Safety of Antipsychotic Medication in Individuals Diagnosed with Autism Spectrum Disorder (ASD)

Basmah Hamed Saleh Alfageh

Thesis submitted in fulfilment of the requirements for the degree of Doctor of Philosophy

School of Pharmacy | University College London

December 2020

Declaration

I, Basmah Hamed Alfageh declare that the work presented in this thesis is my own and has not previously been submitted for any degree other than that of the degree of Doctor of Philosophy at the University College London. Where information has been derived from other sources, I confirm that this has been indicated in the thesis.

Date: 17/12/20

Abstract

Background: Autism spectrum disorder (ASD) is a lifelong neurodevelopmental condition which presents in childhood. In the UK, risperidone is the only antipsychotic drug approved for the management of behavioural disturbance in children and adolescents with ASD.

Aim: To explore the safety of antipsychotic medication use in people with ASD.

Method: Four observational studies using a UK primary care database as a data source. The first study was a descriptive study to provide up-to-date information on the prevalence of ASD and psychotropic medication prescribing. Next, two analytical studies, of different designs, to investigate the risk of incident seizure associated with antipsychotic use, were conducted. A cohort study comparing the risk of incident seizure in people using antipsychotics with the users of other psychotropics; followed by a self-controlled case series analysis on the risk of incident seizure associated with antipsychotic use. Lastly, a cohort study to investigate the relationship between the risk of cardiac events and antipsychotic exposure, compared to other psychotropics, was conducted.

Results: There has been a noticeable increase (3.3-fold) in the prevalence of ASD over the period from 2009 to 2016. Over this period, 12.4% of the treated ASD patients had been prescribed antipsychotics; 50.7% of antipsychotic prescriptions was for risperidone and 49.3% was for other antipsychotics. The hazard ratios of the risk of incident seizure and cardiac events associated with antipsychotic use were 1.28 (95% CI: 0.74-2.19) and 1.27 (95% CI: 0.62-2.62),

respectively. During the first month of other psychotropic medication treatment, the incidence rate ratio of seizure was 1.57, 95% CI:1.03-2.38.

Conclusion: This research found no evidence of an increased risk of incident seizure or cardiac outcomes associated with antipsychotic use compared to other psychotropics ASD patients. A short term increase in the risk of incident seizure was noted with the use of psychotropics other than antipsychotics.

Impact statement

The prevalence of ASD has increased over the years. This condition disturbs the life of the affected children and their families. People with ASD often suffer from challenging behaviours; in some cases, psychosocial intervention is insufficient and the need for pharmacotherapy exists. Antipsychotic medication is considered to manage behavioural disturbance in children and young people with autism. The evidence that guides antipsychotic medication prescribing for this indication is limited, and there is limited evidence focusing on the safety profile of antipsychotic medication in individuals with ASD. Several adverse events have been reported with the use of antipsychotic medication.

This PhD project highlights the association between antipsychotic medication in a population with ASD and the risk of developing incident seizure and cardiac adverse events using a UK anonymised primary care database of general practice records that is generalizable for the UK population. Risperidone is the only antipsychotic medication approved in the UK for the management of behavioural disturbance in children and adolescents affected by autism. However; around half of the antipsychotic medication prescriptions issued for populations with ASD have been for antipsychotics other than risperidone. The retention rate of antipsychotic medication was more than one year for 32.1% of the patients, and reached up to five years in 6.1% of the patients. This research found no evidence of an association between antipsychotic medication exposure and cardiac events or incident seizure in people with ASD compared to other psychotropic medication. Nevertheless, it is recommended to start with the minimum effective dose of antipsychotic

medication. One of the objectives of this PhD project was to investigate the risk of incident seizure associated with antipsychotic use in a population with ASD, and people with a history of seizure or epilepsy were excluded from the analyses. Further studies assessing the risk of seizure associated with antipsychotic medication use in a population with ASD and a history of epilepsy are warranted. This research found some evidence of increased risk of incident seizure during the first month of treatment with psychotropic medication other than antipsychotics. Therefore, psychotropic medication should be prescribed with caution, and close monitoring of the patient upon receiving the medication is recommended, particularly at the initiation of treatment. This is to ensure the safety of the treated patients and to avoid any further treatment complications.

Acknowledgements

To my beloved family: my parents, my husband, my daughters, and my sister and brothers for their unconditional support throughout this intense journey. Without your prayers, love and support, this work would not have been possible.

I would like to express my deepest gratitude to my supervisors at the University College London (UCL) School of Pharmacy, Professor Ian Wong and Dr. Ruth Brauer. Thank you for your invaluable advice, guidance and patience during this PhD journey. I will be always appreciative of them for all the knowledge and the experience that I have received as a member of their research group.

My sincere thanks are extended to all the staff and colleagues at the Practice and Policy department at the UCL School of Pharmacy, with a special reference Dr. Kenneth Man. I want to thank you for your excellent cooperation and motivation; it has been my pleasure to work with you.

Finally, I would like to acknowledge the Saudi Arabian Ministry of Education scholarship I received which was funded by the Saudi Culture Bureau. I am grateful for the opportunities I have been given to conduct my research and obtaining this degree.

Publications and presentations from the PhD work

Publication:

Alfageh BH, Wang Z, Mongkhon P, Besag FM, Alhawassi TM, Brauer R et al. Safety and Tolerability of Antipsychotic Medication in Individuals with Autism Spectrum Disorder: A Systematic Review and Meta-Analysis. Pediatric Drugs 2019: 1-15.

Alfageh BH, Man KK, Besag FM, Alhawassi TM, Wong IC, Brauer R. Psychotropic medication prescribing for neuropsychiatric comorbidities in individuals diagnosed with autism spectrum disorder (ASD) in the UK. Journal of autism and developmental disorders 2020; 50(2): 625-633.

Conference poster presentations:

Alfageh BH, Wang Z, Mongkhon P, Besag FM, Alhawassi TM, Brauer R et al. Safety and Tolerability of Antipsychotic Medication in Individuals with Autism Spectrum Disorder: A Systematic Review and Meta-Analysis. International Congress of the Royal College of Psychiatrists, Birmingham, 24th June 2018.

Alfageh BH, Man KK, Besag FM, Alhawassi TM, Wong IC, Brauer R. Psychotropic medication prescribing for neuropsychiatric comorbidities in individuals diagnosed with autism spectrum disorder (ASD) in the UK. British pharmacology, London, 18th December 2018.

