it: _____

Q.9: 1 2 3 4

If the answer is 2 or 3 kindly provide a suggestion to revise it: _____

Q.10: 1 2 3 4

If the answer is 2 or 3 kindly provide a suggestion to revise it: _____

Q.11: 1 2 3 4

If the answer is 2 or 3 kindly provide a suggestion to revise it: _____

Q.12: 1 2 3 4

If the answer is 2 or 3 kindly provide a suggestion to revise it: _____

Section III- B. The following questions represent pharmacists and their role in treating ASD.

Q.13: 1 2 3 4

If the answer is 2 or 3 kindly provide a suggestion to revise it: _____

Q.14: 1 2 3 4

If the answer is 2 or 3 kindly provide a suggestion to revise it: _____

Q.15: 1 2 3 4

If the answer is 2 or 3 kindly provide a suggestion to revise it: _____

Q.16: 1 2 3 4

If the answer is 2 or 3 kindly provide a suggestion to revise it: _____

Q.17: 1 2 3 4

If the answer is 2 or 3 kindly provide a suggestion to revise it: _____

Q.18: 1 2 3 4

If the answer is 2 or 3 kindly provide a suggestion to revise it: _____

Q.19: 1 2 3 4

If the answer is 2 or 3 kindly provide a suggestion to revise it: _____

Q.20: 1 2 3 4

If the answer is 2 or 3 kindly provide a suggestion to revise it: _____

Q.21: 1 2 3 4

If the answer is 2 or 3 kindly provide a suggestion to revise it: _____

Section IV- C: The following questions will represent the ASD drugs and its accessibility

Q.22: 1 2 3 4

If the answer is 2 or 3 kindly provide a suggestion to revise it: _____

Q.23: 1 2 3 4

If the answer is 2 or 3 kindly provide a suggestion to revise it: _____

Q.24: 1 2 3 4

If the answer is 2 or 3 kindly provide a suggestion to revise it:

Section v: Questions based on the CARS score

Q25: 1 2 3 4

If the answer is 2 or 3 kindly provide a suggestion to revise it:

Q26: 1 2 3 4

If the answer is 2 or 3 kindly provide a suggestion to revise it:

Appendix 4

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: **63/2017**

Wednesday 6th December 2017

Ms. Shaista Sadaf
52, Christopher
~~Triq Sant' Aristarku~~
San Pawl il-Bahar, Bugibba

Dear Ms. Shaista Sadaf,

Please refer to your application submitted to the Research Ethics Committee in connection with your research entitled:

Accessibility and safety of anti-psychotics in the treatment of autism spectrum disorder in children and adolescents

The University Research Ethics Committee granted ethical approval for the above mentioned protocol.

Yours sincerely,

Dr. Mario Vassallo
Chairman
Research Ethics Committee

Appendix 5

PRR reports- Risperidone and Aripiprazole

PRR report- Risperidone

Reaction PT	PRR (-)	PRR	PRR (+)	CHI^2	# Cases
Abnormal weight gain	441.61	628.20	893.62	19,270.5800	442
Accidental exposure to product	1.23	2.10	3.59	7.7607	16
Accidental overdose	1.61	2.24	3.13	23.7989	36
Adverse drug reaction	1.76	3.62	7.42	14.0667	8
Aggression	2.62	3.08	3.62	204.0392	155
Agitation	1.97	2.41	2.95	76.8660	99
Akathisia	11.04	15.16	20.83	500.6551	52
Amenorrhoea	3.26	4.92	7.42	70.7171	26
Anal incontinence	3.83	6.34	10.51	67.4534	17
Anticholinergic syndrome	1.41	3.92	10.86	8.0240	4
Arachnoid cyst	2.90	10.07	35.04	20.1925	3
Atrial tachycardia	1.84	6.13	20.41	11.3986	3
Atrioventricular block first degree	1.14	3.13	8.62	5.4504	4
Bilirubin conjugated increased	3.20	6.72	14.08	34.0612	8
Bipolar disorder	3.11	5.30	9.03	47.0823	15
Blood alkaline phosphatase increased	5.26	6.97	9.24	245.3878	55
Blood cholesterol increased	4.34	6.72	10.38	97.9834	23
Blood creatine phosphokinase increased	3.50	4.54	5.88	156.5885	62
Blood creatinine decreased	13.70	24.18	42.65	264.1573	18
Blood glucose abnormal	0.97	3.13	10.08	4.0874	3
Blood lactate dehydrogenase increased	1.21	2.00	3.30	7.6922	16
Blood prolactin increased	102.93	141.98	195.85	5,158.3350	148
Blood triglycerides increased	2.79	4.41	6.97	48.3314	20
Blunted affect	6.45	18.08	50.69	58.2718	5
Body mass index increased	2.00	6.72	22.51	12.7705	3
Breast cyst	5.21	20.15	77.88	38.2135	3
Breast discharge	22.64	51.28	116.15	282.9776	12
Breast discomfort	6.74	28.20	117.98	49.2026	3
Breast disorder	13.61	47.01	162.32	112.5792	5
Breast enlargement	16.77	27.16	43.98	415.3640	26
Breast mass	2.86	7.35	18.84	23.7067	5
Breast pain	11.01	20.15	36.86	191.1047	15
Breast tenderness	7.75	20.15	52.40	76.4307	6
Bundle branch block	3.09	10.85	38.05	21.7935	3
Bundle branch block left	3.88	14.10	51.22	28.0942	3
Bundle branch block right	3.96	6.93	12.13	61.9191	14
Catatonia	7.92	12.82	20.75	179.9100	21
Cerebral atrophy	1.25	3.09	7.64	6.6456	5
Chorea	2.10	4.57	9.92	17.8003	7
Choreoathetosis	3.66	6.89	12.97	48.3651	11
Cogwheel rigidity	4.22	11.19	29.67	37.4889	5
Compulsions	4.41	11.75	31.30	39.3534	5
Conduct disorder	1.04	3.36	10.83	4.6366	3
Decreased activity	1.17	2.66	6.05	5.8900	6
Delayed puberty	6.84	13.83	27.97	91.9609	10
Delusion	1.30	2.45	4.62	8.1517	10
Dependence	2.43	8.30	28.30	16.3627	3

Depression	1.65	2.01	2.46	48.4415	99
Diabetes mellitus	3.88	5.15	6.82	160.0571	53
Diet refusal	4.22	11.19	29.67	37.4889	5
Disease recurrence	1.08	2.19	4.44	4.9258	9
Disturbance in social behaviour	2.18	4.32	8.54	21.0200	9
Drooling	4.59	7.11	11.02	105.0430	23
Drug effect decreased	1.35	2.54	4.80	8.8745	11
Drug effect incomplete	2.38	4.11	7.10	30.3602	14
Drug ineffective for unapproved indication	2.57	4.10	6.54	40.9627	19
Drug interaction	3.22	3.89	4.71	224.0793	112
Drug prescribing error	1.71	3.15	5.80	15.1681	12
Dry mouth	1.64	2.77	4.65	15.9845	15
Dyskinesia	3.76	4.50	5.39	314.9809	127
Dyslipidaemia	7.28	17.32	41.18	78.6670	7
Dysphemia	3.50	7.05	14.20	40.6550	9
Dystonia	7.60	9.00	10.67	923.9091	171
Echolalia	3.88	14.10	51.22	28.0942	3
Electrocardiogram QT prolonged	2.50	3.40	4.62	68.0478	45
Electrocardiogram abnormal	1.26	2.70	5.77	7.0744	7
Emotional disorder	28.68	34.05	40.42	4,065.6167	218
Emotional distress	23.39	27.51	32.37	3,604.7227	223
Encopresis	2.20	7.42	25.07	14.3994	3
Endocrine disorder	5.45	17.09	53.66	44.4503	4
Energy increased	3.37	9.90	29.08	26.4295	4
Enuresis	5.08	7.46	10.95	145.0284	30
Erection increased	3.78	8.44	18.85	38.9165	7
Excessive eye blinking	1.20	3.30	9.09	5.9894	4
Extrapyramidal disorder	13.08	15.27	17.83	2,072.1884	210
Galactorrhoea	121.41	159.83	210.40	7,938.6621	222
Glossodynia	1.59	5.22	17.21	9.2207	3
Glucose tolerance impaired	8.90	15.37	26.55	172.1579	17
Grimacing	1.44	4.70	15.40	7.9473	3
Gynaecomastia	468.38	563.31	677.47	62,119.6203	1,427
Hallucination, auditory	2.01	2.89	4.15	36.2265	32
Hallucinations, mixed	1.47	3.16	6.80	9.7124	7
Hepatic steatosis	1.22	2.61	5.59	6.5992	7
Homicidal ideation	2.87	4.79	8.01	43.5886	16
Homicide	1.24	4.03	13.10	6.2941	3
Hyperammonaemia	3.74	5.65	8.55	85.5070	25
Hypercholesterolaemia	1.44	3.56	8.84	8.5645	5
Hyperglycaemia	2.61	3.40	4.45	90.6429	58
Hyperinsulinaemia	3.09	10.85	38.05	21.7935	3
Hyperlipidaemia	0.99	2.73	7.46	4.1304	4
Hyperphagia	9.58	16.65	28.92	184.7107	17
Hyperprolactinaemia	278.36	369.86	491.43	17,337.7940	418
Hyperreflexia	1.42	3.05	6.54	9.0445	7
Immobile	1.84	6.13	20.41	11.3986	3
Impulse-control disorder	1.39	4.55	14.87	7.5753	3
Impulsive behaviour	1.40	2.75	5.38	9.4564	9
Incontinence	1.53	3.29	7.08	10.4366	7
Incorrect dose administered	1.85	2.62	3.72	31.5322	33
Increased appetite	20.82	26.59	33.96	1,559.4906	99
Initial insomnia	1.11	2.52	5.72	5.2161	6

Insulin resistance	4.04	9.73	23.41	38.9262	6
Intentional self-injury	2.61	3.49	4.67	79.5504	49
Left ventricular hypertrophy	1.05	2.89	7.94	4.6684	4
Leukopenia	1.71	2.26	3.00	33.8571	50
Mania	3.70	5.21	7.34	110.3595	36
Mastitis	3.72	11.06	32.86	29.6354	4
Mental disorder	1.45	2.36	3.83	12.6739	17
Mental impairment	1.23	2.26	4.13	7.3651	11
Metabolic disorder	1.04	3.36	10.83	4.6366	3
Metabolic syndrome	8.25	21.70	57.05	81.0544	6
Miosis	2.52	4.36	7.53	33.1822	15
Mononucleosis syndrome	3.72	11.06	32.86	29.6354	4
Motor dysfunction	1.30	2.53	4.95	7.9326	9
Movement disorder	2.20	3.32	5.01	36.3720	24
Muscle rigidity	2.68	3.86	5.55	60.7042	31
Mutism	1.64	4.59	12.80	10.2220	4
Negativism	2.12	5.34	13.46	15.8485	5
Neuroleptic malignant syndrome	16.20	20.17	25.12	1,430.6372	112
Nipple disorder	7.87	26.86	91.73	63.3828	4
Obesity	211.74	260.60	320.73	22,640.0704	571
Obsessive thoughts	1.60	3.98	9.92	10.3041	5
Oculogyric crisis	7.53	10.24	13.92	335.8274	53
Off label use	9.12	9.93	10.80	3,900.5680	581
Oromandibular dystonia	6.91	14.59	30.80	86.9518	10
Orthostatic hypotension	1.14	2.32	4.72	5.7389	8
Overweight	48.18	78.97	129.45	1,206.8987	42
Parkinsonism	8.89	14.89	24.92	186.9904	19
Persecutory delusion	6.96	16.45	38.89	75.2659	7
Pituitary tumour	2.53	7.23	20.71	18.6198	4
Pituitary tumour benign	6.14	12.82	26.78	77.0832	9
Polydipsia	2.18	4.04	7.47	23.1850	11
Precocious puberty	5.41	9.08	15.25	102.5107	17
Priapism	9.88	14.26	20.57	350.2269	37
Product use in unapproved indication	23.60	26.00	28.65	9,017.7796	580
Protrusion tongue	16.29	28.81	50.96	316.3253	20
Pseudogynaecomastia	99.90	99.90	99.90	188.0365	4
Psychomotor hyperactivity	1.94	2.72	3.80	37.0285	36
Psychotic disorder	2.03	2.77	3.78	45.1245	43
Rabbit syndrome	11.76	47.01	187.90	90.0625	4
Salivary hypersecretion	4.64	6.61	9.40	146.2379	35
Schizophrenia	7.31	12.26	20.58	147.7402	18
Secondary hypogonadism	6.74	28.20	117.98	49.2026	3
Sedation	10.49	13.34	16.97	748.2979	84
Serum ferritin decreased	2.43	8.30	28.30	16.3627	3
Sinus arrest	6.90	19.59	55.57	62.2562	5
Sinus arrhythmia	1.20	3.30	9.09	5.9894	4
Sinus bradycardia	2.07	3.95	7.53	20.3389	10
Sinus tachycardia	2.28	3.55	5.53	35.8338	21
Sluggishness	5.29	10.14	19.44	74.5600	11
Sopor	2.45	4.86	9.65	25.0396	9
Spontaneous penile erection	3.32	11.75	41.63	23.6109	3
Stereotypy	3.78	8.44	18.85	38.9165	7
Suicidal ideation	1.83	2.24	2.73	65.4488	100

Suspiciousness	5.21	20.15	77.88	38.2135	3
Tardive dyskinesia	60.62	75.07	92.97	6,032.7128	214
Therapy cessation	2.21	6.27	17.78	15.6284	4
Therapy non-responder	2.48	3.87	6.03	41.3742	21
Tic	3.52	4.56	5.91	157.6718	63
Tongue disorder	1.41	3.51	8.70	8.3460	5
Tongue movement disturbance	1.31	4.27	13.93	6.8968	3
Tongue spasm	4.68	17.63	66.42	34.2232	3
Torticollis	3.01	4.96	8.17	48.7097	19
Tourette's disorder	1.81	3.56	7.00	15.3761	9
Treatment noncompliance	7.98	11.21	15.73	308.0486	41
Type 1 diabetes mellitus	3.43	4.76	6.61	105.4604	39
Type 2 diabetes mellitus	12.17	18.56	28.28	357.4515	30
Unevaluable event	1.30	2.45	4.62	8.1517	10
Urinary incontinence	2.89	4.06	5.70	76.5440	36
Weight increased	16.13	17.89	19.85	5,275.7226	464
Wrong technique in product usage process	1.64	2.57	4.02	18.2025	24
Abasia	0.16	0.44	1.17	2.8930	4
Abdominal discomfort	0.19	0.46	1.12	3.0807	5
Abdominal distension	0.27	0.65	1.57	0.9238	5
Abdominal pain	0.15	0.22	0.33	70.6901	25
Abdominal pain lower	0.03	0.22	1.57	2.7621	1
Abdominal pain upper	0.16	0.28	0.49	22.6912	12
Abdominal rigidity	0.21	1.52	11.11	0.1704	1
Abdominal tenderness	0.05	0.36	2.61	1.1008	1
Abnormal behaviour	1.17	1.48	1.86	10.8921	73
Abnormal dreams	0.06	0.44	3.12	0.7264	1
Abulia	0.39	2.94	22.15	1.2033	1
Acanthosis nigricans	1.75	7.83	35.00	10.2218	2
Accidental exposure to product by child	0.26	0.69	1.85	0.5552	5
Accidental poisoning	0.33	2.47	18.48	0.8345	1
Accommodation disorder	0.45	1.84	7.57	0.7429	2
Acidosis	0.33	1.03	3.23	0.0025	3
Acne	0.59	1.14	2.21	0.1521	9
Acne cystic	0.74	5.88	46.97	3.5968	1
Activation syndrome	0.41	3.13	23.72	1.3623	1
Acute kidney injury	0.16	0.30	0.59	14.3143	10
Acute lymphocytic leukaemia	0.04	0.27	1.94	1.9424	1
Adjustment disorder	0.23	1.68	12.34	0.2651	1
Adverse event	0.41	0.99	2.39	0.0008	6
Adverse reaction	0.14	1.02	7.41	0.0005	1
Affect lability	0.41	0.99	2.40	0.0003	5
Affective disorder	0.73	1.79	4.38	1.6943	5
Agranulocytosis	0.40	0.84	1.78	0.2055	7
Akinesia	1.01	4.27	18.17	4.5976	2
Alanine aminotransferase abnormal	0.35	2.61	19.56	0.9422	1
Alanine aminotransferase increased	0.23	0.41	0.74	9.2419	11
Alcohol poisoning	0.47	3.62	27.64	1.7575	1
Alcoholism	2.13	23.50	259.17	14.3646	1
Alopecia	0.15	0.33	0.73	8.3544	6
Altered state of consciousness	0.32	0.62	1.19	2.0970	9
Amaurosis	0.44	3.36	25.53	1.5453	1
Amimia	2.79	13.43	64.64	17.8980	2

Amino acid level decreased	1.63	15.67	150.61	10.3001	1
Amino acid level increased	0.24	1.74	12.81	0.3042	1
Ammonia increased	0.07	0.50	3.59	0.4947	1
Amnesia	0.50	0.93	1.74	0.0533	10
Amylase increased	0.34	0.83	2.02	0.1637	5
Anaemia	0.10	0.24	0.59	11.7211	6
Anal injury	99.90	99.90	99.90	47.0084	1
Anaphylactic reaction	0.01	0.03	0.11	68.9920	2
Anaphylactic shock	0.04	0.11	0.35	20.7321	3
Anger	1.13	1.77	2.76	6.4810	20
Angina pectoris	0.22	0.87	3.52	0.0378	2
Angioedema	0.18	0.30	0.51	23.8953	15
Anhidrosis	0.23	1.68	12.34	0.2651	1
Ankle fracture	0.28	2.04	15.13	0.5110	2
Antiandrogen therapy	99.90	99.90	99.90	47.0084	1
Anticonvulsant drug level decreased	0.14	0.98	7.09	0.0004	1
Anticonvulsant drug level increased	0.10	0.75	5.38	0.0850	1
Antipsychotic drug level below therapeutic	1.63	15.67	150.61	10.3001	1
Antisocial behaviour	0.17	1.24	9.01	0.0443	1
Anuria	0.04	0.30	2.12	1.6495	1
Anxiety	0.79	1.03	1.35	0.0510	54
Anxiety disorder	0.30	1.24	5.04	0.0886	2
Apathy	0.84	1.53	2.79	1.9583	11
Aphasia	0.38	0.80	1.69	0.3349	7
Apnoea	0.07	0.26	1.05	4.1648	2
Apparent life threatening event	1.31	11.75	105.13	7.8699	1
Appendicectomy	0.17	1.21	8.77	0.0341	1
Appendicitis	0.04	0.28	2.03	1.7856	1
Application site erythema	0.01	0.09	0.67	8.7556	1
Areflexia	0.05	0.33	2.38	1.3244	1
Arnold-Chiari malformation	0.09	0.62	4.45	0.2323	1
Arrhythmia	0.77	1.34	2.32	1.0937	13
Arteriovenous malformation	0.66	5.22	41.22	3.0733	1
Arthralgia	0.04	0.10	0.22	50.2879	6
Arthritis	0.06	0.23	0.93	5.0851	2
Arthritis infective	0.41	3.13	23.72	1.3623	1
Arthrodesis	2.94	47.01	751.46	22.5150	1
Arthropathy	0.04	0.30	2.17	1.5915	1
Asocial behaviour	0.44	3.36	25.53	1.5453	1
Aspartate aminotransferase abnormal	0.83	6.72	54.57	4.2565	2
Aspartate aminotransferase increased	0.28	0.50	0.87	6.1431	13
Asphyxia	0.07	0.53	3.79	0.4170	1
Asthenia	0.21	0.33	0.50	29.4787	24
Asthma	0.00	0.03	0.20	33.4209	1
Asthmatic crisis	0.04	0.28	2.00	1.8442	1
Astigmatism	0.19	1.38	10.10	0.1029	1
Astrocytoma	0.18	1.31	9.52	0.0697	1
Ataxia	0.87	1.41	2.28	1.9483	17
Atrioventricular block	0.09	0.67	4.83	0.1584	1
Atrophy	0.30	2.24	16.64	0.6541	1
Attention deficit/hyperactivity disorder	1.05	1.76	2.95	4.7820	16
Auditory disorder	0.12	0.85	6.17	0.0243	1
Autism spectrum disorder	0.50	0.93	1.73	0.0592	10

Autoimmune thyroiditis	0.08	0.55	3.97	0.3572	1
Automatism	0.51	3.92	30.12	2.0056	1
Autonomic nervous system imbalance	0.04	0.28	2.03	1.7856	1
Back disorder	0.66	5.22	41.22	3.0733	1
Back pain	0.11	0.24	0.53	14.8097	6
Balance disorder	0.31	0.70	1.57	0.7517	6
Benign breast neoplasm	5.24	31.34	187.51	35.2457	2
Bilirubin conjugated	2.13	23.50	259.17	14.3646	1
Bipolar I disorder	0.96	4.09	17.33	4.2920	2
Bite	0.47	3.62	27.64	1.7575	1
Bladder spasm	0.94	7.83	65.07	5.1107	1
Blepharophimosis congenital	99.90	99.90	99.90	47.0084	1
Blepharospasm	0.10	0.73	5.29	0.0945	1
Blindness	0.06	0.24	0.97	4.7032	2
Blister	0.02	0.07	0.26	26.9159	2
Blood aldosterone increased	1.31	11.75	105.13	7.8699	1
Blood alkaline phosphatase decreased	0.66	5.22	41.22	3.0733	1
Blood bilirubin increased	0.15	0.41	1.11	3.3106	5
Blood bilirubin unconjugated increased	0.30	2.24	16.64	0.6541	1
Blood calcium decreased	0.10	0.73	5.29	0.0945	1
Blood calcium increased	0.89	3.76	15.87	3.7534	2
Blood cholinesterase	99.90	99.90	99.90	47.0084	1
Blood cholinesterase decreased	0.94	7.83	65.07	5.1107	1
Blood creatine increased	0.22	1.62	11.90	0.2300	1
Blood creatine phosphokinase MB	1.10	9.40	80.46	6.2569	1
Blood creatinine	2.94	47.01	751.46	22.5150	1
Blood creatinine increased	0.15	0.33	0.73	8.2210	6
Blood glucose increased	0.27	0.52	1.00	3.9661	9
Blood growth hormone decreased	0.35	2.61	19.56	0.9422	1
Blood insulin decreased	1.63	15.67	150.61	10.3001	1
Blood insulin increased	1.05	4.48	19.09	4.9316	2
Blood iron decreased	0.21	1.52	11.11	0.1704	1
Blood lactate dehydrogenase abnormal	0.00	0.00	0.00	0.0638	1
Blood lactic acid increased	0.12	0.87	6.29	0.0189	1
Blood parathyroid hormone increased	0.35	2.61	19.56	0.9422	1
Blood phosphorus	2.94	47.01	751.46	22.5150	1
Blood phosphorus increased	1.01	4.27	18.17	4.5976	2
Blood pressure abnormal	0.14	1.02	7.41	0.0005	1
Blood pressure decreased	0.15	0.32	0.67	10.1877	7
Blood pressure inadequately controlled	0.83	6.72	54.57	4.2565	1
Blood pressure increased	0.12	0.33	0.88	5.4793	4
Blood prolactin	99.90	99.90	99.90	47.0084	1
Blood prolactin abnormal	5.24	31.34	187.51	35.2457	2
Blood sodium increased	0.93	3.92	16.57	4.0115	2
Blood test abnormal	0.20	1.47	10.75	0.1452	1
Blood testosterone decreased	0.83	6.72	54.57	4.2565	1
Blood thyroid stimulating hormone increased	0.33	1.34	5.48	0.1705	2
Blood urea increased	0.02	0.14	1.02	5.1344	1
Blood urine present	0.45	1.41	4.45	0.3478	3
Blount's disease	2.13	23.50	259.17	14.3646	1
Body temperature decreased	0.72	1.96	5.32	1.8027	4
Body temperature increased	0.08	0.20	0.54	12.6166	4
Bone density decreased	0.52	2.14	8.81	1.1572	2

Bone disorder	0.08	0.55	3.97	0.3572	1
Bone marrow failure	0.04	0.14	0.56	10.4948	2
Bone pain	0.03	0.21	1.53	2.8634	1
Bradycardia	0.77	1.17	1.77	0.5500	23
Bradykinesia	0.86	3.62	15.23	3.5152	2
Bradyphrenia	0.35	1.45	5.91	0.2674	2
Brain injury	0.05	0.37	2.67	1.0458	1
Brain neoplasm	0.07	0.48	3.44	0.5590	1
Brain oedema	0.53	1.07	2.16	0.0373	8
Brain stem auditory evoked response abnormal	0.60	4.70	36.71	2.6488	1
Breast cancer	0.60	4.70	36.71	2.6488	1
Breast disorder male	2.13	23.50	259.17	14.3646	1
Breast engorgement	2.94	47.01	751.46	22.5150	1
Breast fibrosis	99.90	99.90	99.90	47.0084	1
Breast haematoma	99.90	99.90	99.90	47.0084	1
Breast hyperplasia	1.63	15.67	150.61	10.3001	2
Breast swelling	0.39	2.94	22.15	1.2033	1
Bronchitis	0.42	0.95	2.12	0.0178	7
Bruxism	0.28	1.13	4.60	0.0304	2
Bulimia nervosa	0.24	1.74	12.81	0.3042	1
Buried penis syndrome	2.94	47.01	751.46	22.5150	1
C-reactive protein abnormal	1.31	11.75	105.13	7.8699	1
C-reactive protein increased	0.04	0.17	0.67	8.2418	2
CSF pressure increased	0.18	1.31	9.52	0.0697	1
CSF test abnormal	0.23	1.68	12.34	0.2651	1
Cachexia	0.15	1.07	7.75	0.0043	1
Campylobacter gastroenteritis	0.83	6.72	54.57	4.2565	1
Candida infection	0.06	0.42	2.98	0.8131	1
Cardiac aneurysm	0.47	3.62	27.64	1.7575	1
Cardiac arrest	0.23	0.45	0.91	5.2692	9
Cardiac assistance device user	2.94	47.01	751.46	22.5150	1
Cardiac disorder	0.18	0.57	1.78	0.9568	3
Cardiac failure	0.02	0.12	0.86	6.3918	1
Cardiac failure congestive	0.04	0.26	1.86	2.0806	1
Cardiac flutter	0.83	6.72	54.57	4.2565	1
Cardiac murmur	0.17	0.42	1.00	4.0570	5
Cardio-respiratory arrest	0.49	0.98	1.97	0.0043	8
Cardiomyopathy	0.15	0.60	2.40	0.5447	2
Cardiopulmonary failure	0.12	0.89	6.41	0.0141	1
Cardiovascular disorder	0.04	0.29	2.10	1.6882	1
Cataract	0.28	0.89	2.80	0.0381	3
Cataract subcapsular	0.33	2.47	18.48	0.8345	1
Cellulitis	0.03	0.13	0.53	11.2921	2
Central nervous system lesion	0.06	0.42	3.03	0.7782	1
Cerebral artery embolism	0.83	6.72	54.57	4.2565	1
Cerebral disorder	0.31	1.27	5.17	0.1122	2
Cerebral dysgenesis	2.13	23.50	259.17	14.3646	1
Cerebral infarction	0.48	1.30	3.50	0.2646	4
Cerebral ischaemia	0.13	0.92	6.67	0.0065	1
Cerebral venous thrombosis	0.07	0.49	3.55	0.5106	1
Cerebrovascular accident	0.15	0.48	1.51	1.6460	3
Chest discomfort	0.01	0.05	0.36	17.8109	1
Chest pain	0.25	0.42	0.70	11.9391	15

Chills	0.05	0.13	0.31	29.4390	5
Choking	0.05	0.36	2.59	1.1192	1
Choking sensation	0.11	0.82	5.95	0.0366	1
Cholecystectomy	0.08	0.55	3.92	0.3719	1
Cholelithiasis	0.01	0.09	0.67	8.7556	1
Cholestasis	0.12	0.48	1.93	1.1185	2
Cinchonism	99.90	99.90	99.90	47.0084	1
Circulatory collapse	0.04	0.16	0.65	8.5949	2
Clonus	0.03	0.23	1.64	2.5601	1
Coagulation factor VII level decreased	0.55	4.27	33.09	2.2987	1
Coeliac disease	0.07	0.48	3.47	0.5428	1
Cognitive disorder	0.65	1.15	2.04	0.2265	12
Colitis	0.12	0.47	1.88	1.2006	2
Coma	0.27	0.49	0.92	5.1599	10
Communication disorder	0.07	0.48	3.44	0.5590	1
Completed suicide	0.99	1.51	2.31	3.7342	22
Concomitant disease aggravated	0.18	1.31	9.52	0.0697	1
Condition aggravated	1.44	1.87	2.42	23.1488	61
Conduction disorder	0.73	3.03	12.67	2.5603	2
Conductive deafness	0.23	1.68	12.34	0.2651	1
Confusional state	0.60	0.88	1.29	0.4402	27
Congenital hand malformation	0.37	2.77	20.77	1.0643	1
Congestive cardiomyopathy	0.09	0.68	4.90	0.1470	1
Conjunctival hyperaemia	0.03	0.21	1.52	2.8837	1
Conjunctivitis	0.08	0.25	0.77	6.7710	3
Constipation	0.79	1.23	1.92	0.8668	20
Contraindication to medical treatment	0.55	4.27	33.09	2.2987	1
Contusion	0.05	0.21	0.84	5.9162	2
Conversion disorder	0.17	0.69	2.77	0.2830	2
Coordination abnormal	1.00	2.02	4.10	3.9650	8
Coronary artery stenosis	0.44	3.36	25.53	1.5453	1
Cortisol increased	0.66	5.22	41.22	3.0733	1
Cough	0.03	0.08	0.19	55.0345	6
Crohn's disease	0.02	0.14	1.00	5.2806	1
Crying	0.30	0.54	0.95	4.7389	12
Cryptorchism	0.15	1.12	8.13	0.0124	1
Cyanosis	0.06	0.16	0.43	17.3641	4
Dacryostenosis congenital	0.83	6.72	54.57	4.2565	1
Deafness	0.02	0.14	1.03	5.0717	1
Deafness neurosensory	0.07	0.49	3.51	0.5266	1
Death	0.26	0.45	0.77	8.8505	13
Decerebrate posture	1.31	11.75	105.13	7.8699	1
Decreased appetite	0.31	0.47	0.69	15.3066	28
Decreased interest	0.12	0.85	6.17	0.0243	1
Decubitus ulcer	0.25	1.81	13.32	0.3478	1
Deep vein thrombosis	0.01	0.09	0.66	8.8403	1
Defaecation urgency	0.28	2.04	15.13	0.5110	1
Defect conduction intraventricular	2.79	13.43	64.64	17.8980	2
Deformity	0.09	0.66	4.76	0.1701	1
Dehydration	0.28	0.55	1.06	3.3141	9
Delirium	0.82	1.37	2.29	1.4727	16
Delusional disorder, unspecified type	0.94	7.83	65.07	5.1107	1
Dementia	0.32	2.35	17.51	0.7390	1

Dengue fever	0.14	0.98	7.09	0.0004	1
Depressed level of consciousness	0.64	0.96	1.45	0.0358	23
Depressed mood	0.21	0.47	1.06	3.4933	6
Depressive symptom	0.08	0.55	3.92	0.3719	1
Derealisation	0.19	1.42	10.41	0.1228	1
Dermatitis acneiform	0.25	1.81	13.32	0.3478	1
Dermatitis atopic	0.16	0.63	2.55	0.4262	2
Dermatitis exfoliative	0.13	0.52	2.09	0.8803	2
Dermatitis exfoliative generalised	1.63	15.67	150.61	10.3001	1
Developmental coordination disorder	0.94	7.83	65.07	5.1107	1
Developmental delay	0.07	0.29	1.16	3.4959	2
Device leakage	0.21	1.57	11.49	0.1985	1
Device malfunction	0.08	0.58	4.17	0.2999	1
Diabetes insipidus	0.08	0.60	4.28	0.2723	1
Diabetic coma	0.77	3.24	13.58	2.9012	2
Diabetic hyperglycaemic coma	0.47	3.62	27.64	1.7575	1
Diabetic hyperosmolar coma	1.31	11.75	105.13	7.8699	1
Diabetic ketoacidosis	0.81	1.38	2.35	1.4246	14
Diabetic ketoacidotic hyperglycaemic coma	5.24	31.34	187.51	35.2457	2
Diabetic neuropathy	2.13	23.50	259.17	14.3646	1
Diarrhoea	0.15	0.24	0.39	40.9350	17
Diplopia	0.05	0.18	0.73	7.3108	2
Discomfort	0.07	0.28	1.14	3.5936	2
Disease progression	0.02	0.11	0.77	7.4027	1
Disease risk factor	99.90	99.90	99.90	47.0084	1
Disinhibition	0.34	1.40	5.73	0.2251	2
Disorganised speech	2.06	9.40	42.90	12.5141	2
Disorientation	0.52	0.92	1.63	0.0816	12
Disseminated intravascular coagulation	0.02	0.16	1.12	4.5094	1
Dissociation	0.14	1.04	7.58	0.0019	1
Dissociative amnesia	1.31	11.75	105.13	7.8699	1
Dissociative disorder	0.48	1.96	8.06	0.9011	2
Distractibility	0.66	2.77	11.51	2.1288	2
Disturbance in attention	0.45	0.72	1.15	1.8890	19
Dizziness	0.18	0.25	0.34	91.1523	39
Dizziness postural	0.15	0.60	2.43	0.5177	2
Dreamy state	0.60	4.70	36.71	2.6488	1
Drowning	0.28	2.04	15.13	0.5110	1
Drug abuser	0.20	1.47	10.75	0.1452	1
Drug administered to patient of inappropriate age	0.45	0.79	1.39	0.6847	13
Drug administration error	0.62	1.12	2.04	0.1421	11
Drug dispensing error	0.31	0.97	3.03	0.0035	3
Drug dose omission	0.66	1.23	2.31	0.4326	10
Drug effect increased	1.05	4.48	19.09	4.9316	2
Drug eruption	0.17	0.44	1.18	2.7903	4
Drug hypersensitivity	0.01	0.08	0.55	10.9622	1
Drug ineffective	1.61	1.85	2.11	80.6584	213
Drug intolerance	0.00	0.00	0.00	3.2359	1
Drug level above therapeutic	0.12	0.85	6.17	0.0243	1
Drug level below therapeutic	0.12	0.84	6.06	0.0302	1
Drug level decreased	0.29	0.90	2.81	0.0340	4
Drug level fluctuating	0.25	1.81	13.32	0.3478	1
Drug level increased	0.26	0.58	1.29	1.8309	6

Drug reaction with eosinophilia and systemic symptoms	0.22	0.46	0.98	4.3206	7
Drug resistance	0.35	0.94	2.54	0.0126	4
Drug screen positive	0.19	1.38	10.10	0.1029	1
Drug use disorder	0.44	0.77	1.33	0.9025	13
Drug withdrawal convulsions	0.17	1.27	9.26	0.0561	1
Drug withdrawal syndrome	0.31	0.69	1.55	0.8168	6
Drug-induced liver injury	0.28	0.76	2.03	0.3129	4
Dry eye	0.06	0.40	2.88	0.8837	1
Dry skin	0.63	1.33	2.82	0.5646	7
Dysarthria	1.15	1.76	2.70	7.0489	22
Dysgeusia	0.04	0.27	1.94	1.9424	1
Dysgraphia	0.34	1.38	5.64	0.2058	2
Dyskinesia oesophageal	2.94	47.01	751.46	22.5150	1
Dyslexia	0.19	1.42	10.41	0.1228	1
Dysmenorrhoea	0.04	0.27	1.96	1.9030	1
Dysmorphism	0.07	0.53	3.79	0.4170	1
Dyspepsia	0.10	0.40	1.62	1.7684	2
Dysphagia	0.68	1.06	1.66	0.0773	20
Dysphonia	0.02	0.16	1.16	4.2810	1
Dysphoria	0.68	2.17	6.90	1.8087	3
Dyspnoea	0.15	0.22	0.32	75.6751	27
Dyssomnia	2.06	9.40	42.90	12.5141	2
Dysstasia	0.11	0.43	1.71	1.5399	2
Dysuria	1.07	1.91	3.39	4.9718	12
ECG P wave inverted	2.94	47.01	751.46	22.5150	1
Ear disorder	0.16	1.15	8.33	0.0183	1
Ear infection	0.09	0.36	1.43	2.3138	3
Ear pain	0.03	0.19	1.38	3.3530	1
Eating disorder	0.86	1.83	3.89	2.5298	7
Echocardiogram abnormal	0.47	3.62	27.64	1.7575	1
Echopraxia	2.94	47.01	751.46	22.5150	1
Eczema	0.02	0.14	0.98	5.3642	1
Electrocardiogram PR prolongation	1.89	8.55	38.55	11.2782	2
Electrocardiogram ST segment elevation	0.21	1.52	11.11	0.1704	1
Electrocardiogram change	0.93	3.92	16.57	4.0115	2
Electrocardiogram repolarisation abnormality	2.50	11.75	55.33	15.7402	2
Electroencephalogram abnormal	0.74	1.43	2.77	1.1279	9
Electrolyte imbalance	0.26	1.06	4.29	0.0059	2
Emergency care	0.74	5.88	46.97	3.5968	1
Emotional poverty	0.39	2.94	22.15	1.2033	1
Empty sella syndrome	99.90	99.90	99.90	47.0084	1
Encephalitis	0.38	0.85	1.91	0.1515	6
Encephalitis autoimmune	0.25	1.81	13.32	0.3478	1
Encephalopathy	0.01	0.05	0.38	16.5703	1
Enterocolitis	0.09	0.67	4.83	0.1584	1
Enzyme level increased	2.94	47.01	751.46	22.5150	1
Eosinophil count increased	0.40	1.25	3.93	0.1441	3
Eosinophilia	0.06	0.22	0.89	5.4083	2
Epilepsy	0.51	0.77	1.17	1.5131	23
Epiphysiolysis	0.05	0.33	2.37	1.3433	1
Epistaxis	1.00	1.44	2.08	3.7943	29
Erectile dysfunction	0.93	3.92	16.57	4.0115	2