Alfageh BH, Besag FM, Gao L, Ma TT, Man KK, Wong IC, Brauer R. Risk of Seizure in People with Autism Spectrum Disorder Using Antipsychotic Medication: A Population Based Study. The 36th International Conference on

Pharmacoepidemiology and Therapeutic Risk Management (ICPE), August 26-30, 2020.

Manuscript accepted for publication:

Alfageh BH, Besag FM, Gao L, Ma TT, Man KK, Wong IC, Brauer R. Antipsychotic medication and risk of incident seizure in people with autism spectrum disorder: Analyses with cohort and within individual study designs. Accepted by Journal of autism and developmental disorders.

Table of content

List of tables

List of figures

List of Appendices

List of Abbreviations

ADHD	Attention Deficit Hyperactivity Hisorder
ABC	Autism Behaviour Checklist
ADDM	Autism and Developmental Disabilities Monitoring
ADHD	Attention Deficit Hyperactive Disorder
AEs	Adverse Events
AHD	Additional Health Data
ASD	Autism Spectrum Disorder
ASMs	Anti-Seizure Medications
BBD	Body Dysmorphic Disorder
BMI	Body Mass Index
BNF	British National Formulary
CAD	Coronary Artery Disease
CAMHS	Child and Adolescent Mental Health Services
CDC	Centre for Disease Control and Prevention
CGI-I	Clinical Global Impression-Improvement
CIs	Confidence Intervals
CMORE	Centre for Medication Optimisation Research and Education
CNS	Central Nervous System
COMPASS	Collaborative Model for Promoting Competence and Success
CPRD	The Clinical Practice Research Datalink
CRD	Centre for Reviews and Dissemination
CRO	Contract Research Organizations
CVD	Cardiovascular Disease
DSM-5	Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition
DSM-IV-TR	Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition - Text Revision
DUS	Drug Utilisation Study
EMA	European Medicines Agency
EMBASE	Excerpta Medica Database
EPS	Extrapyramidal Symptoms
ERT	Emotion Recognition Training
FDA	Food and Drug Administration
FGAP	First-Generation Antipsychotic Agents
FRT	Face Recognition Training
GPD	Gross Domestic Product
GPRD	General Practice Research Database
GPs	General Practitioners
HES	Hospital Episode Statistics
HR	Hazard Ratio
ICD-10	International Statistical Classification of Diseases and Related Health Problems, Tenth Edition
ICPE	International Conference on Pharmacoepidemiology
IMRD-UK	IQVIA Medical Research Data

INPS	In Practice Systems Ltd
IPTW	Inverse Probability of Treatment Weighting
IQ	Intelligence Quotient
IRR	Incidence Rate Ratio
KSU	King Saud University
LEAP	Learning Experiences – an Alternative Program for Pre-schoolers and Parents
LMS	Least Mean Square
MAR	Missing at random
MEDLINE	Medical Literature Analysis and Retrieval System Online
MeSH	Medical Subject Heading
MHRA	Medicines and Healthcare Products Regulatory Agency
MI	Myocardial Infarction
MMR	Mumps, Measles and Rubella
MREC	Multicentre Research Ethics Committee
NA	Not Avilable
NAS	National Autistic Society
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NIMH	Institute of Mental Health
NMS	Neuroleptic Malignant Syndrome
NOS	Newcastle-Ottawa
NSAID	Nonsteroidal Anti-Inflammatory Drugs
OCD	Obsessive Compulsive Disorder
Ors	Odds Ratios
PDD-NOS	Pervasive Developmental Disorder- Not Otherwise Specified
P-ESDM	Parent-Mediated Early Start Denver Model
PICOS	Participant-Intervention-Comparison-Outcome-Study Design
POMR	Problem-oriented medical record
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PS	Propensity Score
PTSD	Post-Traumatic Stress Disorder
PVI	Postcode Variable Indicators
PY	Person-years
QOF	Quality and Outcomes Framework
QTs	Corrected QT
RCT	Randomised Controlled Trial
RIT	Reciprocal Imitation Training
RR	Relative Risk
RUPP	Research Units on Paediatric Psychopharmacology
SAS	Statistical Analysis System
SCCS	Self-Controlled Case Series
SCERTS	Social-Communication, Emotional Regulation, and Transactional Support
SD	Standard Deviation
SDD	Smoking, Drinking and Drug Use among Young People survey
SDS	Standard deviation scores
SGAP	Second-Generation Antipsychotic Agent

SMD	Standardised Mean Differences
SMI	Serious Mental Illness
SoP	School of Pharmacy
SRC	Scientific Review Committee
SSRI	Selective Serotonin Reuptake Inhibitors
TD	Tardive Dyskinesia
TEACCH	Treatment and Education of Autistic and Communication-Handicapped Children
TGA	Therapeutic Goods Administration
THIN	The Health Improvement Network
ToM	Theory of Mind
UCL	University College London
VA	Ventricular Arrhythmias
WD	Withdrawal Dyskinesia

Chapter One: Introduction

1.1 Autism Spectrum Disorder (ASD)

1.1.1 Historical context

Autism is a lifelong neurodevelopmental condition, which was first described eight decades ago by Dr. Leo Kanner; an Austrian-American psychiatrist, physician, and social activist. In 1943, he published his landmark paper titled "Autistic Disturbances of Affective Contact" describing 11 children who were highly intelligent but displayed "a powerful desire for aloneness" and "an obsessive insistence on persistent sameness."[1] One year after Kanner's paper, Hans Asperger published a paper to describe children that he also called 'autistic', but who seemed to have high non-verbal intelligence quotients and who used a large vocabulary appropriately[2]. Subsequently, the condition was known as Asperger's syndrome. In the following years, the clinical definitions of autism continued to evolve until the emergence of the term autism spectrum disorder (ASD)[3].

Before 2013, ASD represented pervasive developmental disorders of variable severity, defined as autistic disorder, Asperger's disorder and pervasive developmental disorder-not otherwise specified (PDD-NOS) in the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition - Text Revision (DSM-IV-TR)[4]; and as childhood autism, atypical autism, Rett's syndrome, other childhood disintegrative disorders, Asperger's syndrome, other pervasive developmental disorders and pervasive developmental disorder unspecified in the International Statistical Classification of Diseases and Related Health Problems, Tenth Edition (ICD-10)[5]. In 2013, after the release of the fifth edition of the Diagnostic and Statistical Manual of Mental Disorders

(DSM-5)[6], autistic disorder, Asperger's disorder and PDD-NOS were collapsed into a single diagnosis of ASD.