Erythema	0.04	0.07	0.15	83.2759	7
Erythema multiforme	0.07	0.21	0.65	8.9147	3
Euphoric mood	0.50	1.35	3.65	0.3579	4
Exposure during pregnancy	0.03	0.11	0.45	14.1811	2
Extensor plantar response	0.45	1.84	7.57	0.7429	2
Extra dose administered	0.03	0.25	1.77	2.2594	1
Eye discharge	0.12	0.85	6.17	0.0243	1
Eye disorder	0.37	0.99	2.66	0.0004	4
Eye haemorrhage	0.24	1.74	12.81	0.3042	1
Eye movement disorder	0.39	0.76	1.47	0.6760	10
Eye pain	0.11	0.35	1.08	3.6405	3
Eye pruritus	0.04	0.28	2.00	1.8442	1
Eye swelling	0.11	0.29	0.79	6.7300	4
Eyelid function disorder	0.86	3.62	15.23	3.5152	2
Eyelid oedema	0.09	0.23	0.61	10.2916	4
Eyelid ptosis	0.18	0.72	2.92	0.2088	2
Face oedema	0.12	0.28	0.62	11.2886	7
Facial paralysis	0.28	0.62	1.39	1.3704	6
Facial spasm	0.20	1.47	10.75	0.1452	1
Faecaloma	0.18	1.31	9.52	0.0697	1
Fall	0.16	0.30	0.56	16.5327	10
Fatigue	0.39	0.51	0.66	27.6629	59
Fear	0.37	0.83	1.86	0.2003	6
Fear of death	0.25	1.81	13.32	0.3478	1
Febrile neutropenia	0.00	0.00	0.00	9.9144	1
Feeding disorder	0.24	0.99	4.01	0.0002	2
Feeling abnormal	0.61	0.93	1.43	0.1049	24
Feeling cold	0.20	0.53	1.43	1.6093	4
Feeling of despair	0.65	2.69	11.16	2.0029	2
Femur fracture	0.09	0.66	4.76	0.1701	1
Fine motor skill dysfunction	0.94	7.83	65.07	5.1107	1
Fixed eruption	0.09	0.62	4.45	0.2323	1
Flat affect	0.40	1.62	6.63	0.4600	2
Fluid intake reduced	0.58	2.41	9.98	1.5708	2
Flushing	0.02	0.07	0.29	24.1504	2
Foaming at mouth	0.07	0.52	3.71	0.4477	1
Focal dyscognitive seizures	0.05	0.36	2.61	1.1008	1
Foetal exposure during pregnancy	0.01	0.03	0.11	67.1048	3
Food craving	0.51	3.92	30.12	2.0056	1
Food interaction	0.66	5.22	41.22	3.0733	1
Frequent bowel movements	0.51	2.09	8.61	1.0877	2
Frustration tolerance decreased	0.58	2.41	9.98	1.5708	2
Fungal infection	0.05	0.36	2.55	1.1561	1
Gait disturbance	0.39	0.62	0.97	4.5359	19
Gambling disorder	99.90	99.90	99.90	47.0084	1
Gamma-glutamyltransferase decreased	1.63	15.67	150.61	10.3001	1
Gamma-glutamyltransferase increased	0.21	0.56	1.50	1.3721	4
Gastric dilatation	0.60	4.70	36.71	2.6488	1
Gastric disorder	0.09	0.64	4.57	0.2067	1
Gastric infection	0.44	3.36	25.53	1.5453	1
Gastric ulcer	0.23	0.95	3.85	0.0052	2
Gastritis	0.03	0.20	1.42	3.2097	1
Gastroenteritis	0.02	0.15	1.04	4.9674	1

Gastrointestinal disorder	0.75	1.40	2.62	1.1072	10
Gastrointestinal haemorrhage	0.65	1.26	2.44	0.4683	9
Gastrointestinal hypomotility	1.15	4.95	21.24	5.7012	2
Gastrointestinal motility disorder	0.12	0.89	6.41	0.0141	1
Gastrointestinal ulcer perforation	99.90	99.90	99.90	47.0084	1
Gastrooesophageal reflux disease	0.09	0.37	1.47	2.1846	2
Gaze palsy	1.05	1.92	3.50	4.6284	11
General physical condition abnormal	0.25	1.88	13.87	0.3963	1
General physical health deterioration	0.19	0.46	1.10	3.2145	5
Generalised anxiety disorder	0.28	2.04	15.13	0.5110	1
Generalised erythema	0.14	0.44	1.37	2.1301	3
Generalised oedema	0.21	0.64	2.01	0.5833	3
Generalised tonic-clonic seizure	0.15	0.29	0.56	15.4473	9
Gingival bleeding	0.07	0.49	3.55	0.5106	1
Gingival swelling	0.24	1.74	12.81	0.3042	1
Glaucoma	0.20	0.80	3.25	0.0945	2
Glossitis	0.20	1.47	10.75	0.1452	1
Glucose tolerance test abnormal	2.13	23.50	259.17	14.3646	1
Glucose urine present	0.25	1.81	13.32	0.3478	1
Glycosuria	0.28	1.12	4.55	0.0248	2
Glycosylated haemoglobin increased	0.38	1.54	6.30	0.3682	2
Grandiosity	0.51	3.92	30.12	2.0056	1
Granulocytopenia	0.46	1.25	3.38	0.2000	4
Growth accelerated	0.32	2.35	17.51	0.7390	1
Growth retardation	0.08	0.24	0.75	7.1518	3
Haemangioma	0.19	1.42	10.41	0.1228	1
Haematemesis	0.18	0.48	1.29	2.2229	4
Haematochezia	0.26	0.63	1.53	1.0477	5
Haematocrit decreased	0.19	0.76	3.06	0.1519	2
Haematoma	0.02	0.18	1.27	3.7847	1
Haemodynamic instability	0.09	0.64	4.63	0.1943	1
Haemoglobin decreased	0.14	0.37	0.98	4.3378	5
Haemoptysis	0.03	0.24	1.73	2.3593	1
Haemorrhage	0.04	0.17	0.68	8.1589	2
Haemorrhagic diathesis	0.19	1.42	10.41	0.1228	1
Hair growth abnormal	0.14	1.04	7.58	0.0019	2
Hallucination	0.58	0.82	1.15	1.3723	35
Hallucination, visual	0.72	1.18	1.93	0.4251	16
Hand deformity	0.22	1.62	11.90	0.2300	1
Hangover	2.13	23.50	259.17	14.3646	1
Head banging	0.58	2.41	9.98	1.5708	2
Head discomfort	0.10	0.70	5.05	0.1251	1
Head injury	0.07	0.27	1.09	3.8880	2
Headache	0.16	0.21	0.27	176.7103	59
Heart disease congenital	0.09	0.35	1.40	2.4254	2
Heart rate decreased	0.10	0.39	1.57	1.8935	2
Heart rate increased	0.38	0.66	1.14	2.2329	13
Helicobacter test positive	1.10	9.40	80.46	6.2569	1
Hemiparesis	0.07	0.28	1.13	3.6523	2
Hemiplegia	0.19	0.76	3.06	0.1519	2
Henoch-Schonlein purpura	0.02	0.11	0.78	7.2762	1
Hepatic enzyme abnormal	0.51	2.09	8.61	1.0877	2
Hepatic enzyme increased	0.35	0.63	1.15	2.3076	11

Hepatic function abnormal	0.30	0.58	1.12	2.7216	10
Hepatic necrosis	0.26	1.04	4.24	0.0037	2
Hepatitis	0.07	0.23	0.71	7.7969	3
Hepatitis acute	0.06	0.46	3.27	0.6416	1
Hepatocellular injury	0.48	1.01	2.14	0.0011	7
Hepatomegaly	0.19	0.51	1.37	1.8399	4
High density lipoprotein increased	1.10	9.40	80.46	6.2569	1
Hirsutism	0.37	1.52	6.20	0.3408	2
Hormone level abnormal	0.23	1.68	12.34	0.2651	1
Hospitalisation	0.47	0.94	1.89	0.0324	9
Hostility	0.08	0.55	3.92	0.3719	1
Hunger	0.93	3.00	9.64	3.7622	3
Hydrocele	0.19	1.42	10.41	0.1228	1
Hydrocephalus	0.04	0.28	2.00	1.8442	1
Hyperacusis	0.22	0.70	2.18	0.3862	3
Hyperaesthesia	0.27	0.84	2.64	0.0845	3
Hyperbilirubinaemia	0.11	0.43	1.72	1.5226	2
Hyperchromic anaemia	99.90	99.90	99.90	47.0084	1
Hyperglycaemic hyperosmolar nonketotic syndrome	0.51	3.92	30.12	2.0056	1
Hypergonadism	2.94	47.01	751.46	22.5150	1
Hyperhidrosis	0.40	0.62	0.95	4.9284	22
Hyperkinesia	0.82	2.61	8.35	2.8272	3
Hypermagnesaemia	0.51	3.92	30.12	2.0056	1
Hypernatraemia	0.09	0.62	4.45	0.2323	1
Hyperpyrexia	0.06	0.19	0.59	10.4743	3
Hypersensitivity	0.04	0.09	0.20	57.0035	6
Hypersexuality	1.35	5.88	25.55	7.1939	2
Hypersomnia	1.21	1.91	3.02	7.9146	19
Hypertension	0.86	1.19	1.64	1.1337	39
Hypertensive crisis	0.10	0.72	5.21	0.1044	1
Hyperthermia	0.53	1.07	2.15	0.0343	8
Hyperthermia malignant	0.03	0.21	1.47	3.0465	1
Hyperthyroidism	0.05	0.39	2.78	0.9552	1
Hypertonia	0.47	0.87	1.63	0.1896	10
Hypertrichosis	0.37	1.52	6.20	0.3408	2
Hypertriglyceridaemia	0.15	0.59	2.38	0.5584	2
Hyperuricaemia	0.00	0.00	0.00	0.7660	1
Hypervigilance	0.55	4.27	33.09	2.2987	1
Hypoaesthesia	0.08	0.19	0.42	21.0052	6
Hypochloraemia	0.55	4.27	33.09	2.2987	1
Hypoglycaemia	0.19	0.41	0.86	5.9226	7
Hypoglycaemic seizure	0.05	0.39	2.76	0.9732	1
Hypogonadism	1.89	8.55	38.55	11.2782	2
Hypogonadism male	2.13	23.50	259.17	14.3646	1
Hypokalaemia	0.11	0.35	1.09	3.6218	4
Hypokinesia	0.95	1.92	3.89	3.3845	8
Hypomagnesaemia	0.00	0.00	0.00	1.5961	1
Hyponatraemia	0.17	0.41	0.99	4.1979	6
Hyponatraemic seizure	2.13	23.50	259.17	14.3646	1
Hypophagia	0.39	1.06	2.86	0.0143	4
Hypoplastic anaemia	1.10	9.40	80.46	6.2569	1
Hyposideraemia	99.90	99.90	99.90	94.0173	2
Hypospadias	0.07	0.47	3.37	0.5917	1

Hypotension	0.47	0.66	0.93	5.7327	35
Hypothalamo-pituitary disorder	0.65	2.69	11.16	2.0029	2
Hypothermia	0.78	1.46	2.73	1.3842	10
Hypothyroidism	0.53	1.12	2.37	0.0870	7
Hypotonia	0.03	0.11	0.45	14.2022	2
Hypotonic-hyporesponsive episode	0.19	0.75	3.04	0.1609	2
Hypovolaemic shock	0.16	1.15	8.33	0.0183	1
Hypoxia	0.02	0.13	0.94	5.7201	1
Hypoxic-ischaemic encephalopathy	0.17	1.27	9.26	0.0561	1
Idiopathic intracranial hypertension	0.26	0.63	1.51	1.0986	5
Ileus	0.05	0.34	2.42	1.2867	1
Ileus paralytic	0.06	0.43	3.09	0.7436	1
Ill-defined disorder	0.11	0.45	1.82	1.3175	2
Illusion	0.41	1.29	4.07	0.1949	3
Immune system disorder	0.06	0.41	2.95	0.8306	1
Immune thrombocytopenic purpura	0.24	0.65	1.75	0.7291	4
Impaired self-care	0.51	3.92	30.12	2.0056	1
Impatience	0.37	2.77	20.77	1.0643	1
Impetigo	0.12	0.85	6.17	0.0243	1
Imprisonment	2.13	23.50	259.17	14.3646	1
Inappropriate affect	0.32	1.32	5.40	0.1544	2
Inappropriate antidiuretic hormone secretion	0.19	0.76	3.06	0.1519	2
Inappropriate schedule of drug administration	0.13	0.24	0.47	21.2959	10
Incoherent	0.41	1.28	4.03	0.1813	3
Incorrect dosage administered	0.44	3.36	25.53	1.5453	1
Incorrect drug administration duration	0.43	1.77	7.28	0.6509	2
Incorrect product storage	0.02	0.13	0.91	5.9507	1
Increased bronchial secretion	0.13	0.92	6.67	0.0065	1
Infection	0.05	0.17	0.52	12.5254	3
Infectious mononucleosis	0.04	0.31	2.24	1.4955	1
Inflammation	0.01	0.07	0.48	12.9841	1
Influenza	0.10	0.27	0.72	7.9278	4
Influenza like illness	0.07	0.21	0.66	8.6699	3
Infrequent bowel movements	0.47	3.62	27.64	1.7575	1
Inguinal hernia	0.16	1.18	8.55	0.0255	1
Injection site pain	0.01	0.03	0.11	71.3425	2
Injury	0.71	1.23	2.13	0.5445	13
Insomnia	1.39	1.79	2.31	20.3456	61
Insulin resistance syndrome	2.94	47.01	751.46	22.5150	1
Intellectual disability	0.53	1.42	3.85	0.4914	4
Intention tremor	0.25	1.88	13.87	0.3963	1
Intentional overdose	0.98	1.30	1.71	3.4274	52
Intentional product misuse	1.10	1.79	2.90	5.6980	17
Internal haemorrhage	0.60	4.70	36.71	2.6488	1
Intestinal haemorrhage	0.73	3.03	12.67	2.5603	2
Intestinal obstruction	0.23	0.92	3.73	0.0130	2
Intestinal transit time decreased	99.90	99.90	99.90	47.0084	1
Intracranial pressure increased	0.02	0.11	0.79	7.1075	1
Intraocular pressure increased	0.17	0.69	2.77	0.2830	2
Intussusception	0.17	1.27	9.26	0.0561	1
Irritability	1.02	1.44	2.02	4.4142	35
Ischaemia	0.25	1.81	13.32	0.3478	1
Ischaemic cardiomyopathy	2.13	23.50	259.17	14.3646	1

Jaundice	0.04	0.15	0.59	9.9714	2
Jaundice neonatal	0.13	0.96	6.95	0.0017	1
Jaw disorder	0.35	2.61	19.56	0.9422	1
Joint dislocation	0.60	1.91	6.04	1.2416	3
Joint hyperextension	0.25	1.88	13.87	0.3963	1
Joint stiffness	0.64	1.74	4.72	1.2173	4
Joint swelling	0.01	0.09	0.65	9.0521	1
Ketoacidosis	0.05	0.38	2.69	1.0276	1
Klinefelter's syndrome	99.90	99.90	99.90	94.0173	2
Knee deformity	0.18	1.31	9.52	0.0697	1
Kyphosis	0.24	1.74	12.81	0.3042	1
Laboratory test abnormal	0.30	1.24	5.04	0.0886	2
Laceration	0.26	1.07	4.34	0.0086	2
Lactic acidosis	0.05	0.36	2.57	1.1376	1
Language disorder	0.08	0.59	4.22	0.2860	1
Laryngospasm	0.05	0.35	2.51	1.1933	1
Learning disability	0.10	0.70	5.05	0.1251	1
Learning disorder	0.05	0.34	2.45	1.2492	1
Lethargy	0.74	1.09	1.59	0.1835	28
Leukaemia	0.09	0.63	4.51	0.2194	1
Leukocytosis	0.73	1.33	2.41	0.8585	11
Libido decreased	0.28	2.04	15.13	0.5110	1
Limb discomfort	0.24	0.75	2.33	0.2553	3
Limb injury	0.12	0.89	6.41	0.0141	1
Lip oedema	0.08	0.26	0.82	6.1337	3
Lip swelling	0.05	0.15	0.48	13.8813	3
Lipase increased	0.03	0.21	1.52	2.8837	1
Lipids increased	1.63	7.23	32.04	9.3092	2
Lipodystrophy acquired	0.16	1.15	8.33	0.0183	1
Liquid product physical issue	0.74	5.88	46.97	3.5968	1
Listless	0.30	0.81	2.19	0.1673	4
Liver disorder	0.19	0.50	1.34	1.9975	4
Liver function test	2.13	23.50	259.17	14.3646	1
Liver function test abnormal	0.82	1.49	2.72	1.7473	11
Local swelling	0.02	0.14	1.01	5.1970	1
Localised oedema	0.03	0.25	1.76	2.2994	1
Logorrhoea	0.89	2.18	5.33	3.0400	5
Loss of consciousness	0.22	0.33	0.49	33.5796	27
Loss of libido	6.62	47.01	333.65	45.0304	2
Loss of personal independence in daily activities	0.11	0.44	1.78	1.4022	2
Low birth weight baby	0.65	2.69	11.16	2.0029	2
Low density lipoprotein increased	1.10	4.70	20.11	5.2979	2
Lower respiratory tract infection	0.05	0.35	2.53	1.1747	1
Lung disorder	0.19	0.59	1.85	0.8311	3
Lupus-like syndrome	0.06	0.47	3.34	0.6083	1
Lymphadenopathy	0.03	0.09	0.28	27.4224	3
Lymphocyte count decreased	0.12	0.85	6.17	0.0243	1
Lymphocyte stimulation test positive	0.17	1.21	8.77	0.0341	1
Lymphoedema	0.21	1.52	11.11	0.1704	1
Lymphopenia	0.17	0.68	2.75	0.2942	2
Madarosis	0.22	1.62	11.90	0.2300	1
Major depression	0.95	2.61	7.14	3.7699	4
Malaise	0.27	0.38	0.53	34.1614	33