1.1.2 Definition

Despite the differences in terminologies used to describe the disease, ASD is defined by DSM-5 as a developmental disorder characterised by persistent problems in social communication and interaction, along with restricted and repetitive patterns of behaviour, interests or activities[6].

The following sections are written following the National Institute for Health and Care Excellence guidelines (NICE) for children, adolescents and adults[7, 8].

1.1.3 Signs and symptoms

A. Children and young people

Children and adolescents with ASD usually present with signs and symptoms that indicate a delay in normal growth. These sign and symptoms help the healthcare providers to recognise the possibility of ASD diagnosis in a child or adolescent. The NICE guidelines have categorised the signs and symptoms of ASD in children and young people into three categories[7]: in preschool children, in primary school children (aged 5–11 years) and in secondary school children (older than 11 years). These signs and symptoms take into account three main characteristics: 1) social interaction and reciprocal communication behaviours, such as delayed response to people's facial expressions, inability to tolerate people entering their personal space, and limited or no imagination ability in pretend play; 2) unusual or restricted interests and/or rigid and repetitive behaviours, such as stereotyped repetitive

movements, a preference for highly specific interests or hobbies, and unacceptance of changes; 3) other factors that could support ASD diagnosis, such as defective social or motor coordination skills, despite being advanced in other areas or express social and emotional immaturity compared to other areas of development.

B. Adults

In adults, a significant number of patients with ASD will not have had a diagnosis[9]. For adults who have previously been diagnosed with ASD during childhood, but have not been in contact with services since childhood, they are also unlikely to be recognised as having ASD as they do not often present to health or social care services with a complaint directly concerning its core symptoms. Instead, they are more likely to present with a coexisting mental or physical disorder or with a social problem arising from the autism or the coexisting condition. The under-recognition of ASD diagnosis may lead to poor quality of life and inadequate care and support for both the autism disorder and the associated coexisting conditions[8].

The signs and symptoms of ASD in adults appear in the same areas of children, including the persistent difficulties in social interaction and communication in addition to the stereotypic behaviours and resistance to change, for example, diet, routine or environment[8].

There are several factors associated with ASD in adults including:

- Problems in obtaining or sustaining employment or education.
- Difficulties in initiating or sustaining social relationships.

- Previous or current contact with mental health or learning disability services.
- History of a neurodevelopmental condition (including learning disabilities and attention deficit hyperactivity disorder (ADHD)) or mental disorder.

1.1.4 Diagnosis

According to the available evidence, an ASD diagnosis can be reliably made at age 2[10, 11]. However, most children are not diagnosed until the age of 4. According to estimates from the Centre for Disease Control and Prevention CDC's Autism and Developmental Disabilities Monitoring (ADDM) Network[12], the median age of the first diagnosis by subtype is as follows:

- Autistic disorder: 3 years 10 months
- Pervasive developmental disorder-not otherwise specified (PDD-NOS): 4 years 1 month
- Asperger's disorder: 6 years 2 months

The American Diagnostic and Statistical Manual of Mental Disorders 5th Revision (DSM-5) and the International Statistical Classification of Diseases and Related Health Problems 10th Revision (ICD-10) are used in the diagnosis of ASD. In the DSM-4 the diagnostic criteria for ASD comprised three main domains: (1) impairment in social interaction, (2) impairment in communication, and (3) restricted, repetitive, and stereotyped patterns of behaviour, interests, and activities. With the release of the fifth edition of the DSM (DSM-5) in 2013, the diagnostic criteria changed significantly[6]. The first two domains of ASD were combined, leaving two key symptom domains: (1) social communication and (2) restricted and repetitive behaviours. The following are the diagnostic criteria for ASD according to DSM-5[6]:

A. Current or history of persistent deficits in social communication and social interaction across multiple contexts.

B. Current or history of restricted, repetitive behaviour, interests, or activities.

C. Symptoms are present in the early developmental period; however, it could be masked or not fully manifest until social demands exceed the limit.

D. Symptoms lead to clinically significant impairment in social, occupational, or other vital areas of current functioning.

E. These disturbances are not better explained by intellectual disability. Intellectual disability and autism spectrum disorder are frequently combined; to make comorbid diagnoses of autism spectrum disorder and intellectual disability, social communication should be below that expected for the general developmental level.

When a diagnosis of ASD is confirmed, clinicians must specify if it is accompanied by intellectual or language impairment or associated with a known genetic or medical condition, such as catatonia.

1.1.4.1. Instruments used for ASD screening and diagnosis

There are a number of instruments that are used for diagnosing, or screening for, ASD[13]. However, due to insufficient evidence on sensitivity and specificity; there is no specific screening instrument recommended by both the NICE guidelines and the UK National Screening Committee[14, 15]. The NICE guidelines recommend that the sensitivity and specificity of screening and diagnostic instruments should be at least 80%, with the lower 95% confidence interval estimated above 70%[15].

1.1.5 Risk factor

The following are factors associated with an increased prevalence of autism[16]:

- A sibling with autism: studies have shown that for parents who have a child with ASD, the chance of having a second child affected by ASD is up to 18%[17].
- Birth defects associated with central nervous system malformation and/or dysfunction.
- Children who are born prematurely (< 37 weeks).
- Parental schizophrenia-like psychosis or affective disorder.
- Children born to older parents are at a higher risk of having ASD[18].
- Maternal use of sodium valproate in pregnancy.
- Neonatal encephalopathy or epileptic encephalopathy, including infantile spasms.
- Chromosomal and genetic disorders: the prevalence of ASD among children with disorders such as Down's syndrome or fragile X is substantially higher than in the general population[19, 20].
- Muscular dystrophy, neurofibromatosis or tuberous sclerosis.

1.1.6 Prevalence and incidence

The worldwide prevalence of ASD was estimated to be 7.6 per 1,000 persons in 2010[21]. In a school-based population study carried out in the UK, the estimated prevalence of ASD was 15.7 per 1,000 children in 2004. Another study conducted in the UK using the primary care database found that the prevalence of diagnosed ASD increased[22] 6-fold from 0.08 per 1,000 persons

in 1992 to 5.04 per 1,000 persons in 2008; the incidence of ASD also rose 23.7-fold in the same period from 0.03 per 1,000 persons to 0.67 per 1,000 persons[22]. Based on ADDM data, ASD prevalence in the United States almost doubled from 6.7 per 1,000 children in 2000 to 14.6 per 1,000 children in 2012[12]. Although the prevalence of ASD shows an increasing trend, this could be partially due to the broader diagnostic criteria and increased awareness of autism[23].