Malignant hypertension	0.83	6.72	54.57	4.2565	1
Mastectomy	2.13	23.50	259.17	14.3646	1
Mastication disorder	0.73	3.03	12.67	2.5603	2
Mauriac syndrome	2.94	47.01	751.46	22.5150	1
Medication error	1.00	1.42	2.00	3.9687	33
Melaena	0.05	0.35	2.49	1.2119	1
Memory impairment	0.11	0.30	0.79	6.6133	4
Meningeal disorder	0.19	1.42	10.41	0.1228	1
Meningomyelocele	0.27	1.96	14.48	0.4505	1
Menorrhagia	0.03	0.24	1.68	2.4797	1
Menstrual disorder	0.45	1.10	2.66	0.0431	5
Menstruation irregular	0.18	0.56	1.76	0.9998	3
Mental status changes	0.07	0.28	1.13	3.6719	2
Metabolic acidosis	0.10	0.31	0.96	4.6468	4
Micropenis	8.53	94.02	1,036.68	61.3523	2
Micturition disorder	0.25	1.88	13.87	0.3963	1
Micturition urgency	0.14	1.04	7.58	0.0019	1
Middle insomnia	0.44	1.38	4.36	0.3087	3
Migraine	0.17	0.37	0.82	6.4597	6
Mitral valve incompetence	0.06	0.44	3.12	0.7264	1
Mitral valve prolapse	0.25	1.81	13.32	0.3478	1
Mobility decreased	0.03	0.19	1.32	3.5788	1
Monocytopenia	2.13	23.50	259.17	14.3646	1
Monocytosis	0.37	2.77	20.77	1.0643	1
Monoparesis	0.09	0.66	4.76	0.1701	1
Monoplegia	0.06	0.41	2.90	0.8659	1
Mood altered	0.27	0.61	1.37	1.4753	6
Mood swings	0.55	1.00	1.82	0.0000	11
Mucosal dryness	0.17	1.27	9.26	0.0561	1
Mucous stools	0.96	4.09	17.33	4.2920	2
Multiple allergies	0.96	4.09	17.33	4.2920	2
Multiple organ dysfunction syndrome	0.26	0.59	1.32	1.7054	6
Munchausen's syndrome	1.31	11.75	105.13	7.8699	1
Muscle contractions involuntary	0.29	0.90	2.81	0.0340	3
Muscle contracture	0.95	2.61	7.14	3.7699	5
Muscle disorder	0.49	2.00	8.23	0.9599	2
Muscle hypertrophy	0.94	7.83	65.07	5.1107	1
Muscle spasms	0.67	1.00	1.50	0.0005	25
Muscle spasticity	0.04	0.17	0.67	8.2626	2
Muscle strain	0.21	1.57	11.49	0.1985	1
Muscle tightness	0.11	0.45	1.79	1.3682	2
Muscle twitching	1.14	1.76	2.72	6.6575	21
Muscular weakness	0.12	0.23	0.47	20.1779	8
Musculoskeletal chest pain	0.07	0.52	3.75	0.4323	1
Musculoskeletal discomfort	0.09	0.67	4.83	0.1584	1
Musculoskeletal pain	0.02	0.13	0.89	6.0976	1
Musculoskeletal stiffness	1.04	1.51	2.20	4.7113	28
Myalgia	0.08	0.15	0.31	37.9738	8
Mydriasis	0.23	0.49	1.04	3.6004	7
Myocardial infarction	0.26	1.04	4.24	0.0037	2
Myocardial necrosis marker increased	0.18	1.31	9.52	0.0697	1
Myocarditis	0.14	0.55	2.20	0.7441	2
Myoclonus	0.27	0.65	1.58	0.8996	5

Myoglobin blood increased	2.26	10.45	48.33	13.9786	2
Myopathy	0.07	0.47	3.40	0.5753	1
Nail discolouration	0.24	1.74	12.81	0.3042	1
Nasal congestion	0.07	0.29	1.18	3.3986	3
Nasal obstruction	0.24	1.74	12.81	0.3042	1
Nasal oedema	0.23	1.68	12.34	0.2651	1
Nausea	0.11	0.15	0.22	142.6862	31
Neck mass	0.47	3.62	27.64	1.7575	1
Neck pain	0.08	0.24	0.73	7.4335	3
Negative thoughts	0.83	3.48	14.64	3.2950	2
Neologism	99.90	99.90	99.90	47.0084	1
Nephrolithiasis	0.20	0.62	1.95	0.6715	3
Nervous system disorder	0.14	0.44	1.36	2.1472	3
Nervousness	0.33	0.75	1.67	0.5110	7
Neurogenic bladder	0.12	0.89	6.41	0.0141	1
Neurological decompensation	0.11	0.78	5.65	0.0589	1
Neurological examination abnormal	0.41	3.13	23.72	1.3623	1
Neuropsychiatric symptoms	6.62	47.01	333.65	45.0304	2
Neuropsychiatric syndrome	1.10	9.40	80.46	6.2569	1
Neurotransmitter level altered	2.94	47.01	751.46	22.5150	1
Neutropenia	0.98	1.33	1.82	3.3710	41
Neutropenic sepsis	0.47	3.62	27.64	1.7575	1
Neutrophil count decreased	0.76	1.53	3.09	1.4186	8
Night sweats	0.08	0.55	3.97	0.3572	1
Nightmare	0.12	0.32	0.87	5.5934	4
Nipple exudate bloody	99.90	99.90	99.90	47.0084	1
Nipple resection	99.90	99.90	99.90	47.0084	1
No adverse event	0.02	0.06	0.18	44.9742	3
Nocturia	0.15	1.09	7.94	0.0078	1
Nodule	0.09	0.64	4.57	0.2067	1
Non-cardiac chest pain	0.30	2.24	16.64	0.6541	1
Nonspecific reaction	0.39	2.94	22.15	1.2033	1
Nuchal rigidity	0.32	1.32	5.40	0.1544	2
Nutritional condition abnormal	0.51	3.92	30.12	2.0056	1
Nystagmus	0.02	0.17	1.24	3.8878	1
Obsessive-compulsive disorder	1.00	1.87	3.52	3.9170	10
Ocular hyperaemia	0.06	0.25	0.99	4.5631	2
Ocular hypertension	0.30	2.24	16.64	0.6541	1
Oedema	0.06	0.15	0.41	18.7039	4
Oedema peripheral	0.16	0.33	0.69	9.7092	7
Oesophageal atresia	1.53	6.72	29.54	8.5133	2
Oesophageal pain	0.35	2.61	19.56	0.9422	1
Onychophagia	0.44	3.36	25.53	1.5453	1
Opisthotonus	0.59	1.61	4.35	0.8876	7
Oppositional defiant disorder	0.37	1.52	6.20	0.3408	2
Oral discomfort	0.07	0.52	3.71	0.4477	1
Oral disorder	0.06	0.43	3.09	0.7436	1
Ornithine transcarbamoylase deficiency	1.63	15.67	150.61	10.3001	1
Oropharyngeal pain	0.04	0.12	0.36	20.3927	3
Oropharyngeal spasm	0.94	7.83	65.07	5.1107	1
Oroticaciduria	99.90	99.90	99.90	47.0084	1
Osteogenesis imperfecta	1.10	9.40	80.46	6.2569	1
Osteomyelitis	0.05	0.38	2.73	0.9913	1

Osteopenia	0.00	0.00	0.00	1.3193	1
Osteoporosis	0.04	0.32	2.28	1.4382	1
Otitis media	0.04	0.25	1.78	2.2395	1
Otoacoustic emissions test abnormal	99.90	99.90	99.90	47.0084	1
Overdose	1.00	1.26	1.58	4.0005	79
Pain	0.11	0.18	0.29	62.6079	16
Pain in extremity	0.03	0.08	0.19	54.4915	5
Pain in jaw	0.20	0.82	3.34	0.0733	2
Pain of skin	0.30	1.21	4.90	0.0682	2
Painful erection	2.79	13.43	64.64	17.8980	2
Pallor	0.01	0.04	0.14	61.8220	3
Palpitations	0.32	0.56	0.98	4.2032	12
Pancreatic disorder	0.27	1.96	14.48	0.4505	1
Pancreatic failure	0.41	3.13	23.72	1.3623	1
Pancreatitis	0.53	0.85	1.35	0.4852	18
Pancreatitis acute	0.52	0.91	1.61	0.1019	12
Pancreatitis chronic	0.30	2.24	16.64	0.6541	1
Pancytopenia	0.25	0.52	1.10	3.0185	7
Panel-reactive antibody	2.94	47.01	751.46	22.5150	1
Panic attack	0.39	0.88	1.97	0.0989	6
Panic disorder	0.18	1.34	9.80	0.0852	1
Panic reaction	0.08	0.54	3.88	0.3868	1
Papilloedema	0.19	0.51	1.35	1.9183	4
Paraesthesia	0.06	0.13	0.32	28.4416	5
Paraesthesia oral	0.04	0.26	1.82	2.1599	1
Paranoia	0.96	1.94	3.93	3.4943	8
Parkinson's disease	0.74	5.88	46.97	3.5968	1
Paronychia	0.13	0.94	6.80	0.0037	1
Parosmia	0.11	0.81	5.85	0.0436	1
Paroxysmal perceptual alteration	99.90	99.90	99.90	47.0084	1
Partial seizures	0.10	0.38	1.54	1.9838	2
Patella fracture	1.31	11.75	105.13	7.8699	1
Patent ductus arteriosus	0.01	0.10	0.69	8.4592	1
Pectus excavatum	0.41	3.13	23.72	1.3623	2
Pelvic pain	0.10	0.73	5.29	0.0945	1
Penile size reduced	6.62	47.01	333.65	45.0304	2
Penile swelling	0.94	7.83	65.07	5.1107	1
Penis disorder	0.32	2.35	17.51	0.7390	1
Pericardial effusion	0.03	0.22	1.54	2.8229	1
Perineal pain	2.13	23.50	259.17	14.3646	1
Periorbital oedema	0.02	0.13	0.90	5.9927	1
Peripheral circulatory failure	0.29	2.14	15.85	0.5785	1
Peripheral coldness	0.42	0.85	1.71	0.2118	8
Peripheral ischaemia	0.23	1.68	12.34	0.2651	1
Peripheral swelling	0.12	0.26	0.54	15.0216	7
Personality change	0.02	0.15	1.10	4.6341	1
Personality disorder	0.07	0.53	3.79	0.4170	1
Petechiae	0.01	0.08	0.60	9.9639	1
Phalangeal agenesis	2.13	23.50	259.17	14.3646	1
Pharyngeal disorder	0.20	1.47	10.75	0.1452	1
Pharyngeal oedema	0.02	0.12	0.88	6.2237	1
Pharyngitis	0.02	0.14	0.96	5.5316	1
Pharyngitis streptococcal	0.14	0.58	2.34	0.6000	2

Phobia	0.15	1.09	7.94	0.0078	1
Photophobia	0.01	0.07	0.53	11.6001	1
Physical assault	0.17	1.21	8.77	0.0341	1
Pickwickian syndrome	2.13	23.50	259.17	14.3646	1
Pituitary cyst	2.50	11.75	55.33	15.7402	2
Platelet count decreased	0.51	0.90	1.59	0.1362	13
Platelet count increased	0.26	1.06	4.29	0.0059	2
Platelet morphology abnormal	2.13	23.50	259.17	14.3646	1
Pleural effusion	0.02	0.12	0.83	6.6442	1
Pleurothotonus	99.90	99.90	99.90	47.0084	1
Pneumonia	0.17	0.31	0.57	16.6304	11
Pneumonia aspiration	0.19	0.77	3.12	0.1344	2
Pneumonitis	0.78	2.14	5.82	2.3148	4
Pneumothorax	0.04	0.26	1.82	2.1599	1
Poisoning	0.74	1.68	3.79	1.5916	6
Pollakiuria	0.40	1.09	2.93	0.0272	4
Polyuria	0.52	1.26	3.07	0.2681	5
Poor personal hygiene	2.13	23.50	259.17	14.3646	1
Poor quality drug administered	0.15	1.09	7.94	0.0078	1
Poor quality sleep	0.14	0.55	2.23	0.7147	3
Post transplant lymphoproliferative disorder	0.00	0.00	0.00	3.8751	1
Post-traumatic stress disorder	0.25	1.88	13.87	0.3963	1
Posterior reversible encephalopathy syndrome	0.25	0.53	1.12	2.8655	7
Posture abnormal	0.45	1.42	4.49	0.3685	3
Posturing	0.83	3.48	14.64	3.2950	2
Pre-existing condition improved	0.51	3.92	30.12	2.0056	1
Premature baby	0.07	0.29	1.17	3.4180	2
Prescribed overdose	0.44	0.93	1.97	0.0339	7
Pressure of speech	0.28	2.04	15.13	0.5110	1
Presyncope	0.00	0.03	0.20	33.0538	1
Product availability issue	0.37	2.77	20.77	1.0643	1
Product friable	99.90	99.90	99.90	47.0084	1
Product measured potency issue	0.33	2.47	18.48	0.8345	1
Product odour abnormal	0.37	2.77	20.77	1.0643	1
Product quality issue	0.49	0.83	1.41	0.4750	14
Product selection error	0.66	5.22	41.22	3.0733	1
Product substitution issue	0.79	1.67	3.55	1.8203	7
Product taste abnormal	0.55	2.29	9.48	1.3908	2
Product use issue	1.05	1.64	2.56	4.8501	21
Product used for unknown indication	1.10	9.40	80.46	6.2569	1
Productive cough	0.05	0.33	2.35	1.3622	1
Progressive multifocal leukoencephalopathy	0.44	3.36	25.53	1.5453	1
Prolactin-producing pituitary tumour	5.24	31.34	187.51	35.2457	2
Prostatic calcification	99.90	99.90	99.90	47.0084	1
Protein C deficiency	1.10	9.40	80.46	6.2569	1
Prothrombin time prolonged	0.05	0.38	2.69	1.0276	1
Pruritus	0.07	0.12	0.21	78.2577	12
Pruritus generalised	0.01	0.08	0.59	10.0488	1
Psoriasis	0.03	0.20	1.43	3.1893	1
Psychiatric decompensation	1.75	7.83	35.00	10.2218	2
Psychiatric symptom	0.66	2.10	6.69	1.6658	3
Psychogenic seizure	0.16	1.18	8.55	0.0255	1
Psychological trauma	0.44	3.36	25.53	1.5453	1

Psychomotor retardation	0.66	2.10	6.69	1.6658	3
Psychotic behaviour	0.39	1.59	6.52	0.4277	2
Psychotic symptom	6.62	47.01	333.65	45.0304	2
Pulmonary artery stenosis congenital	0.05	0.35	2.47	1.2305	1
Pulmonary embolism	0.08	0.25	0.77	6.8910	3
Pupillary light reflex tests abnormal	0.93	3.92	16.57	4.0115	2
Pupillary reflex impaired	0.00	0.00	0.00	1.8515	1
Purpura	0.14	0.44	1.37	2.1301	3
Pyrexia	0.11	0.15	0.20	260.4066	50
QRS axis abnormal	0.66	5.22	41.22	3.0733	1
Quadriplegia	0.10	0.72	5.21	0.1044	1
Rash	0.16	0.22	0.31	95.8471	35
Rash erythematous	0.13	0.29	0.65	10.2085	6
Rash generalised	0.01	0.04	0.25	26.0503	1
Rash papular	0.01	0.09	0.65	9.0309	1
Rash pruritic	0.06	0.18	0.56	11.0731	3
Reaction to colouring	1.63	15.67	150.61	10.3001	1
Reading disorder	0.20	1.47	10.75	0.1452	1
Rebound effect	0.12	0.84	6.06	0.0302	1
Rectal discharge	2.94	47.01	751.46	22.5150	1
Rectal haemorrhage	0.72	1.75	4.28	1.5635	5
Red blood cell count decreased	0.25	1.01	4.10	0.0002	2
Reduced facial expression	0.37	2.77	20.77	1.0643	1
Regressive behaviour	0.17	1.21	8.77	0.0341	1
Regurgitation	0.25	1.88	13.87	0.3963	1
Renal disorder	0.14	0.57	2.31	0.6281	2
Renal failure	0.01	0.06	0.42	15.1387	1
Renal neoplasm	1.31	11.75	105.13	7.8699	1
Renal tubular disorder	0.00	0.00	0.00	2.3200	1
Renin increased	0.66	5.22	41.22	3.0733	1
Respiration abnormal	0.08	0.60	4.28	0.2723	1
Respiratory arrest	0.26	0.58	1.30	1.8028	7
Respiratory depression	0.09	0.37	1.48	2.1478	2
Respiratory disorder	0.05	0.22	0.87	5.6111	2
Respiratory distress	0.09	0.23	0.62	10.2107	4
Respiratory failure	0.09	0.25	0.66	9.1231	4
Respiratory rate decreased	0.09	0.65	4.70	0.1821	2
Respiratory syncytial virus infection	0.00	0.00	0.00	1.2129	1
Restless legs syndrome	0.80	2.56	8.19	2.7150	3
Restlessness	0.83	1.27	1.93	1.2134	23
Retching	0.17	0.52	1.62	1.3133	3
Retinal tear	2.94	47.01	751.46	22.5150	1
Retracted nipple	99.90	99.90	99.90	47.0084	1
Retrograde amnesia	0.21	1.52	11.11	0.1704	1
Rhabdomyolysis	1.01	1.66	2.74	4.1039	18
Rhinitis	0.17	0.54	1.69	1.1464	3
Rhinorrhoea	0.02	0.13	0.89	6.1186	1
Scar	0.31	0.99	3.09	0.0006	3
Schizoaffective disorder	3.65	18.80	96.89	24.0815	2
School refusal	0.13	0.94	6.80	0.0037	1
Scleral oedema	2.94	47.01	751.46	22.5150	1
Scratch	0.14	1.02	7.41	0.0005	1
Screaming	0.24	0.65	1.73	0.7656	4

Seborrhoea	0.94	7.83	65.07	5.1107	1
Seborrhoeic dermatitis	0.41	3.13	23.72	1.3623	1
Seizure	0.55	0.66	0.80	19.3471	115
Seizure like phenomena	0.35	1.45	5.91	0.2674	2
Self esteem decreased	0.45	1.84	7.57	0.7429	2
Self-injurious ideation	0.35	1.09	3.43	0.0233	3
Sensation of foreign body	0.05	0.36	2.61	1.1008	1
Sense of oppression	0.30	2.24	16.64	0.6541	1
Separation anxiety disorder	0.37	2.77	20.77	1.0643	1
Sepsis	0.03	0.12	0.46	13.5046	2
Septic shock	0.08	0.34	1.36	2.5565	2
Serology negative	99.90	99.90	99.90	47.0084	1
Serotonin syndrome	0.89	1.90	4.05	2.8807	8
Severe mental retardation	2.13	23.50	259.17	14.3646	1
Sexual dysfunction	1.63	7.23	32.04	9.3092	2
Shock	0.06	0.24	0.96	4.8034	2
Sickle cell anaemia	0.44	3.36	25.53	1.5453	1
Sinusitis	0.01	0.10	0.71	8.1631	1
Skin discolouration	0.14	0.38	1.02	4.0087	5
Skin disorder	0.56	1.36	3.30	0.4604	5
Skin exfoliation	0.01	0.09	0.67	8.6709	1
Skin lesion	0.06	0.25	1.01	4.4433	2
Skin odour abnormal	0.25	1.88	13.87	0.3963	1
Skin striae	0.98	2.22	5.03	3.8477	6
Sleep apnoea syndrome	0.71	1.73	4.22	1.4809	5
Sleep disorder	0.41	0.71	1.23	1.4847	13
Sleep terror	0.19	0.78	3.17	0.1178	2
Sleep-related eating disorder	2.13	23.50	259.17	14.3646	1
Slow response to stimuli	0.31	1.27	5.17	0.1122	2
Snoring	0.13	0.96	6.95	0.0017	1
Social anxiety disorder	0.83	3.48	14.64	3.2950	2
Social avoidant behaviour	0.76	1.53	3.09	1.4186	8
Social problem	0.14	1.02	7.41	0.0005	1
Soft tissue disorder	1.10	9.40	80.46	6.2569	1
Soliloquy	2.06	9.40	42.90	12.5141	2
Somatic delusion	2.94	47.01	751.46	22.5150	1
Somatic symptom disorder	0.07	0.48	3.47	0.5428	1
Somnambulism	0.22	0.89	3.59	0.0283	2
Somnolence	1.55	1.82	2.14	53.5881	149
Speech disorder	0.84	1.27	1.92	1.2825	23
Speech disorder developmental	0.05	0.37	2.67	1.0458	1
Spina bifida	0.06	0.40	2.88	0.8837	1
Spine malformation	0.51	3.92	30.12	2.0056	1
Splenomegaly	0.20	0.62	1.92	0.7105	3
Staphylococcal infection	0.02	0.16	1.12	4.5094	1
Staring	0.22	0.68	2.12	0.4527	3
Status epilepticus	0.28	0.62	1.39	1.3704	6
Stevens-Johnson syndrome	0.02	0.08	0.24	33.4267	3
Stomatitis	0.00	0.00	0.00	10.1281	1
Strabismus	0.04	0.27	1.95	1.9227	1
Streptococcal infection	0.48	1.52	4.79	0.5113	3
Stress	0.66	1.60	3.90	1.0856	5
Stupor	0.29	0.90	2.81	0.0340	3

Substance use disorder	0.08	0.55	3.97	0.3572	1
Substance-induced psychotic disorder	0.68	2.85	11.87	2.2632	2
Sudden death	0.16	0.65	2.63	0.3643	2
Sudden onset of sleep	0.16	1.15	8.33	0.0183	1
Suicidal behaviour	0.70	1.70	4.15	1.4019	5
Suicide attempt	1.39	1.74	2.17	24.4763	82
Suicide threat	2.94	47.01	751.46	22.5150	1
Supernumerary nipple	2.13	23.50	259.17	14.3646	1
Supraventricular extrasystoles	0.14	1.00	7.25	0.0000	1
Supraventricular tachycardia	0.11	0.44	1.76	1.4364	2
Surgery	0.14	0.55	2.20	0.7441	2
Swelling	0.13	0.28	0.63	11.0520	6
Swelling face	0.14	0.29	0.61	12.0694	7
Swollen tongue	0.31	0.74	1.80	0.4350	5
Sympathomimetic effect	2.13	23.50	259.17	14.3646	1
Syncope	0.16	0.23	0.34	69.6908	27
Systemic lupus erythematosus	0.03	0.19	1.37	3.3940	1
Systolic dysfunction	0.83	6.72	54.57	4.2565	1
T-cell lymphoma	0.66	5.22	41.22	3.0733	1
Tachycardia	1.15	1.44	1.79	10.5652	82
Tachycardia paroxysmal	0.94	7.83	65.07	5.1107	1
Tachyphrenia	1.21	5.22	22.50	6.1469	2
Tachypnoea	0.17	0.46	1.23	2.5200	4
Talipes	0.00	0.00	0.00	7.1167	1
Tearfulness	0.86	2.10	5.14	2.7542	5
Temperature intolerance	0.13	0.92	6.67	0.0065	1
Tendon pain	0.39	2.94	22.15	1.2033	1
Tendonitis	0.09	0.67	4.83	0.1584	1
Tension	0.32	1.32	5.40	0.1544	2
Testicular atrophy	1.10	9.40	80.46	6.2569	1
Testicular cyst	99.90	99.90	99.90	47.0084	1
Testicular mass	99.90	99.90	99.90	47.0084	1
Testicular microlithiasis	99.90	99.90	99.90	47.0084	1
Testicular pain	0.25	1.88	13.87	0.3963	1
Therapeutic product ineffective	0.65	2.69	11.16	2.0029	2
Therapeutic response decreased	0.65	1.16	2.05	0.2470	13
Therapeutic response increased	0.66	5.22	41.22	3.0733	1
Therapeutic response unexpected	0.65	1.38	2.92	0.7022	7
Thinking abnormal	0.40	1.07	2.88	0.0171	4
Thirst	0.82	1.84	4.17	2.2299	6
Thought insertion	1.63	15.67	150.61	10.3001	1
Thought withdrawal	99.90	99.90	99.90	47.0084	1
Throat tightness	0.01	0.10	0.73	7.7827	1
Thrombocytopenia	0.54	0.78	1.12	1.8127	29
Thrombosis	0.10	0.39	1.57	1.8756	2
Thyroid disorder	0.64	2.04	6.49	1.5332	3
Thyroid function test abnormal	0.32	2.35	17.51	0.7390	1
Thyroid hormones increased	0.66	5.22	41.22	3.0733	1
Thyroid stimulating immunoglobulin	2.94	47.01	751.46	22.5150	1
Tinnitus	0.06	0.23	0.91	5.2667	2
Tongue coated	0.37	2.77	20.77	1.0643	1
Tongue discolouration	0.14	1.02	7.41	0.0005	1
Tongue oedema	0.34	1.07	3.35	0.0128	3

Tonic clonic movements	0.03	0.21	1.50	2.9447	1
Tonsillitis	0.08	0.32	1.30	2.8212	2
Tonsillitis bacterial	0.44	3.36	25.53	1.5453	1
Tooth discolouration	0.04	0.30	2.11	1.6689	1
Torsade de pointes	0.06	0.45	3.21	0.6753	1
Toxic encephalopathy	0.04	0.27	1.93	1.9621	1
Toxicity to various agents	0.45	0.68	1.04	3.2013	23
Trance	3.16	15.67	77.61	20.6006	2
Transaminases increased	0.59	1.00	1.69	0.0001	14
Transferrin	99.90	99.90	99.90	47.0084	1
Transferrin increased	2.94	47.01	751.46	22.5150	1
Transient ischaemic attack	0.92	2.94	9.43	3.6104	3
Treatment failure	0.06	0.40	2.83	0.9193	1
Tremor	0.90	1.16	1.48	1.3244	63
Trismus	0.42	1.14	3.07	0.0668	5
Tumour lysis syndrome	0.00	0.00	0.00	1.6599	1
Tumour rupture	2.94	47.01	751.46	22.5150	1
Type I hypersensitivity	0.16	0.63	2.55	0.4262	2
Type V hyperlipidaemia	99.90	99.90	99.90	47.0084	1
Ulcer	0.10	0.69	4.98	0.1359	1
Ultrasound thyroid	99.90	99.90	99.90	47.0084	1
Underdose	0.17	0.53	1.67	1.2065	3
Unresponsive to stimuli	0.31	0.62	1.25	1.7855	8
Upper respiratory tract infection	0.22	0.54	1.29	1.9974	5
Upper respiratory tract infection bacterial	2.94	47.01	751.46	22.5150	1
Urinary hesitation	0.41	3.13	23.72	1.3623	1
Urinary retention	0.70	1.31	2.45	0.6980	10
Urinary tract infection	0.02	0.11	0.77	7.3606	1
Urinary tract inflammation	0.94	7.83	65.07	5.1107	1
Urinary tract injury	99.90	99.90	99.90	47.0084	1
Urine abnormality	0.51	3.92	30.12	2.0056	1
Urine analysis abnormal	0.12	0.89	6.41	0.0141	1
Urine ketone body present	0.15	1.09	7.94	0.0078	1
Urine output decreased	0.06	0.41	2.93	0.8483	1
Urine output increased	0.47	3.62	27.64	1.7575	1
Urticaria	0.03	0.05	0.11	140.3540	8
Vaginal haemorrhage	0.19	0.76	3.09	0.1430	2
Varicose vein	1.10	9.40	80.46	6.2569	1
Vasculitis	0.11	0.44	1.75	1.4536	2
Vasospasm	0.37	2.77	20.77	1.0643	1
Ventricular extrasystoles	0.54	1.31	3.17	0.3487	5
Ventricular fibrillation	0.17	0.69	2.79	0.2719	2
Ventricular septal defect	0.01	0.08	0.54	11.2173	1
Ventricular tachycardia	0.20	0.64	1.98	0.6206	3
Vertigo	0.13	0.28	0.62	11.1703	6
Victim of abuse	2.94	47.01	751.46	22.5150	1
Violence-related symptom	0.53	2.19	9.02	1.2306	2
Viral infection	0.20	0.45	1.00	4.0113	6
Viral myositis	0.94	7.83	65.07	5.1107	1
Viral upper respiratory tract infection	0.11	0.31	0.82	6.3034	4
Vision blurred	0.39	0.64	1.05	3.2126	16
Visual acuity reduced	0.09	0.36	1.46	2.2030	2
Visual field defect	0.03	0.18	1.29	3.6817	1

Visual impairment	0.36	0.59	0.94	4.9483	17
Vomiting	0.19	0.25	0.32	130.4168	58
Vomiting in pregnancy	2.94	47.01	751.46	22.5150	1
Waist circumference increased	0.60	4.70	36.71	2.6488	1
Waxy flexibility	2.13	23.50	259.17	14.3646	1
Weight bearing difficulty	0.19	1.38	10.10	0.1029	1
Weight decreased	0.50	0.75	1.13	1.9133	23
White blood cell count abnormal	1.28	5.53	23.93	6.6417	2
White blood cell count decreased	0.79	1.30	2.14	1.0891	18
White blood cell count increased	0.41	0.87	1.84	0.1326	7
Withdrawal hypertension	0.83	6.72	54.57	4.2565	1
Withdrawal syndrome	1.03	1.72	2.88	4.4086	15
Wolff-Parkinson-White syndrome	0.65	2.69	11.16	2.0029	2
Wrong drug administered	0.09	0.29	0.91	5.1311	3
Wrong patient received medication	0.22	1.62	11.90	0.2300	1

PRR report- Aripiprazole

Reaction PT	PRR (-)	PRR	PRR (+)	CHI^2	# Cases
Abnormal weight gain	2.87	4.64	7.52	47.0397	17
Acanthosis nigricans	8.00	27.81	96.67	63.8502	3
Acute myeloid leukaemia	1.18	3.16	8.52	5.7871	4
Adverse event	3.43	6.11	10.87	49.0010	13
Affect lability	1.07	2.58	6.26	4.7696	5
Affective disorder	1.82	4.44	10.82	12.9119	5
Aggression	2.68	3.42	4.35	109.6145	66
Agitation	1.49	2.09	2.94	18.7440	34
Akathisia	13.74	19.87	28.73	497.8126	34
Akinesia	5.09	16.93	56.32	39.7715	4
Anger	2.25	3.68	6.04	30.4666	16
Apathy	2.87	4.98	8.64	39.8427	13
Autonomic nervous system imbalance	1.07	2.87	7.71	4.7645	4
Binge eating	7.52	25.95	89.56	59.9823	3
Bipolar I disorder	6.30	17.90	50.85	56.0896	4
Bipolar disorder	5.33	9.55	17.13	85.6617	14
Blood alkaline phosphatase increased	1.51	2.81	5.26	11.4776	10
Blood creatine phosphokinase increased	2.26	3.44	5.24	37.3115	22
Blood prolactin decreased	158.31	713.69	3,217.38	1,204.4748	11
Blood prolactin increased	1.55	3.48	7.81	10.3160	6
Bradykinesia	6.51	18.54	52.79	58.0785	4
Breast pain	1.88	5.99	19.04	11.9217	3
Bulbar palsy	11.72	43.25	159.63	92.8786	3
Bundle branch block right	3.23	7.35	16.69	31.1416	6
Catatonia	6.48	11.99	22.20	101.5415	11
Cerebral venous thrombosis	1.15	3.60	11.34	5.4961	3
Cerebrovascular accident	1.22	2.57	5.41	6.5709	7
Cogwheel rigidity	9.59	24.95	64.90	96.4417	5
Complex regional pain syndrome	1.07	3.36	10.55	4.8393	3

Delusion	3.08	5.79	10.89	38.0028	10
Diabetes mellitus	4.23	6.20	9.09	112.7236	27
Diabetic ketoacidosis	1.50	2.72	4.93	11.7372	11
Disease recurrence	2.02	4.55	10.26	16.0855	6
Disinhibition	1.78	5.64	17.91	10.9835	3
Drooling	6.15	10.81	19.00	106.9566	13
Drug administered to patient of inappropriate age	1.99	3.16	5.04	26.1142	20
Drug effect incomplete	1.89	4.25	9.58	14.4759	6
Drug interaction	2.67	3.60	4.86	79.3297	43
Dysarthria	1.83	3.04	5.06	20.1430	15
Dyskinesia	2.40	3.30	4.53	59.7791	38
Dystonia	11.86	14.48	17.68	1,145.7848	101
Dysuria	1.55	3.12	6.27	11.2536	8
Electrocardiogram QT prolonged	1.88	3.08	5.04	21.9676	16
Emotional disorder	2.51	4.12	6.76	36.7218	16
Emotional distress	1.32	2.29	3.95	9.2725	13
Enuresis	2.50	5.06	10.25	25.1361	8
Erection increased	2.58	8.28	26.58	18.0619	3
Extrapyramidal disorder	7.23	9.35	12.09	418.9275	62
Flat affect	1.83	5.81	18.45	11.4388	3
Galactorrhoea	3.67	6.14	10.28	61.7254	15
Gaze palsy	1.22	2.74	6.14	6.5089	6
Glycosylated haemoglobin increased	1.91	6.08	19.34	12.1743	3
Gynaecomastia	4.88	6.14	7.73	302.4180	73
Hallucination, auditory	1.55	2.74	4.85	13.0356	13
Heart rate decreased	1.02	2.47	5.97	4.2856	5
Hepatic steatosis	4.35	8.52	16.70	56.1300	9
Hiccups	6.44	14.97	34.81	70.1616	6
Homicidal ideation	2.98	6.04	12.24	32.1425	8
Hospitalisation	3.17	5.14	8.33	54.6741	18
Hyperglycaemia	1.21	2.06	3.48	7.4967	14
Hyperprolactinaemia	1.92	3.32	5.75	20.6081	13
Hypomania	5.28	12.17	28.05	56.2327	6
Impulsive behaviour	1.12	3.02	8.12	5.2781	4
Incontinence	1.81	4.90	13.27	11.9587	4
Increased appetite	5.83	9.27	14.72	130.9873	19
Insomnia	1.44	2.08	3.01	15.6293	29
Insulin resistance	5.28	14.83	41.68	46.3067	4
Intentional self-injury	1.80	2.91	4.69	20.8683	17
Irritability	1.48	2.29	3.55	14.3689	20
Joint stiffness	1.10	3.45	10.83	5.0740	3
Ketoacidosis	1.41	3.82	10.30	8.0820	4
Libido increased	16.30	51.90	165.33	142.6494	4
Liver function test increased	1.43	3.22	7.22	8.9570	6
Logorrhoea	2.21	5.41	13.21	17.2503	5
Mania	2.54	4.32	7.33	34.5793	15
Metabolic syndrome	14.87	40.55	110.56	146.9678	5
Motor dysfunction	1.51	3.67	8.90	9.4338	5
Muscle contractions involuntary	2.08	4.69	10.58	16.8263	6
Muscle rigidity	4.71	7.14	10.83	115.3471	23
Muscle twitching	1.14	2.12	3.95	5.8148	10
Musculoskeletal stiffness	1.57	2.50	3.97	15.9372	18
Neuroleptic malignant syndrome	10.86	14.48	19.32	565.8871	50