ASD is diagnosed three times more often in males than in females[24]. In clinic samples, females tend to be more likely to show accompanying intellectual disability[25], suggesting that girls without accompanying intellectual impairments or language delays may be underdiagnosed, perhaps because of subtler manifestations of social and communication difficulties[26].

However, the prevalence rate also differs among diverse ethnic groups. Prevalence rate estimates from the Centre for Disease Control and Prevention (CDC) show that non-Hispanic white children were approximately 30% more likely to be identified with ASD than non-Hispanic black children, and were almost 50% more likely to be identified with ASD than Hispanic children[27].

1.1.7 Comorbidities

ASD is frequently associated with intellectual impairment (intelligence quotient IQ < 70%), which occurs in approximately 50% of young people with autism[28] and structural language disorder. Many individuals with ASD have psychiatric symptoms that do not form part of the diagnostic criteria for the disorder; about 70% of individuals with ASD may have one comorbid mental disorder and 40% may have two or more comorbid mental disorders[29]. The most common

comorbid conditions include ADHD, developmental coordination disorder, anxiety, depression and epilepsy[6].

1.1.8 Management

Although there is no cure for ASD, there are several interventions available to control the autism symptoms to improve the quality of life of the affected people, together with their families and caregivers[30]. The established therapies for ASD are non-pharmacological therapies, which may include behavioural, educational, and cognitive treatment. No pharmacologic agent is effective in the treatment of the core behavioural manifestations of ASD. However, medications may be effective in the treatment of comorbid disorders, including self-injurious behaviours[8]. **Figure 1.1** summarises ASD management. The following subsections refer to the management of ASD as recommended by the NICE guidelines[31].

1.1.8.1 Psychosocial treatments for the core features

Psychosocial interventions to improve social and communication outcomes

Several training programmes are offered for the parents of children diagnosed with ASD. These programmes aim to increase the parents' knowledge and confidence to improve their ability to manage their child's behaviour and to communicate with their child successfully.

EarlyBird (for parents of children aged less than five years old) and EarlyBird Plus (for parents of children aged four to eight years) are both programmes provided by The National Autistic Society (NAS) for the parent of a child with

ASD[31]. Additional programmes are available, such as the Treatment and Education of Autistic and Communication-Handicapped Children (TEACCH) programme[32] and the Social-Communication, Emotional Regulation, and Transactional Support (SCERTS) approach[33]. These programmes are usually implemented in educational settings and aim to provide a structure for everyday activities.

Psychosocial interventions to improve the negative impacts of repetitive, stereotyped or rigid behaviours or sensory sensitivities

There are no parent training programmes, or other programmes or frameworks, currently delivered in education settings that focus specifically on helping parents and carers to understand and manage children and young people's repetitive stereotyped and rigid behaviours. Most of the intervention programmes described above will include some information about such behaviours typical of autism to minimise their maladaptive aspects and, thus, countering the developmental effects.

Educational interventions

The Collaborative Model for Promoting Competence and Success (COMPASS) and Learning Experiences – an Alternative Program (LEAP) are educational interventions which aim to improve the objectives of individual education plans for children with autism by promoting home-school collaboration and teacher training.

Behavioural interventions

Reciprocal imitation training (RIT) is a behavioural intervention that uses naturalistic techniques to teach imitation during social interaction. A

behavioural intervention trial compared RIT intervention and treatment as usual in preschool children with autism[34]; this study found evidence of statistically significant treatment effects on impaired social communication and interaction. However, this evidence could be of low quality due to the non-blind outcome assessment and small sample size.

The Parent-mediated Early Start Denver Model (P-ESDM) is another behavioural intervention that focuses on a range of skills including: joint attention routines; developing non-verbal skills; encouraging speech; and conducting functional assessments of behaviour. There is no evidence the treatment effects of P-ESDM are statistically significant on social communication or interaction compared to treatment as usual in pre-school children with autism[35].

Cognitive interventions

Cognitive interventions, such as emotion recognition training (ERT), face recognition training (FRT) and theory of mind (ToM) training, are available for children with autism. These interventions aim to improve the ability of children with autism to deal with socioemotional cues such as facial expressions, and body language and to interpret them correctly and respond to them appropriately, in addition to improve their social skills, such as listening to others, making friends, and enjoying a sense of humour. However, there is no strong evidence of these interventions having a significant effect on the core autism feature of impaired reciprocal behaviour[36].

1.1.8.2 Psychosocial interventions for behaviour that challenges

If no coexisting mental health or behavioural problem, physical disorder or environmental problem has been identified as triggering or maintaining the behaviour that challenges, the first-line treatment is a psychosocial intervention[36].

1.1.8.3 Pharmacological interventions for behaviour that challenges

If psychosocial or other interventions are inadequate or could not be delivered due to the severity of the behaviour, antipsychotic medication is considered for managing behaviour that challenges in children and young people with autism [36]. Antipsychotic medication should initially be prescribed and monitored by a paediatrician or psychiatrist and repeat prescriptions can be prescribed by GPs. Antipsychotic medication prescribers should follow these steps:

- Identify the target behaviour
- Decide on an appropriate measure to monitor effectiveness, including the frequency and severity of the behaviour
- Review the effectiveness and any side effects of the medication after three to four weeks
- If no clinical response has been observed after six weeks of treatment, the medication should be discontinued.

Further details of antipsychotic medication use in ASD will be provided in section 1.3 in this chapter.