Neutrophil count decreased	1.18	2.65	5.93	6.0403	6
Non-alcoholic fatty liver	14.39	55.61	214.87	112.6287	3
Non-alcoholic steatohepatitis	15.04	47.19	148.04	132.6175	4
Obesity	6.44	8.70	11.76	282.0825	44
Oculogyric crisis	10.63	15.11	21.48	401.8612	34
Off label use	6.89	7.87	8.99	1,161.7047	205
Oromandibular dystonia	6.26	15.82	39.99	61.9047	5
Painful erection	12.92	48.66	183.26	101.8553	3
Panic reaction	1.50	4.75	15.01	8.5643	3
Paranoia	1.48	3.33	7.47	9.5333	6
Parkinsonism	13.56	23.45	40.55	273.1822	15
Physical assault	4.44	12.36	34.42	38.1340	4
Polyneuropathy	1.33	4.19	13.20	7.0502	3
Post-traumatic stress disorder	4.09	13.42	44.02	31.2653	3
Posture abnormal	1.15	3.60	11.34	5.4961	3
Pregnancy	1.26	3.97	12.52	6.4770	3
Prescribed underdose	10.72	38.93	141.32	85.2842	4
Priapism	7.41	12.56	21.29	145.5963	15
Product use in unapproved indication	3.59	4.64	5.98	163.8267	60
Protrusion tongue	2.69	8.65	27.81	19.0348	3
Psychiatric symptom	1.39	4.37	13.81	7.5565	4
Psychomotor hyperactivity	2.09	3.42	5.61	26.7791	16
Psychotic behaviour	1.88	5.99	19.04	11.9217	3
Psychotic disorder	4.30	5.90	8.10	152.3902	40
Rabbit syndrome	18.62	77.86	325.52	142.2615	3
Raynaud's phenomenon	1.01	2.72	7.31	4.2569	4
Restlessness	1.44	2.39	3.98	12.0034	16
Rhabdomyolysis	1.19	2.21	4.12	6.5369	11
Salivary hypersecretion	1.83	3.69	7.45	15.3055	8
Schizophrenia	5.03	9.90	19.46	66.9220	9
Sedation	4.33	6.70	10.35	96.9418	24
Serotonin syndrome	1.64	3.69	8.29	11.4519	7
Sinus tachycardia	1.21	2.56	5.40	6.5292	7
Suicidal ideation	3.42	4.26	5.30	192.8747	82
Suicide attempt	2.31	2.94	3.74	82.2688	67
Tardive dyskinesia	7.03	10.37	15.29	211.9388	27
Tension headache	2.34	7.49	23.95	15.9440	3
Thinking abnormal	2.28	4.83	10.26	20.5250	7
Tic	2.96	4.47	6.75	60.0430	23
Tongue disorder	3.55	8.77	21.66	32.2430	5
Torticollis	2.86	5.80	11.76	30.4422	8
Tourette's disorder	2.82	6.38	14.46	25.9698	6
Treatment noncompliance	3.98	6.94	12.10	62.8367	13
Tremor	1.81	2.38	3.13	40.7071	51
Trismus	2.51	5.34	11.36	23.7545	7
Type 1 diabetes mellitus	4.10	6.34	9.79	90.1912	21
Type 2 diabetes mellitus	2.84	6.43	14.58	26.2539	6
Urinary retention	5.79	8.65	12.93	158.8863	25
Vision blurred	1.67	2.48	3.67	21.7678	25
Weight increased	9.78	11.47	13.47	1,320.3343	150
Withdrawal syndrome	1.47	2.74	5.12	10.8743	10
Wrong technique in product usage process	7.88	11.33	16.30	269.0440	31
Abasia	0.14	0.57	2.27	0.6666	2

Abdominal discomfort	0.35	0.94	2.50	0.0169	4
Abdominal distension	0.17	0.67	2.68	0.3268	2
Abdominal pain	0.08	0.16	0.33	31.7260	7
Abdominal pain lower	0.06	0.46	3.25	0.6441	1
Abdominal pain upper	0.15	0.34	0.76	7.7651	6
Abdominal tenderness	0.13	0.93	6.67	0.0047	1
Abnormal behaviour	0.74	1.14	1.77	0.3435	22
Abnormal dreams	0.15	1.10	7.87	0.0090	1
Abortion induced	0.36	1.46	5.87	0.2848	2
Abulia	0.96	7.21	53.97	5.0667	1
Accidental exposure to product	0.24	0.95	3.80	0.0059	2
Accidental exposure to product by child	0.10	0.69	4.90	0.1425	1
Accidental overdose	0.27	0.71	1.89	0.4842	4
Acidosis	0.12	0.87	6.22	0.0190	1
Acne	0.60	1.44	3.47	0.6627	5
Acute kidney injury	0.28	0.58	1.22	2.1143	8
Acute myopia	3.63	32.44	290.10	24.3776	1
Acute psychosis	0.85	3.46	14.08	3.4090	2
Adverse drug reaction	0.16	1.12	8.00	0.0125	1
Adverse reaction	0.36	2.60	18.78	0.9616	1
Agranulocytosis	0.61	1.46	3.53	0.7302	5
Alanine aminotransferase increased	0.56	1.01	1.82	0.0005	11
Alcohol poisoning	0.87	6.49	48.32	4.4216	1
Alcohol withdrawal syndrome	99.90	99.90	99.90	129.7625	1
Alopecia	0.13	0.40	1.24	2.7092	3
Altered state of consciousness	0.09	0.37	1.47	2.1770	2
Amenorrhoea	0.60	1.60	4.28	0.8834	5
Amnesia	0.72	1.52	3.20	1.2402	7
Anaemia	0.06	0.25	1.01	4.4764	2
Anal incontinence	0.46	1.85	7.48	0.7758	2
Anaphylactic reaction	0.18	0.34	0.65	11.6420	9
Anaphylactic shock	0.10	0.29	0.91	5.0845	3
Anaphylactoid reaction	0.04	0.29	2.03	1.7844	1
Angioedema	0.08	0.22	0.58	11.4714	4
Anhedonia	0.09	0.63	4.49	0.2166	1
Anti-GAD antibody positive	5.89	64.88	715.20	41.9315	1
Anti-ganglioside antibody positive	99.90	99.90	99.90	129.7625	1
Antiandrogen therapy	99.90	99.90	99.90	129.7625	1
Anticonvulsant drug level increased	0.25	1.83	13.15	0.3697	1
Antidepressant drug level increased	3.03	25.95	222.02	19.9930	1
Antipsychotic drug level above therapeutic	2.61	21.63	179.54	16.8633	1
Anxiety	0.67	1.01	1.53	0.0024	22
Anxiety disorder	0.21	1.53	10.96	0.1796	1
Apgar score low	0.00	0.00	0.00	0.2081	1
Aphasia	0.62	1.50	3.61	0.8211	5
Appetite disorder	1.37	5.64	23.22	7.3215	2
Arrhythmia	0.56	1.34	3.22	0.4230	5
Arthralgia	0.16	0.33	0.66	11.1395	8
Aspartate aminotransferase increased	0.34	0.71	1.48	0.8514	7
Asthenia	0.29	0.50	0.87	6.3932	13
Asthmatic crisis	0.11	0.80	5.72	0.0492	1
Ataxia	0.11	0.45	1.78	1.3822	2
Atrial fibrillation	0.26	1.85	13.34	0.3878	1

Atrioventricular block first degree	0.89	3.60	14.68	3.6634	2
Attention deficit/hyperactivity disorder	0.49	1.30	3.48	0.2761	4
Auditory disorder	0.30	2.20	15.86	0.6433	1
Autism spectrum disorder	0.98	2.06	4.33	3.7404	7
Autoimmune thyroiditis	0.18	1.31	9.39	0.0730	1
Back pain	0.09	0.28	0.86	5.7203	3
Balance disorder	0.61	1.47	3.55	0.7478	5
Bicytopenia	2.56	10.81	45.72	16.4438	2
Bile duct stenosis	3.03	25.95	222.02	19.9930	1
Biliary colic	0.00	0.00	0.00	0.3546	1
Biliary dilatation	2.61	21.63	179.54	16.8633	1
Bilirubin conjugated increased	0.90	3.66	14.89	3.7533	2
Bite	1.14	8.65	65.45	6.3440	1
Blepharospasm	0.85	3.46	14.08	3.4090	2
Blindness	0.15	0.61	2.45	0.4952	2
Blister	0.01	0.10	0.73	7.8843	1
Blood bilirubin increased	0.54	1.30	3.12	0.3335	5
Blood bilirubin unconjugated increased	0.63	4.63	34.04	2.7522	1
Blood cholesterol increased	0.31	1.24	4.97	0.0892	2
Blood copper increased	4.50	43.25	415.62	30.9584	1
Blood creatinine decreased	0.37	2.70	19.57	1.0516	1
Blood creatinine increased	0.02	0.14	0.97	5.4460	1
Blood glucose fluctuation	0.21	1.49	10.70	0.1602	1
Blood glucose increased	0.71	1.37	2.64	0.8966	10
Blood insulin decreased	4.50	43.25	415.62	30.9584	1
Blood insulin increased	0.68	4.99	36.76	3.0734	1
Blood lactate dehydrogenase increased	0.15	0.60	2.41	0.5244	2
Blood potassium decreased	0.17	1.20	8.60	0.0335	1
Blood potassium increased	0.32	2.32	16.73	0.7358	1
Blood pressure abnormal	0.35	2.50	18.04	0.8795	1
Blood pressure decreased	0.11	0.34	1.06	3.7861	5
Blood pressure fluctuation	0.31	2.24	16.14	0.6728	1
Blood pressure increased	0.98	1.89	3.64	3.7271	10
Blood pressure systolic increased	0.63	4.63	34.04	2.7522	1
Blood triglycerides increased	0.43	1.35	4.20	0.2658	3
Blood urine present	0.16	1.15	8.22	0.0190	1
Blunted affect	3.53	15.27	66.02	23.8587	2
Body dysmorphic disorder	2.03	16.22	129.62	12.6955	1
Body height increased	2.28	18.54	150.59	14.5180	1
Body mass index increased	2.56	10.81	45.72	16.4438	2
Body temperature fluctuation	0.37	2.70	19.57	1.0516	1
Body temperature increased	0.43	0.95	2.11	0.0168	6
Bradycardia	0.28	0.67	1.62	0.7853	5
Brain injury	0.14	1.00	7.14	0.0000	1
Brain neoplasm	0.18	1.31	9.39	0.0730	1
Brain oedema	0.05	0.36	2.59	1.1067	1
Breast disorder	1.66	12.98	101.31	10.0489	1
Bronchitis	0.06	0.44	3.15	0.6994	1
Bronchopulmonary dysplasia	0.00	0.00	0.00	0.1696	1
Bruxism	0.75	3.05	12.40	2.6991	2
Bundle branch block	3.35	14.42	62.09	22.4793	2
Bundle branch block left	1.66	12.98	101.31	10.0489	1
Burning sensation	0.06	0.45	3.23	0.6563	1

C-reactive protein increased	0.03	0.21	1.48	3.0134	1
Cardiac arrest	0.30	0.71	1.71	0.5771	5
Cardiac disorder	0.07	0.52	3.71	0.4388	1
Cardiac failure	0.04	0.31	2.21	1.5241	1
Cardiac failure congestive	0.11	0.77	5.51	0.0667	1
Cardio-respiratory arrest	0.94	1.98	4.17	3.3462	7
Cardiopulmonary failure	0.32	2.28	16.43	0.7036	1
Cataract	0.81	2.53	7.92	2.7193	3
Cellulitis	0.03	0.23	1.64	2.5641	1
Cerebellar infarction	1.08	8.11	61.12	5.8672	1
Cerebral infarction	0.11	0.77	5.48	0.0699	1
Ceruloplasmin decreased	99.90	99.90	99.90	129.7625	1
Chest pain	0.36	0.68	1.26	1.5483	12
Chills	0.10	0.28	0.73	7.6729	5
Choking	0.51	2.06	8.32	1.0740	2
Cholangitis sclerosing	0.73	5.41	39.94	3.4484	1
Cholecystitis	0.13	0.90	6.44	0.0108	1
Cholelithiasis	0.03	0.23	1.60	2.6668	1
Chorea	0.21	1.51	10.83	0.1697	1
Choreoathetosis	0.79	3.20	13.02	2.9603	2
Chromaturia	0.28	1.14	4.58	0.0333	2
Circulatory collapse	0.10	0.38	1.53	1.9910	2
Circumstance or information capable of leading to medication error	2.56	10.81	45.72	16.4438	2
Clonic convulsion	0.18	1.31	9.39	0.0730	1
Clonus	0.08	0.58	4.15	0.2994	1
Clostridium test positive	1.08	8.11	61.12	5.8672	1
Coeliac disease	0.17	1.22	8.77	0.0407	1
Cognitive disorder	0.63	1.40	3.11	0.6665	6
Cold sweat	0.25	0.77	2.39	0.2067	3
Coma	0.26	0.64	1.53	1.0455	5
Coma scale abnormal	0.22	1.54	11.09	0.1899	1
Completed suicide	1.20	1.96	3.21	7.4766	16
Compulsions	0.68	4.99	36.76	3.0734	1
Concussion	0.16	1.11	7.93	0.0106	1
Condition aggravated	0.80	1.30	2.12	1.1055	16
Conduct disorder	0.40	2.88	20.91	1.2039	1
Conduction disorder	2.07	8.65	36.17	12.6889	2
Confusional state	0.69	1.16	1.96	0.3195	14
Conjunctivitis	0.03	0.22	1.59	2.6888	1
Consciousness fluctuating	0.51	3.71	27.05	1.9226	1
Constipation	0.86	1.60	2.97	2.2077	10
Conversion disorder	0.13	0.90	6.44	0.0108	1
Coordination abnormal	0.09	0.68	4.82	0.1548	1
Corneal disorder	0.91	6.83	50.99	4.7276	1
Corneal oedema	0.76	5.64	41.75	3.6604	1
Coronary artery stenosis	1.22	9.27	70.45	6.8853	1
Cough	0.02	0.09	0.35	19.0064	2
Crohn's disease	0.15	0.62	2.48	0.4665	2
Crying	0.36	0.80	1.79	0.2934	6
Crystal urine present	2.61	21.63	179.54	16.8633	1
Cyanosis	0.31	0.70	1.55	0.7901	6
Cyst	0.30	2.20	15.86	0.6433	1

Cytotoxic oedema	0.87	6.49	48.32	4.4216	1
Death	0.47	0.87	1.62	0.1878	10
Decreased appetite	0.41	0.70	1.17	1.8675	14
Decreased immune responsiveness	0.41	2.95	21.39	1.2599	1
Deep vein thrombosis	0.24	0.64	1.71	0.8136	4
Dehydration	0.08	0.32	1.30	2.8245	2
Delayed puberty	1.43	5.90	24.31	7.7836	2
Delirium	0.36	0.97	2.60	0.0032	4
Demyelination	0.17	1.21	8.68	0.0370	1
Dental caries	0.21	1.53	10.96	0.1796	1
Depressed level of consciousness	0.23	0.56	1.33	1.7861	5
Depressed mood	0.52	1.16	2.59	0.1321	6
Depression	0.88	1.27	1.82	1.6724	29
Depression suicidal	0.42	3.02	21.90	1.3187	1
Depressive symptom	0.18	1.28	9.20	0.0625	1
Derealisation	1.65	6.83	28.29	9.4562	2
Dermatillomania	1.31	9.98	76.26	7.5051	1
Developmental delay	0.07	0.47	3.34	0.6018	1
Diabetes insipidus	0.22	1.58	11.36	0.2119	1
Diabetes mellitus inadequate control	0.19	1.35	9.69	0.0906	1
Diabetic coma	0.57	4.19	30.65	2.3493	1
Diabetic ketoacidotic hyperglycaemic coma	3.63	32.44	290.10	24.3776	1
Diarrhoea	0.21	0.38	0.71	10.1586	10
Diastolic hypotension	2.28	18.54	150.59	14.5180	1
Diet refusal	2.14	8.95	37.47	13.2125	2
Diplopia	0.35	0.93	2.48	0.0209	4
Discomfort	0.05	0.35	2.51	1.1874	1
Disorientation	0.19	0.58	1.81	0.8899	3
Dissociative disorder	0.32	2.32	16.73	0.7358	1
Distractibility	0.43	3.09	22.44	1.3807	1
Disturbance in attention	0.27	0.61	1.36	1.4867	8
Disturbance in sexual arousal	14.46	86.51	517.39	101.4257	2
Disturbance in social behaviour	0.17	1.25	8.94	0.0487	1
Dizziness	0.38	0.53	0.74	14.2157	33
Drowning	0.76	5.64	41.75	3.6604	1
Drug administration error	0.14	0.57	2.30	0.6302	2
Drug clearance decreased	0.23	1.66	11.95	0.2615	1
Drug dose omission	0.61	1.47	3.55	0.7478	5
Drug effect decreased	0.00	0.00	0.00	1.6122	1
Drug eruption	0.15	0.58	2.34	0.5893	2
Drug ineffective	1.41	1.76	2.19	25.0313	76
Drug ineffective for unapproved indication	0.08	0.55	3.95	0.3567	1
Drug intolerance	0.00	0.00	0.00	1.2880	1
Drug level above therapeutic	0.30	2.20	15.86	0.6433	1
Drug level below therapeutic	0.30	2.16	15.60	0.6150	1
Drug level fluctuating	0.65	4.81	35.35	2.9068	1
Drug level increased	0.12	0.48	1.93	1.1155	2
Drug prescribing error	0.11	0.79	5.65	0.0548	1
Drug reaction with eosinophilia and systemic symptoms	0.08	0.33	1.34	2.6657	2
Drug resistance	0.31	1.23	4.95	0.0853	2
Drug screen false positive	1.66	12.98	101.31	10.0489	1
Drug screen positive	0.43	3.09	22.44	1.3807	1

Drug use disorder	0.40	0.83	1.75	0.2330	7
Drug withdrawal syndrome	0.04	0.27	1.95	1.9269	1
Drug-induced liver injury	0.22	0.87	3.50	0.0381	2
Dry eye	0.13	0.93	6.62	0.0057	1
Dry mouth	0.21	0.86	3.44	0.0478	2
Dry skin	0.06	0.41	2.89	0.8637	1
Dysgeusia	0.32	1.30	5.25	0.1406	2
Dysphagia	0.72	1.34	2.49	0.8480	10
Dysphemia	0.86	3.51	14.27	3.4914	2
Dysphonia	0.22	0.87	3.48	0.0400	2
Dyspnoea	0.25	0.39	0.62	18.1962	19
Dyspnoea exertional	0.17	1.21	8.68	0.0370	1
Dyspraxia	0.83	6.18	45.91	4.1441	1
Dyssomnia	2.03	16.22	129.62	12.6955	1
Dysstasia	0.07	0.53	3.74	0.4276	1
Ear infection	0.28	1.14	4.60	0.0356	2
Eating disorder	0.62	1.93	6.02	1.3199	3
Echolalia	1.14	8.65	65.45	6.3440	1
Echopraxia	5.89	64.88	715.20	41.9315	1
Ectopic pregnancy	1.41	10.81	83.12	8.2214	1
Ejaculation failure	2.61	21.63	179.54	16.8633	1
Electrocardiogram P wave abnormal	2.03	16.22	129.62	12.6955	1
Electrocardiogram PR prolongation	1.83	14.42	113.74	11.2391	1
Electrocardiogram ST segment elevation	0.44	3.16	23.00	1.4459	1
Electrocardiogram abnormal	0.49	1.97	7.94	0.9358	2
Electrocardiogram change	0.70	5.19	38.28	3.2534	1
Electrocardiogram repolarisation abnormality	6.24	28.84	133.36	43.9724	2
Electroconvulsive therapy	99.90	99.90	99.90	129.7625	1
Electroencephalogram abnormal	0.40	1.24	3.87	0.1421	3
Emergency care	1.83	14.42	113.74	11.2391	1
Encephalitis	0.38	1.19	3.71	0.0907	3
Encephalitis allergic	8.12	129.76	2,073.78	63.8854	1
Encephalitis autoimmune	0.63	4.63	34.04	2.7522	1
Encopresis	0.83	6.18	45.91	4.1441	1
Endocrine disorder	1.14	8.65	65.45	6.3440	1
Energy increased	0.68	4.99	36.76	3.0734	1
Eosinophilia	0.04	0.28	2.01	1.8199	1
Epilepsy	0.42	0.81	1.55	0.4099	9
Epistaxis	0.35	0.78	1.73	0.3896	6
Epstein-Barr virus antibody positive	0.80	5.90	43.73	3.8914	1
Eructation	1.57	6.49	26.82	8.8441	2
Erythema	0.05	0.12	0.33	25.1425	4
Euphoric mood	0.11	0.75	5.38	0.0795	1
Excoriation	0.49	3.60	26.28	1.8314	1
Exercise lack of	5.89	64.88	715.20	41.9315	1
Exercise tolerance decreased	0.14	1.01	7.25	0.0002	1
Extraocular muscle disorder	3.03	25.95	222.02	19.9930	1
Extrasystoles	0.18	1.28	9.20	0.0625	1
Extremity necrosis	1.41	10.81	83.12	8.2214	1
Eye disorder	0.09	0.65	4.65	0.1849	1
Eye inflammation	0.35	2.50	18.04	0.8795	1
Eye movement disorder	0.35	0.94	2.50	0.0179	5
Eye pain	0.04	0.30	2.15	1.6080	1

Eye swelling	0.03	0.20	1.39	3.3253	1
Eyelid ptosis	0.15	1.05	7.54	0.0028	1
Face oedema	0.02	0.12	0.87	6.2939	1
Facial asymmetry	1.14	8.65	65.45	6.3440	1
Facial nerve disorder	1.83	14.42	113.74	11.2391	1
Facial paralysis	0.54	1.31	3.15	0.3546	5
Faecaloma	0.46	3.33	24.20	1.5874	1
Fall	0.11	0.30	0.80	6.5424	4
Fatigue	0.83	1.09	1.44	0.3601	49
Fear	0.54	1.44	3.85	0.5283	4
Feeding disorder	0.00	0.00	0.00	0.7247	1
Feeling abnormal	0.37	0.78	1.64	0.4265	8
Feeling cold	0.17	0.67	2.68	0.3268	2
Feeling drunk	0.47	3.41	24.86	1.6641	1
Feeling guilty	3.96	17.30	75.60	27.1070	2
Feeling hot	0.09	0.35	1.41	2.3993	2
Feelings of worthlessness	1.41	10.81	83.12	8.2214	1
Femur fracture	0.25	1.80	12.96	0.3523	1
Fibrosis	2.29	9.61	40.39	14.3697	2
Flatulence	0.16	1.13	8.07	0.0145	1
Fluid retention	0.75	3.05	12.40	2.6991	2
Flushing	0.01	0.10	0.74	7.7918	1
Foaming at mouth	0.19	1.38	9.90	0.1038	1
Focal dyscognitive seizures	0.15	1.07	7.67	0.0049	1
Foetal exposure during pregnancy	0.02	0.09	0.34	19.7913	4
Folliculitis	0.44	3.16	23.00	1.4459	1
Food craving	1.14	8.65	65.45	6.3440	1
Foot amputation	8.12	129.76	2,073.78	63.8854	1
Foot fracture	0.65	4.81	35.35	2.9068	1
Formication	0.65	2.65	10.73	2.0115	2
Fracture	0.00	0.00	0.00	0.5088	1
Frustration tolerance decreased	0.45	3.24	23.58	1.5147	1
Full blood count decreased	1.41	10.81	83.12	8.2214	1
Fumbling	3.63	32.44	290.10	24.3776	1
Fungal infection	0.13	0.89	6.39	0.0123	1
Gait disturbance	0.40	0.77	1.48	0.6295	9
Gamma-glutamyltransferase increased	0.67	1.61	3.88	1.1435	5
Gastroenteritis	0.21	0.85	3.40	0.0541	2
Gastrointestinal disorder	0.33	1.03	3.21	0.0031	3
Gastrointestinal haemorrhage	0.18	0.71	2.87	0.2265	2
Gastrointestinal pain	0.64	2.60	10.51	1.9236	2
Gastrointestinal sounds abnormal	0.35	2.50	18.04	0.8795	1
Gastrointestinal tube insertion	0.00	0.00	0.00	0.1619	1
Gastrooesophageal reflux disease	0.06	0.46	3.29	0.6259	1
Gastrostomy	0.65	4.81	35.35	2.9068	1
General physical condition abnormal	0.68	4.99	36.76	3.0734	1
General physical health deterioration	0.03	0.21	1.51	2.9320	1
Generalised oedema	0.08	0.60	4.24	0.2743	1
Generalised tonic-clonic seizure	0.27	0.57	1.20	2.2332	7
Gilbert's syndrome	0.52	3.82	27.86	2.0195	1
Gingival bleeding	0.18	1.31	9.39	0.0730	1
Glomerular filtration rate decreased	0.26	1.85	13.34	0.3878	1
Glucose tolerance impaired	0.94	3.82	15.56	4.0396	2

Granuloma	0.27	1.94	13.94	0.4466	1
Granulomatous dermatitis	99.90	99.90	99.90	129.7625	1
Growth retardation	0.03	0.22	1.57	2.7477	1
Haematemesis	0.16	0.64	2.58	0.3970	2
Haematuria	0.03	0.20	1.44	3.1320	1
Haemodialysis	0.80	5.90	43.73	3.8914	1
Haemoptysis	0.08	0.59	4.18	0.2893	1
Haemorrhage	0.00	0.00	0.00	4.6292	1
Hallucination	0.83	1.30	2.04	1.3436	19
Hallucination, visual	0.66	1.38	2.91	0.7354	7
Hallucinations, mixed	0.15	1.09	7.80	0.0074	1
Hand-foot-and-mouth disease	1.41	10.81	83.12	8.2214	1
Head banging	0.47	3.41	24.86	1.6641	1
Head discomfort	0.22	1.54	11.09	0.1899	1
Head injury	0.17	0.68	2.73	0.2975	2
Headache	0.15	0.23	0.34	65.8448	24
Heart disease congenital	0.08	0.54	3.87	0.3836	1
Heart rate increased	0.99	1.70	2.93	3.7061	15
Heart rate irregular	0.93	2.91	9.11	3.6683	3
Heat illness	2.61	21.63	179.54	16.8633	1
Heat stroke	3.18	13.66	58.59	21.2321	2
Hemiparesis	0.05	0.36	2.56	1.1335	1
Hemiplegia	0.13	0.96	6.87	0.0016	1
Hepatic enzyme increased	0.29	0.71	1.70	0.6115	5
Hepatic failure	0.13	0.51	2.05	0.9238	2
Hepatic fibrosis	1.74	7.21	29.92	10.1343	2
Hepatic function abnormal	0.54	1.14	2.39	0.1147	7
Hepatitis	0.18	0.54	1.69	1.1480	3
Hepatitis B	0.32	2.28	16.43	0.7036	1
Hepatitis cholestatic	0.21	1.47	10.58	0.1511	1
Hepatocellular injury	0.05	0.35	2.52	1.1807	1
Hepatotoxicity	0.23	0.94	3.76	0.0084	2
Hernia repair	0.00	0.00	0.00	0.0308	1
Herpes simplex test positive	4.50	43.25	415.62	30.9584	1
High risk sexual behaviour	8.12	129.76	2,073.78	63.8854	1
Histrionic personality disorder	5.89	64.88	715.20	41.9315	1
Hodgkin's disease	0.21	1.47	10.58	0.1511	1
Hostility	0.21	1.47	10.58	0.1511	1
Hot flush	0.08	0.60	4.26	0.2693	1
Hunger	0.35	2.54	18.40	0.9196	1
Hyperacusis	0.55	1.71	5.33	0.8688	3
Hyperglycaemic hyperosmolar nonketotic syndrome	1.41	10.81	83.12	8.2214	1
Hyperhidrosis	0.86	1.36	2.16	1.7209	18
Hyperkinesia	0.33	2.36	17.04	0.7694	1
Hypernatraemia	0.24	1.73	12.44	0.3042	1
Hyperosmolar state	8.12	129.76	2,073.78	63.8854	1
Hyperphagia	0.91	3.71	15.11	3.8459	2
Hyperpyrexia	0.03	0.22	1.60	2.6742	1
Hyperreflexia	0.54	2.18	8.81	1.2584	2
Hypersensitivity	0.06	0.16	0.43	17.9454	4
Hypersexuality	1.02	7.63	57.32	5.4443	1
Hypersomnia	0.13	0.51	2.03	0.9523	2
Hypertension	0.27	0.56	1.18	2.3697	7

Hypertensive crisis	0.26	1.88	13.53	0.4066	1
Hyperthermia	0.36	1.11	3.45	0.0320	3
Hyperthermia malignant	0.08	0.59	4.20	0.2842	1
Hypertonia	0.03	0.23	1.65	2.5495	1
Hypertrichosis	0.30	2.16	15.60	0.6150	1
Hypertriglyceridaemia	0.11	0.79	5.61	0.0577	1
Hyperventilation	0.13	0.51	2.06	0.9125	3
Hypoaesthesia	0.04	0.15	0.59	9.8147	2
Hypoaesthesia oral	0.12	0.88	6.30	0.0155	1
Hypocalcaemia	0.10	0.69	4.95	0.1344	1
Hypoglycaemia	0.24	0.64	1.70	0.8319	4
Hypogonadism	1.14	8.65	65.45	6.3440	1
Hypokalaemia	0.15	0.59	2.35	0.5792	2
Hypokinesia	0.96	2.58	6.94	3.8063	4
Hypophagia	0.10	0.73	5.20	0.1003	1
Hypotension	0.30	0.54	0.97	4.4840	11
Hypothermia	0.20	0.82	3.29	0.0799	2
Hypothyroidism	0.41	1.28	3.99	0.1828	3
Hypotonia	0.08	0.33	1.32	2.7208	3
Hypotonia neonatal	0.00	0.00	0.00	0.0925	1
Idiopathic intracranial hypertension	0.04	0.32	2.27	1.4476	1
Illusion	0.14	0.98	6.97	0.0006	1
Immune thrombocytopenic purpura	0.06	0.44	3.14	0.7056	1
Impaired reasoning	4.50	43.25	415.62	30.9584	1
Impaired self-care	4.22	18.54	81.50	29.0371	2
Implant site infection	0.62	1.93	6.02	1.3199	3
Imprisonment	3.63	32.44	290.10	24.3776	1
Impulse-control disorder	1.84	7.63	31.75	10.8895	2
Inappropriate affect	0.24	1.75	12.61	0.3196	1
Inappropriate antidiuretic hormone secretion	0.14	1.01	7.19	0.0000	1
Inappropriate schedule of drug administration	0.01	0.06	0.46	13.5912	1
Incoherent	0.15	1.09	7.80	0.0074	1
Incorrect dose administered	0.42	1.01	2.44	0.0009	5
Infection	0.07	0.29	1.16	3.4629	2
Influenza	0.09	0.37	1.48	2.1503	2
Influenza like illness	0.02	0.18	1.26	3.8414	1
Injection site pain	0.01	0.04	0.27	24.6747	1
Injury	0.02	0.18	1.26	3.8189	1
Insulin C-peptide decreased	3.63	32.44	290.10	24.3776	1
Intention tremor	2.78	11.80	50.13	18.1178	2
Intentional overdose	0.81	1.21	1.82	0.8459	23
Intentional product misuse	0.36	0.97	2.59	0.0036	4
Intentional product use issue	0.23	1.62	11.65	0.2357	1
Intracranial venous sinus thrombosis	0.18	1.27	9.11	0.0577	1
Irregular breathing	0.68	4.99	36.76	3.0734	1
Irritable bowel syndrome	0.17	1.21	8.68	0.0370	1
Ischaemic cardiomyopathy	8.12	129.76	2,073.78	63.8854	1
Jaundice	0.03	0.19	1.32	3.5941	1
Jaw disorder	0.65	4.81	35.35	2.9068	1
Joint crepitation	0.96	7.21	53.97	5.0667	1
Joint effusion	0.15	1.08	7.73	0.0061	1
Joint hyperextension	0.73	5.41	39.94	3.4484	1
Joint swelling	0.12	0.49	1.97	1.0507	2

Ketonuria	1.34	5.52	22.71	7.1051	2
Ketosis	0.55	4.06	29.66	2.2323	1
Kleptomania	8.12	129.76	2,073.78	63.8854	1
Laboratory test abnormal	0.22	1.58	11.36	0.2119	1
Laceration	0.17	1.20	8.60	0.0335	1
Learning disability	0.27	1.94	13.94	0.4466	1
Lethargy	0.50	0.97	1.86	0.0113	9
Leukocytosis	0.15	0.59	2.37	0.5591	2
Leukopenia	0.83	1.43	2.47	1.6933	13
Libido disorder	99.90	99.90	99.90	129.7625	1
Lip disorder	0.43	3.09	22.44	1.3807	1
Lip swelling	0.02	0.14	0.97	5.4688	1
Lipase increased	0.08	0.56	3.97	0.3514	1
Listless	0.08	0.57	4.04	0.3303	2
Live birth	0.54	3.93	28.73	2.1225	2
Liver disorder	0.49	1.30	3.48	0.2761	4
Liver function test abnormal	0.05	0.33	2.33	1.3785	2
Liver transplant	0.36	2.60	18.78	0.9616	1
Lividity	0.65	4.81	35.35	2.9068	1
Loss of consciousness	0.53	0.79	1.19	1.2851	23
Loss of personal independence in daily activities	0.07	0.52	3.70	0.4444	1
Low birth weight baby	0.51	3.71	27.05	1.9226	1
Lower limb fracture	1.40	5.77	23.75	7.5475	2
Lung infection	0.15	1.08	7.73	0.0061	1
Lymphadenopathy	0.04	0.16	0.66	8.5576	2
Lymphocytosis	0.22	1.58	11.36	0.2119	1
Lymphopenia	0.12	0.85	6.10	0.0249	1
Macroglossia	1.31	9.98	76.26	7.5051	1
Major depression	0.18	1.31	9.39	0.0730	1
Malaise	0.24	0.41	0.69	12.0369	15
Mastication disorder	0.54	3.93	28.73	2.1225	1
Mastitis	2.66	11.28	47.82	17.2470	2
Maternal exposure during pregnancy	0.39	2.82	20.44	1.1507	2
Medication error	0.25	0.60	1.45	1.2978	5
Meige's syndrome	99.90	99.90	99.90	129.7625	1
Memory impairment	0.18	0.55	1.71	1.1047	3
Mental disorder	0.45	1.22	3.25	0.1518	4
Mental impairment	0.99	2.39	5.79	3.9907	6
Mental status changes	0.17	0.70	2.81	0.2572	2
Metrorrhagia	0.39	1.58	6.38	0.4239	2
Micturition urgency	0.39	2.82	20.44	1.1507	1
Migraine	0.02	0.15	1.04	4.9972	1
Mobility decreased	0.07	0.48	3.42	0.5600	1
Monocyte count increased	0.68	4.99	36.76	3.0734	1
Mood altered	0.39	1.05	2.80	0.0090	4
Mood swings	0.47	1.12	2.70	0.0645	5
Movement disorder	0.05	0.35	2.46	1.2348	1
Multiple organ dysfunction syndrome	0.24	0.74	2.31	0.2660	3
Muscle contracture	0.21	1.49	10.70	0.1602	1
Muscle spasms	0.99	1.62	2.65	3.8051	16
Muscle tightness	0.86	2.30	6.17	2.8805	4
Muscular weakness	0.07	0.22	0.68	8.3633	3
Musculoskeletal pain	0.04	0.30	2.16	1.6010	1

Mutism	0.34	2.45	17.69	0.8411	1
Myalgia	0.29	0.53	0.95	4.7423	11
Mydriasis	0.48	1.06	2.37	0.0217	6
Myeloid leukaemia	0.73	5.41	39.94	3.4484	1
Myoclonus	0.05	0.33	2.37	1.3373	1
Myoglobin urine present	2.61	21.63	179.54	16.8633	1
Myopia	0.57	2.32	9.37	1.4720	2
Myositis	0.34	1.37	5.50	0.1942	2
Nausea	0.37	0.51	0.70	19.0674	39
Neck pain	0.18	0.57	1.77	0.9775	3
Necrosis	0.29	2.06	14.84	0.5369	1
Negativism	0.38	2.76	20.00	1.0999	1
Neonatal respiratory distress syndrome	0.00	0.00	0.00	0.6707	2
Neonatal tachycardia	0.00	0.00	0.00	0.0154	1
Neoplasm malignant	0.35	2.50	18.04	0.8795	1
Nervousness	0.16	0.66	2.64	0.3526	2
Neuralgia	0.11	0.77	5.48	0.0699	1
Neutropenia	0.73	1.22	2.02	0.5845	15
Neutrophil count increased	0.19	1.40	10.00	0.1108	1
Nightmare	0.48	1.15	2.77	0.0952	5
Nipple disorder	2.03	16.22	129.62	12.6955	1
Nipple exudate bloody	99.90	99.90	99.90	129.7625	1
Nipple resection	99.90	99.90	99.90	129.7625	1
No adverse event	0.08	0.20	0.54	12.5824	5
Nystagmus	0.23	0.94	3.76	0.0084	2
Obsessive thoughts	0.24	1.75	12.61	0.3196	1
Obsessive-compulsive disorder	0.71	1.92	5.13	1.7264	4
Obsessive-compulsive symptom	3.63	32.44	290.10	24.3776	1
Ocular icterus	0.14	0.98	6.97	0.0006	1
Oedema	0.27	0.65	1.57	0.9103	5
Oedema peripheral	0.20	0.54	1.43	1.6054	4
Oesophageal spasm	3.03	25.95	222.02	19.9930	1
Onychalgia	8.12	129.76	2,073.78	63.8854	1
Onychomadesis	2.46	10.38	43.79	15.7007	2
Open angle glaucoma	3.03	25.95	222.02	19.9930	1
Ophthalmoplegia	1.65	6.83	28.29	9.4562	2
Opisthotonus	0.16	1.12	8.00	0.0125	1
Oppositional defiant disorder	0.30	2.20	15.86	0.6433	1
Oropharyngeal pain	0.05	0.20	0.79	6.5370	2
Orthostatic hypotension	0.09	0.63	4.51	0.2120	2
Osteomyelitis	0.15	1.07	7.67	0.0049	1
Otitis media	0.11	0.77	5.51	0.0667	1
Ovarian cyst torsion	8.12	129.76	2,073.78	63.8854	1
Overdose	0.94	1.32	1.86	2.6377	35
Pain	0.11	0.22	0.45	22.1206	8
Pain in extremity	0.11	0.25	0.56	13.7023	6
Pain in jaw	0.13	0.96	6.87	0.0016	1
Pallor	0.17	0.33	0.66	10.9360	8
Palpitations	0.45	0.90	1.80	0.0911	8
Pancreatic disorder	0.65	4.81	35.35	2.9068	1
Pancreatitis	0.32	0.71	1.58	0.7198	6
Pancreatitis acute	0.10	0.38	1.53	1.9844	2
Pancytopenia	0.19	0.58	1.79	0.9360	3