1.1.8.4 Interventions for coexisting problems

The NICE guidelines recommend both psychosocial and pharmacological interventions for the management of coexisting mental health or medical problems in children and young people with autism. The pharmacotherapy for the coexisting conditions includes:

- **Attention deficit hyperactivity disorder (ADHD)**: the first-line treatment is methylphenidate, and other options include lisdexamfetamine, dexamfetamine, atomoxetine and guanfacine.
- **Conduct disorders**: pharmacotherapy includes methylphenidate or atomoxetine; risperidone is considered for the short-term management of severely aggressive behaviour in young people with a conduct disorder.
- **Depression**: combined therapy (fluoxetine and psychological therapy) is considered for the initial treatment of moderate to severe depression in young people (12–18 years); in children (5-11 years), fluoxetine is considered with caution if the patient does not respond to a specific psychological therapy after four to six sessions.
- **Epilepsy:** anticonvulsants are considered; selecting the specific anticonvulsant is dependent on the type of seizure experienced.
- **Obsessive-compulsive disorder (OCD) and body dysmorphic disorder (BBD)**: cognitive behavioural therapy (CBT) and selective serotonin reuptake inhibitors (SSRI) are considered in the treatment of both OCD and BBD.
- **Post-traumatic stress disorder (PTSD)**: drug treatments should not be routinely prescribed for children and young people with PTSD. In adults,

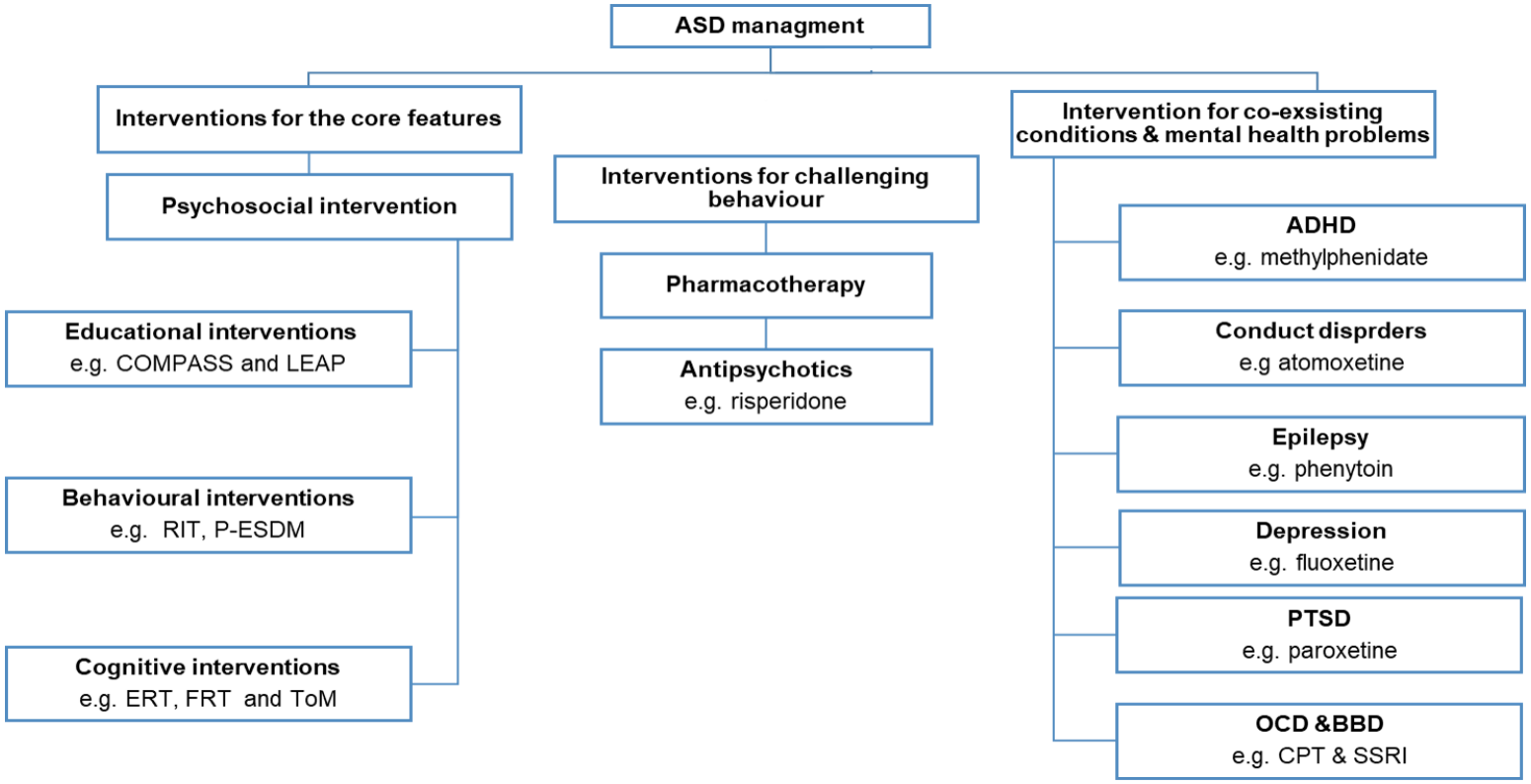
hypnotic medication may be appropriate for short-term use to manage sleep disturbance associated with PTSD but, if longer-term drug treatment is required, antidepressants may be considered. Paroxetine, mirtazapine, amitriptyline or phenelzine are also considered in PTSD treatment in adults.

- **Sleep problems:** Sleep behavioural intervention (a sleep plan) is recommended to establish a regular night-time sleep pattern. Pharmacological intervention for sleep problems is not recommended in children and young people except if sleep problems persist despite following the sleep plan or if the sleep problems are having a negative impact on the child or young person and their family or carers.

1.1.8.6 Transition to adult services

Young people with autism who are receiving treatment and care from child and adolescent mental health services (CAMHS) or child health services must be reassessed at around 14 years to establish the need for continuing treatment into adulthood. The timing of transition may vary but should usually be completed by the time the young person is 18 years. The overall criteria of the management of ASD in adults are similar to that of the management for children. However, there are a few differences with regard to the choice of medication and the objectives of psychosocial therapy according to the different level of signs and symptoms between children and adults[8].

Figure 1.1: Summary of ASD management



ASD, Autism Spectrum Disorder; **COMPASS**, Collaborative Model for Promoting Competence and Success; **P-ESDM**, Parent-Mediated Early Start Denver Model; **ToM**, Theory of Mind; **OCD**, Obsessive Compulsive Disorder; **LEAP**, Learning Experiences – an Alternative Program for Pre-schoolers and Parents; **ERT**, Emotion Recognition Training; **ADHD**, Attention Deficit Hyperactive Disorder; **BBD**, Body Dysmorphic Disorder; **RIT**, Reciprocal Imitation Training; **FRT**, Face Recognition Training; **PTSD**, Post-Traumatic Stress Disorder; **CPT**, Cognitive Behavioural Therapy; **SSRI**, Selective Serotonin Reuptake Inhibitor.

1.2 Antipsychotics

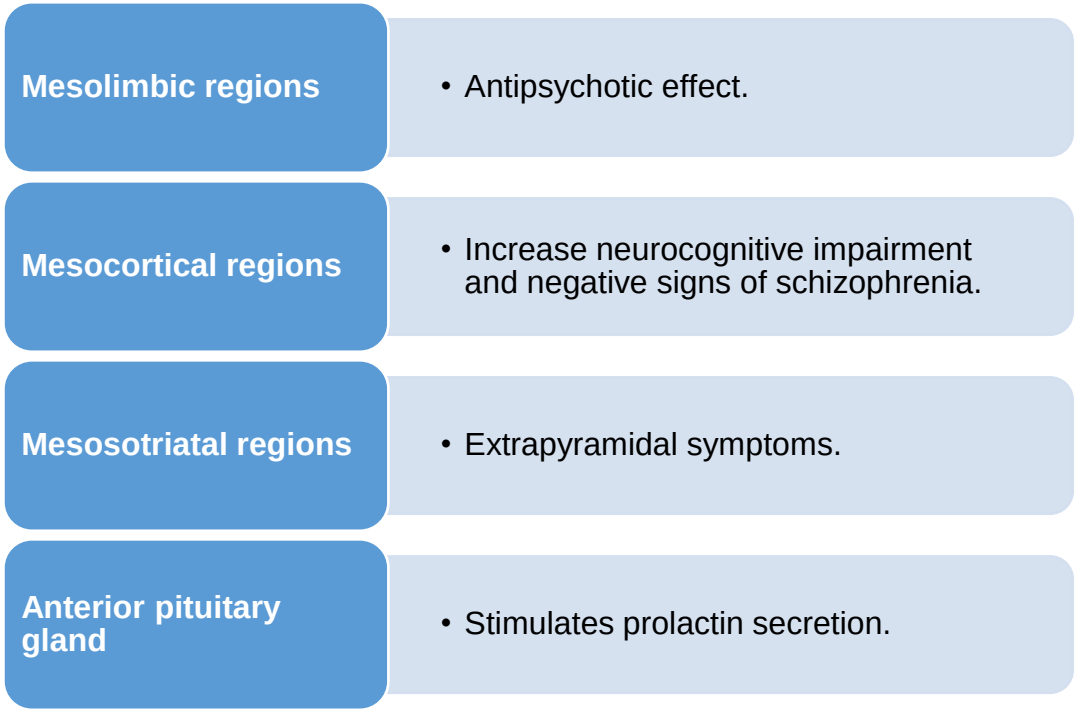
Antipsychotic drugs are also known as 'neuroleptics' and as 'major tranquillisers'. They are used in the short-term to control patient's disruptive behaviours whatever the underlying psychopathology condition. This condition could be schizophrenia, brain damage, mania, autism spectrum disorder or agitated depression.

Antipsychotics were introduced into psychiatric practice in the 1950's, initially with chlorpromazine for the treatment of delusions and hallucinations which comprise the positive symptoms of schizophrenia and other psychotic disorders [37]. After discovering the mechanism of the action of chlorpromazine and the role of dopamine receptors antagonist on psychosis, this area of research became motivated and revealed other medications with a similar action in the brain.

1.2.1 Typical antipsychotics

Typical antipsychotics, (first-generation antipsychotics (FGAPs)) act primarily by blocking dopamine D_2 receptors in the brain[38]. They are not selective for any of the four dopamine pathways in the brain and so can cause a range of side-effects, particularly extrapyramidal symptoms and elevated prolactin[39] (**see Figure 1.2**).

Figure 1.2: The effect of typical antipsychotic on the dopamine pathways in the brain



According to their chemical structure, typical antipsychotic drugs are classified into five main groups: phenothiazine derivatives, butyrophenones, thioxanthenes, diphenylpiperidines and substituted benzamides[40].

Typical antipsychotic medication has been found to be useful in the treatment of schizophrenia and other psychotic disorders. This can be achieved by the control of active psychotic symptoms, reduction of assaultive behaviour, management of severe agitation and a decrease in the risk of psychotic relapse in patients suffering from schizophrenia and other psychotic disorders during maintenance treatment[41].

However, it has been shown that conventional antipsychotics exhibit limited effectiveness in treating both the negative symptoms and cognitive deficits associated with the schizophrenia[42, 43]. Furthermore, it has been found that between 30 and 60% of patients with acutely exacerbated psychotic symptoms either fail to respond to these drugs or respond inadequately or partially[44].

The non-selectivity of the typical antipsychotics towards the four different dopamine pathways, particularly their high affinity to both mesolimbic and mesostriatal pathways in the brain, is responsible for the fact that their wanted effect is accompanied by extrapyramidal symptoms (EPS)[37]. In addition to EPS, typical antipsychotics cause significant rates of undesirable acute and chronic adverse events, including increased serum prolactin levels, anticholinergic effects like constipation, dry mouth, blurred vision, and urinary hesitancy, weight gain, hyperglycaemia and dyslipidaemia[41, 45, 46].

Accordingly, the need for a new antipsychotic generation with both a broader efficacy spectrum and a better safety profile arose. This has led to the introduction of the second-generation antipsychotics (SGAPs).

1.2.2 Atypical antipsychotics

SGAPs, ‘referred to as atypical antipsychotics’, offer some advantages over the typical or first-generation antipsychotics FGAPs. These include greater improvement in negative symptoms, cognitive impairment, relapse prevention and quality of life with fewer EPS, and less tardive dyskinesia (TD)[47].

The SGAPs are often termed ‘’atypical’’ because, in contrast to most FGAPs, they demonstrate substantial separation between the doses at which they exhibit antipsychotic action and the doses at which they are likely to induce EPS[47]. SGAPs act on a range of receptors (dopamine $D_{1\text{-}4}$, 5-HT_{2A}, $alpha_1$-adrenoceptor, muscarinic-receptor and histamine-1) in comparison to FGAPs and have more distinct clinical profiles, particularly with regard to adverse events[40]. Clozapine was the prototype second-generation antipsychotic, being introduced into the market in 1989 for the treatment of schizophrenia. Despite its clinical advantages, the use of clozapine has been limited by the risk of potentially fatal agranulocytosis estimated to occur in the patients who are treated with this compound[48].