Panic attack	0.49	1.31	3.50	0.2868	4
Papilloedema	0.05	0.33	2.36	1.3441	1
Paraesthesia	0.03	0.13	0.51	11.9334	2
Paralysis	0.04	0.31	2.23	1.4962	1
Paranoid personality disorder	0.00	0.00	0.00	0.0154	1
Paresis	0.13	0.95	6.82	0.0022	1
Parkinson's disease	7.71	37.07	178.34	54.6051	2
Partial seizures	0.27	1.07	4.31	0.0097	2
Pemphigoid	1.22	9.27	70.45	6.8853	1
Performance status decreased	0.18	1.30	9.30	0.0676	1
Pericardial effusion	0.08	0.55	3.88	0.3782	1
Pericarditis	0.12	0.88	6.30	0.0155	1
Peripheral coldness	0.26	0.82	2.55	0.1187	3
Peripheral swelling	0.02	0.11	0.80	7.0686	1
Peripheral vascular disorder	0.11	0.75	5.38	0.0795	1
Peroneal nerve palsy	1.17	4.81	19.70	5.8144	2
Persecutory delusion	0.57	4.19	30.65	2.3493	1
Personality change	0.06	0.40	2.83	0.9090	1
Personality disorder	0.67	2.73	11.07	2.1515	2
Petit mal epilepsy	0.31	0.96	3.00	0.0041	3
Pharyngeal oedema	0.15	0.60	2.41	0.5244	2
Pharyngitis streptococcal	0.38	1.53	6.15	0.3594	2
Photophobia	0.09	0.37	1.49	2.1236	2
Photosensitivity reaction	0.06	0.41	2.92	0.8445	1
Pigmentation disorder	0.20	1.41	10.11	0.1182	1
Pituitary tumour	0.61	4.47	32.83	2.6085	1
Platelet count decreased	0.28	0.76	2.03	0.3058	4
Pneumonia	0.04	0.16	0.63	9.0366	2
Pneumonia mycoplasmal	0.28	2.00	14.38	0.4899	1
Poisoning	0.10	0.69	4.90	0.1425	1
Pollakiuria	0.35	1.40	5.65	0.2291	2
Polycystic ovaries	0.42	3.02	21.90	1.3187	1
Polydipsia	0.89	2.80	8.78	3.4019	3
Polyuria	0.66	2.06	6.44	1.6115	3
Poor personal hygiene	5.89	64.88	715.20	41.9315	1
Poor quality sleep	0.11	0.78	5.55	0.0637	1
Post procedural haemorrhage	0.27	1.91	13.74	0.4262	1
Posterior reversible encephalopathy syndrome	0.11	0.44	1.75	1.4569	2
Posturing	0.54	3.93	28.73	2.1225	1
Pre-existing condition improved	1.31	9.98	76.26	7.5051	1
Premature baby	0.00	0.00	0.00	2.3848	2
Premature delivery	0.91	6.83	50.99	4.7276	1
Prescribed overdose	0.83	2.01	4.87	2.5209	5
Presyncope	0.01	0.08	0.54	11.2297	1
Product counterfeit	0.59	4.33	31.70	2.4745	1
Product quality issue	0.08	0.33	1.31	2.7553	2
Product substitution issue	0.31	1.23	4.95	0.0853	2
Product use issue	0.83	1.66	3.32	2.0571	8
Prolactin-producing pituitary tumour	3.63	32.44	290.10	24.3776	1
Protein urine present	0.35	2.50	18.04	0.8795	1
Pruritus	0.03	0.08	0.26	31.0427	3
Pseudogynaecomastia	4.50	43.25	415.62	30.9584	1
Pseudologia	99.90	99.90	99.90	129.7625	1

Pseudomonas infection	0.18	1.28	9.20	0.0625	1
Psoriasis	0.06	0.45	3.22	0.6625	1
Psychiatric decompensation	1.02	7.63	57.32	5.4443	1
Psychomotor retardation	0.28	2.00	14.38	0.4899	1
Pulmonary mass	0.37	2.65	19.17	1.0055	1
Pulse abnormal	0.12	0.86	6.14	0.0229	1
Pupil fixed	0.23	1.64	11.80	0.2483	1
Pupillary reflex impaired	0.74	3.02	12.25	2.6380	2
Pyrexia	0.08	0.13	0.22	91.4529	15
Rash	0.03	0.07	0.19	49.7426	4
Rash erythematous	0.07	0.26	1.05	4.1647	2
Rash generalised	0.10	0.30	0.92	5.0065	3
Rash macular	0.11	0.45	1.81	1.3329	2
Rash morbilliform	0.09	0.65	4.63	0.1893	1
Rash papular	0.04	0.27	1.89	2.0343	1
Rash pruritic	0.02	0.16	1.17	4.2477	1
Rash pustular	0.08	0.59	4.18	0.2893	1
Reduced facial expression	1.08	8.11	61.12	5.8672	1
Refusal of treatment by patient	2.61	21.63	179.54	16.8633	2
Regressive behaviour	0.46	3.33	24.20	1.5874	1
Renal disorder	0.10	0.71	5.03	0.1227	1
Renal impairment	0.03	0.21	1.51	2.9173	1
Respiratory arrest	0.12	0.49	1.94	1.0918	2
Respiratory depression	0.07	0.47	3.36	0.5898	1
Respiratory distress	0.08	0.31	1.26	2.9844	2
Respiratory rate increased	0.11	0.77	5.51	0.0667	1
Resting tremor	0.00	0.00	0.00	0.0385	1
Restless legs syndrome	0.27	1.97	14.16	0.4678	1
Retching	0.23	0.94	3.78	0.0075	2
Retinal tear	5.89	64.88	715.20	41.9315	1
Retracted nipple	99.90	99.90	99.90	129.7625	1
Rhinorrhoea	0.05	0.37	2.64	1.0667	1
Road traffic accident	0.16	1.15	8.22	0.0190	1
Scarlet fever	0.55	4.06	29.66	2.2323	1
Schizoaffective disorder	1.41	10.81	83.12	8.2214	1
Screaming	0.24	0.96	3.86	0.0031	2
Sebaceous glands overactivity	99.90	99.90	99.90	129.7625	1
Seborrhoea	6.24	28.84	133.36	43.9724	2
Seizure	0.85	1.07	1.36	0.3273	68
Self-injurious ideation	0.91	2.84	8.91	3.5059	3
Self-medication	2.28	18.54	150.59	14.5180	1
Seminal vesicular disorder	99.90	99.90	99.90	129.7625	1
Sensation of foreign body	0.12	0.87	6.18	0.0209	1
Sepsis	0.02	0.16	1.14	4.4138	1
Sever's disease	4.50	43.25	415.62	30.9584	1
Sexual activity increased	99.90	99.90	99.90	129.7625	1
Sexual dysfunction	0.87	6.49	48.32	4.4216	1
Sexually inappropriate behaviour	0.00	0.00	0.00	0.0539	1
Shock symptom	0.59	4.33	31.70	2.4745	1
Sinus bradycardia	0.91	2.84	8.91	3.5059	3
Sinusitis	0.04	0.25	1.81	2.1785	1
Skin discolouration	0.38	1.00	2.68	0.0001	4
Skin exfoliation	0.24	0.74	2.30	0.2695	3

Skin graft	4.50	43.25	415.62	30.9584	1
Skin haemorrhage	0.42	3.02	21.90	1.3187	1
Skin hyperpigmentation	0.22	1.58	11.36	0.2119	1
Skin odour abnormal	0.68	4.99	36.76	3.0734	1
Skin striae	0.12	0.84	5.98	0.0315	1
Sleep apnoea syndrome	0.13	0.96	6.87	0.0016	1
Sleep disorder	1.07	1.84	3.17	4.9154	13
Sleep paralysis	0.22	1.54	11.09	0.1899	1
Social avoidant behaviour	0.24	0.95	3.83	0.0044	2
Soliloquy	3.73	16.22	70.49	25.3922	2
Somnolence	1.09	1.45	1.94	6.3372	45
Spasmodic dysphonia	3.03	25.95	222.02	19.9930	1
Speech disorder	0.49	1.03	2.17	0.0075	7
Splenomegaly	0.07	0.50	3.60	0.4842	1
Staphylococcal infection	0.06	0.41	2.91	0.8509	1
Staring	0.61	1.92	5.99	1.2995	3
Status epilepticus	0.04	0.29	2.04	1.7703	1
Steatohepatitis	4.50	43.25	415.62	30.9584	1
Stevens-Johnson syndrome	0.04	0.14	0.56	10.6263	2
Stomatitis	0.04	0.27	1.89	2.0272	1
Strabismus	0.12	0.87	6.22	0.0190	1
Stress	0.10	0.71	5.06	0.1188	1
Stress urinary incontinence	3.63	32.44	290.10	24.3776	1
Stupor	0.79	2.46	7.71	2.5624	3
Substance-induced psychotic disorder	0.40	2.88	20.91	1.2039	1
Sudden cardiac death	1.14	8.65	65.45	6.3440	1
Sudden death	0.86	2.70	8.47	3.1563	3
Sudden onset of sleep	0.41	2.95	21.39	1.2599	1
Suicidal behaviour	0.78	2.43	7.62	2.4874	4
Supraventricular tachycardia	0.08	0.60	4.28	0.2644	1
Surgery	0.34	1.38	5.56	0.2077	2
Swelling	0.02	0.14	0.97	5.4460	1
Swelling face	0.05	0.22	0.88	5.5698	2
Swollen tongue	0.99	2.22	4.98	3.9827	6
Syncope	0.27	0.41	0.65	16.0894	19
Tachycardia	0.53	0.83	1.30	0.6416	19
Tachyphrenia	0.63	4.63	34.04	2.7522	2
Tachypnoea	0.31	0.97	3.00	0.0036	3
Teeth brittle	4.50	43.25	415.62	30.9584	1
Temperature intolerance	0.30	2.20	15.86	0.6433	1
Tension	0.23	1.64	11.80	0.2483	1
Tetany	0.22	1.60	11.50	0.2235	1
Therapeutic aspiration	3.63	32.44	290.10	24.3776	1
Therapeutic product ineffective	0.73	5.41	39.94	3.4484	1
Therapeutic response decreased	0.67	1.49	3.32	0.9539	6
Therapeutic response unexpected	0.07	0.51	3.67	0.4557	1
Therapy cessation	0.44	3.16	23.00	1.4459	1
Therapy non-responder	0.23	0.91	3.64	0.0188	2
Thirst	0.41	1.65	6.66	0.5098	2
Throat tightness	0.13	0.51	2.03	0.9580	2
Thrombocytopenia	0.15	0.35	0.84	6.0333	5
Thrombocytopenic purpura	0.12	0.88	6.30	0.0155	1
Thrombosis	0.05	0.38	2.72	1.0005	1

Thyroid function test abnormal	0.83	6.18	45.91	4.1441	1
Thyroxine increased	1.31	9.98	76.26	7.5051	1
Tinnitus	0.42	1.11	2.98	0.0462	4
Tongue biting	0.44	3.16	23.00	1.4459	1
Tongue discomfort	0.76	5.64	41.75	3.6604	1
Tongue dysplasia	99.90	99.90	99.90	129.7625	1
Tongue movement disturbance	0.55	4.06	29.66	2.2323	1
Tongue paralysis	0.83	6.18	45.91	4.1441	1
Tonsillar hypertrophy	0.18	1.30	9.30	0.0676	1
Tooth abscess	1.41	10.81	83.12	8.2214	1
Tooth loss	0.96	7.21	53.97	5.0667	1
Torsade de pointes	0.17	1.24	8.85	0.0446	1
Toxicity to various agents	0.30	0.60	1.20	2.1254	8
Transaminases increased	0.09	0.35	1.40	2.4265	2
Transfusion	0.46	3.33	24.20	1.5874	1
Transient ischaemic attack	0.29	2.09	15.09	0.5618	1
Treatment failure	0.15	1.04	7.42	0.0014	1
Tri-iodothyronine increased	1.31	9.98	76.26	7.5051	1
Trichotillomania	0.65	4.81	35.35	2.9068	1
Tuberculosis	0.17	1.24	8.85	0.0446	1
Tympanic membrane perforation	1.08	8.11	61.12	5.8672	1
Underdose	0.06	0.45	3.23	0.6563	1
Unevaluable event	0.30	1.22	4.92	0.0814	2
Unresponsive to stimuli	0.68	1.42	2.99	0.8680	7
Upper limb fracture	0.26	1.88	13.53	0.4066	1
Urethral repair	99.90	99.90	99.90	129.7625	1
Urinary hesitation	1.02	7.63	57.32	5.4443	1
Urinary incontinence	0.42	1.11	2.98	0.0462	4
Urinary tract infection	0.14	0.56	2.26	0.6771	2
Urine abnormality	1.66	12.98	101.31	10.0489	1
Urine ketone body present	0.42	3.02	21.90	1.3187	1
Urine odour abnormal	1.83	14.42	113.74	11.2391	1
Urine output increased	0.87	6.49	48.32	4.4216	1
Urobilinogen urine	99.90	99.90	99.90	129.7625	1
Urticaria	0.00	0.02	0.13	53.9896	1
Vaginal haemorrhage	0.10	0.69	4.90	0.1425	1
Vasculitis	0.07	0.52	3.70	0.4444	1
Ventricular extrasystoles	0.62	1.95	6.08	1.3615	3
Ventricular fibrillation	0.12	0.85	6.10	0.0249	1
Verbal abuse	1.31	9.98	76.26	7.5051	1
Vertigo	0.11	0.35	1.09	3.5747	3
Violence-related symptom	0.34	2.45	17.69	0.8411	1
Viral infection	0.20	0.61	1.90	0.7411	3
Viral upper respiratory tract infection	0.30	0.79	2.11	0.2226	4
Visual acuity reduced	0.07	0.46	3.30	0.6198	1
Visual field defect	0.22	0.89	3.56	0.0293	2
Visual impairment	0.41	0.78	1.50	0.5493	9
Vital capacity abnormal	99.90	99.90	99.90	129.7625	1
Vitamin D deficiency	0.32	2.28	16.43	0.7036	1
Vomiting	0.42	0.56	0.74	16.5793	46
Weight decreased	0.88	1.40	2.23	2.0763	18
Weight fluctuation	0.76	5.64	41.75	3.6604	1
White blood cell count decreased	0.41	0.99	2.38	0.0004	5

White blood cell count increased	0.30	0.94	2.91	0.0132	3
Yawning	0.80	5.90	43.73	3.8914	1

Appendix 6

Abstract for the ACCP Global Conference on Clinical Pharmacy (2018)

Accessibility and safety of antipsychotics in the treatment of Autism Spectrum Disorder in children and adolescents

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Introduction: The FDA approved risperidone and aripiprazole for the treatment of irritability associated with Autism Spectrum Disorder (ASD) in children and adolescents. Cultural and economic differences in countries like India and Malta may affect the prescription of these drugs in ASD.

Research Question or Hypothesis: Are risperidone and aripiprazole easily accessible in India and Malta? Is it safe to prescribe these drugs in this cohort? Do ASD screening tools influence the prescribing behaviour of these drugs?

Study Design: Cross-sectional study

Methods: Availability, price and national policies were compared in India and Malta to study the accessibility of risperidone and aripiprazole. Safety signals were accessed from the European Pharmacovigilance system and were assessed using the French causality assessment. The Indian Scale of Assessment of Autism (ISAA) and the Childhood Autism Rating Scale (CARS) were compared by developing and validating an ASD comparative questionnaire (ASD-Q_{IND-MT}) intended for psychiatrists (India, Malta) and consisting of 140 close-ended questions

Results: Risperidone and aripiprazole are available in India and but are not indicated for ASD and the cost difference between a single tablet of the same strength and dosage form is €0.04 and €0.07 respectively. The French causality assessment of the detected signals (141-aripiprazole and 177-risperidone) concluded uncertain/ unlikely relationship between the signal and the drugs. ASD-Q_{IND-MT} was disseminated to psychiatrists in India (n=31) and Malta (n=16) and a larger percentage (41.9 %) of psychiatrists in India agreed that screening tools have a positive influence on the prescribing behaviour compared to psychiatrists in Malta (12.5 %)

Conclusion: Accessibility of drugs to the patient is affected by the high cost which can be lowered by including risperidone and aripiprazole on national formularies for the indication of ASD. It is safe to prescribe these drugs in this cohort but continuous monitoring is recommended. Cultural and economic differences significantly affect the approach towards treatment of ASD in different countries.

Appendix 7

Abstract for the 78th FIP World Congress of Pharmacy and Pharmaceutical Sciences

Affordability of Risperidone and Aripiprazole for the Treatment Of Autism Spectrum Disorder

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My preferred method of presentation is: Poster Presentation

Background: The use of risperidone and aripiprazole in children and adolescents with Autism Spectrum Disorder (ASD) is off-label in India and Malta and is not included in the national formularies. The European Medicines Agency and the Central Drug Standard Control Organisation (India) have not approved the drug for the indication of ASD.

Purpose: To compare the use and cost of the treatment of irritability associated with autism using risperidone and aripiprazole, inIndia and Malta.

Methods: A questionnaire was developed, validated and disseminated to psychiatrists (N=47) in India (n=31) and Malta (n=16) to assess their prescribing behaviour concerning risperidone and aripiprazole in the management of ASD, using a 5 point Likert scale.Cost analysis and the Monthly Per Capita Expenditure (MPCE) were undertaken for both countries, to assess the affordability of treatment.

Results: Psychiatrists in Malta (n=14) prescribe risperidone and aripiprazole off-label in patients with severe autism compared to psychiatrists in India (n=13) who prescribe these drugs in moderate autism ($p<0.05$). Psychiatrists and in Malta (n=11) and in India(n=21) agreed that accessibility of drugs (risperidone and aripiprazole) is a matter of concern ($p>0.05$). The cost of one month of treatment with risperidone and aripiprazole is €3.5 and €3.9 in India and €26.7 and €28.8 in Malta respectively. The MPCE of risperidone is 3.30% in Malta and 11.30% in India. The MPCE of aripiprazole is 3.56% in Malta and 12.60% in India. Conclusion: The cost of treatment in India is less when compared to Malta, but when cost is measured against the MPCE in both countries, Malta is more affordable than India