In the years that have followed the reintroduction of clozapine, intensive research has taken place to introduce a drug with similar efficacy but without the associated risk of agranulocytosis. Several atypical antipsychotics have been revealed, including amisulpride, olanzapine, paliperidone, quetiapine, lurasidone, asenapine, iloperidone, remoxipride, risperidone and aripiprazole. Remoxipride was withdrawn after approval because of an identified risk of aplastic anaemia[49]. Although none of these newer agents has matched the singular effectiveness of clozapine, they have broadened the therapeutic selection available for the treatment of psychosis.

1.3 Antipsychotics use in ASD efficacy and safety

1.3.1 Typical antipsychotics

Since the 1960s, many studies have been published that have examined the effect of different conventional antipsychotics in diverse groups of participants that included subjects with autism[50]. The agents which have been studied include chlorpromazine, trifluoperazine, thiothixene, trifluperidol, fluphenazine and molindone. Despite the proven efficacy of these agents, their non-selective mechanism of action nature has been associated with a wide range of adverse events.

Haloperidol was the most studied typical antipsychotic for the management of behavioural disorders associated with autism. Many published studies have examined the efficacy of this agent in young children with autism[51-55]. These studies found that haloperidol is effective in the management of several symptoms associated with autism, including stereotypes, aggression, hyperactivity and irritability. However, haloperidol use in autism has been limited due to a potential risk of dyskinesia associated with treatment with this agent.

A randomised control trial (RCT) compared the use of haloperidol and a placebo in combination with language training in 40 autistic children aged 2.6 to 7.2 years[51]. This study found that haloperidol was associated with a significant improvement in withdrawal and stereotypy in children who were aged 4.5 years or older. The most frequent untoward effect was sedation which occurred in 12 of the 20 subjects who received haloperidol. Further, acute dystonic reactions occurred in two participants of the haloperidol group.

In a study of 60 children with autism, previous responders to haloperidol treatment participated in the study and were randomised to six months of either

continuous or discontinuous (five days on, two days off) haloperidol administration[55]. After six months of the treatment with haloperidol, subjects were given a placebo for four weeks. Three children developed dyskinesia during the treatment and nine other children developed dyskinesia upon medication withdrawal.

Campbell et al. studied the haloperidol related dyskinesia in 118 children with autism aged 2.3 to 8.2 years, after six-month haloperidol treatment periods followed by a four-week placebo[56]. Withdrawal dyskinesia (WD) developed in 40 (33.9%) of the children and 20 had more than one dyskinesia episode. In a subgroup of 10 children who received a higher cumulative dose of the haloperidol, nine of them developed dyskinesia.

1.3.2 Atypical antipsychotics

Atypical antipsychotics are considered more effective than typical antipsychotics in improving the negative symptoms of schizophrenia which have similarities to the social impairment characteristics of autism[50].

The most common atypical antipsychotics prescribed for autism include risperidone, olanzapine, quetiapine, ziprasidone and aripiprazole. There are number of published reports of clozapine in the treatment of autism[57-59]. Nevertheless, clozapine use is limited due to the potential risk of seizures associated with high doses[60] and the potential to cause life-threatening agranulocytosis[48], which requires frequent (weekly to biweekly) venepuncture to monitor the white blood cell counts.

Two atypical antipsychotics have been approved by the Food and Drug Administration (FDA) in the USA for the treatment of irritability associated with autistic disorder in children. In 2006, risperidone was approved for children with

autism aged 5–16 years old[61]. A few years later, the FDA approved the use of aripiprazole for the same indication in 6–17-year-old children with autism[62]. The European Medicines Agency (EMA), the Medicines and Healthcare Products Regulatory Agency (MHRA) of the United Kingdom, and the Australian Therapeutic Goods Administration (TGA) have all approved the use of risperidone in schizophrenia, mania associated with bipolar disorder, and behavioural disturbance in children and adolescents associated with autism and conduct disorder[63, 64].

The first placebo-controlled study of risperidone use in autism was published in 1998[65]. In this study, 31 adults with autism were treated with risperidone or a placebo for 12 weeks. For subjects who completed at least four weeks of treatment, risperidone was found to be effective in eight of 14 subjects compared to none of the 16 subjects treated with the placebo. The improvement was seen in aggression, anxiety, depression, irritability and the overall behavioural symptoms of autism. Sedation was the most frequently reported adverse event in participants who received risperidone.

In children, a double-blind, placebo-controlled study of risperidone was conducted by the Research Units on Paediatric Psychopharmacology (RUPP) Autism Network[66]. The RUPP network is a research unit on Paediatric Psychopharmacology created in 1997 by the American Institute of Mental Health (NIMH) to investigate favourable new medication treatments for the maladaptive symptoms associated with autism [67]. In the RUPP study, 101 children with a mean age of 8.8 years were randomised to receive eight weeks of risperidone or placebo. Treatment with risperidone for eight weeks resulted in a 57% reduction in the irritability as compared with a 14% decrease in the placebo group.

However, risperidone was associated with an average weight gain of 2.7 kg, as compared with 0.8 kg with placebo.

In the following years, several RCTs and open-label studies investigated the short and long-term efficacy and safety of risperidone use in autism[61, 68-79]. These studies have shown that risperidone was effective in the management of behavioural symptoms of autism including aggression, hyperactivity, irritability, repetitive language and behaviour and social withdrawal. Sedation and weight gain are the most pronounced adverse events reported with the use of risperidone. In addition, a study of short and long-term effects of risperidone have shown that it was associated with a four-fold increase in prolactin at eight weeks, but this decreased at six and 18 months[73].

Following the FDA approval of aripiprazole use in autism in 2009, multiple RCTs were conducted to further investigate the efficacy and safety of this agent in individuals with ASD[80-82]. First, an RCT composed of two phases, aimed to determine if patients with irritability associated with autistic disorder who had become stable on aripiprazole should be maintained on long-term treatment, was conducted[80]. Patients whose symptoms of irritability demonstrated a stable response to aripiprazole therapy for 12 consecutive weeks in phase 1 were eligible for phase 2. One hundred and fifty-seven subjects participated in phase 1 (stabilisation phase) which comprised 13-26 weeks of single-blind aripiprazole treatment, and 85 subjects participated in phase 2 (randomisation phase) for up to 16 weeks of double-blind treatment with aripiprazole or placebo. This study suggests that some patients will benefit from maintenance of aripiprazole treatment. Weight gain was noticed in 25% of the participants in phase 1 and it led to treatment discontinuation in two participants. In phase 2, EPS were observed in three participants in each of the treatment and placebo groups. None

of the participants reported serious adverse events, and no one was discontinued due to adverse events in this phase.

Another RCT study compared the safety and efficacy of aripiprazole and risperidone in 59 children and adolescents with ASD[81]. The means of age, weight, and height of the children at the baseline was similar between the two groups. The mean age of the children in the aripiprazole and risperidone groups was 9.6 (SD = 3.3) and 9.5 (SD = 4.6) years, respectively. Both aripiprazole and risperidone resulted in lowered ABC scores during the two months' duration. The rates of adverse events were not significantly different between the two groups. Two patients withdrew from the trial because of adverse events. One patient experienced exacerbated epilepsy in the aripiprazole group and one patient dropped out because of severe crying and agitation after taking risperidone. This study showed the comparable safety and efficacy of aripiprazole and risperidone.

An RCT of 92 children and adolescents with ASD who were randomised to either aripiprazole or placebo for eight weeks aimed to assess aripiprazole efficacy[82]. This study found that study participants on aripiprazole had a significant improvement in both the mean parent/caregiver-rated Autism Behaviour Checklist (ABC) irritability subscale score and the mean clinician-rated Clinical Global Impression-Improvement (CGI-I) scores relative to a placebo group during the study period. All patients randomised to aripiprazole completed the study, and no serious adverse events were reported.

1.3.3 Antipsychotic medication prescribing in ASD

Antipsychotics have been used frequently for the management of the challenging behaviours of people affected by autism. In 2016, a systematic review study investigated the pattern of antipsychotic medication prescribing in adolescents[83].

This review found that for every 10 adolescents treated with antipsychotics one had a diagnosis of ASD, and 1 in 6 adolescents with ASD received antipsychotics. These two proportions have increased over the years. Children with intellectual difficulty/autism were more likely to be prescribed antipsychotics. They are used at a younger age and for a longer time period, and in this population, there are higher rates of adverse events[84]. Even though only one antipsychotic agent (risperidone) has been approved for the management of behavioural disorders in children and adolescents diagnosed with ASD in the UK, a drug utilisation study has used real-world data in the UK to reveal that several antipsychotic agents were prescribed to ASD patients[22]. However, this study covered the prescribing data up to 2008 and risperidone was approved in the UK in 2007; hence, the prescribing pattern of antipsychotic medication in ASD might have changed since then. Moreover, it was shown that many ASD patients remained on multiple antipsychotic medication therapies i.e. two or more antipsychotics, for more than a year[85].

As previously mentioned, although the efficacy of antipsychotic medication in the management of irritability and behavioural disorder associated with ASD has been proven, its use is linked with a wide range of adverse events. Weight gain, hyperprolactinemia and sedation are examples of common adverse events associated with antipsychotic medication. To explore the published literature about the safety of antipsychotic medication in individuals with ASD, **Chapter Three** in this thesis presents a comprehensive literature review on the available evidence in this area.

Also, the guidance on antipsychotic medication prescribing in patients with ASD remains unclear; therefore, it is important to explore the current practice of antipsychotic medication prescribing for patients with ASD. This will help to

optimise its management with antipsychotics and reduce the occurrence of unwanted effects. A drug utilisation study conducted by using a real-world database in the UK is presented in **Chapter Five**. This study aimed to provide an insight into the current practice of pharmacological therapy prescribing in populations with ASD.

Chapter Two: Aim and Objectives

2.1 Aim

The overall aim of this PhD project was to study the safety of antipsychotic medication use in individuals with ASD.

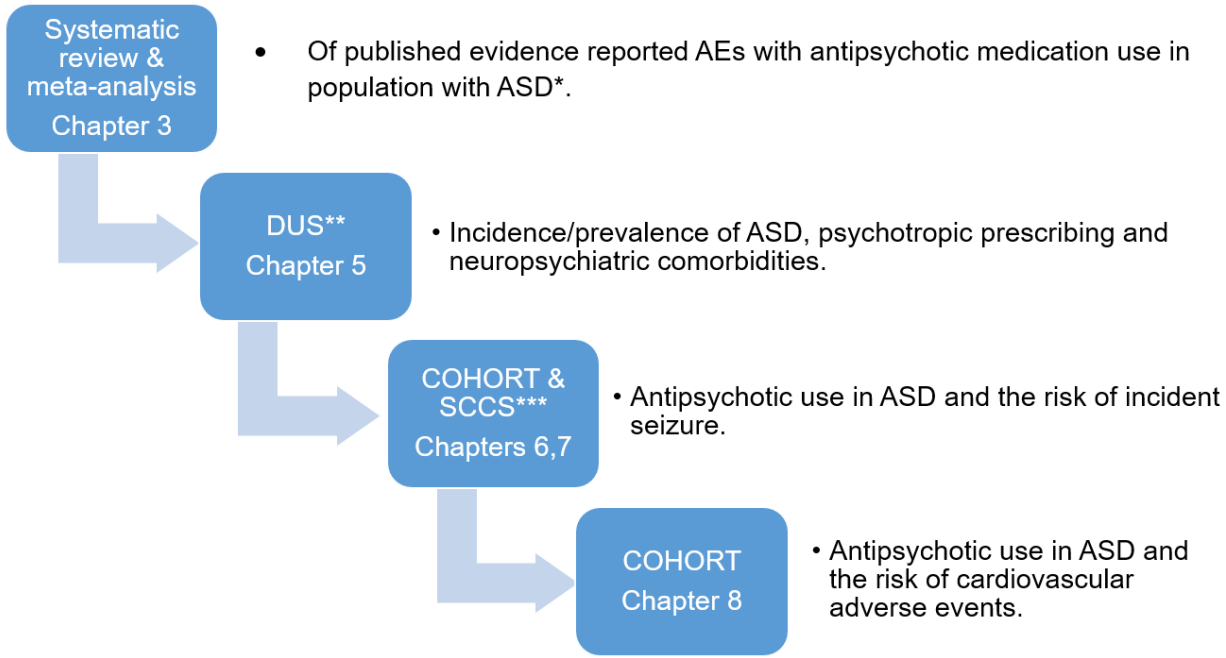
2.2 Objectives

The specific objectives of this project are summarised as follows:

1. To summarise the published evidence of the adverse events reported with antipsychotic medication use in patients with ASD. (**Chapter 3)**.
2. To identify the annual incidence and prevalence of ASD in the UK from 2009 to 2016. **(Chapter 5)**
3. To describe the annual proportions of individuals with ASD prescribed psychotropic medication and to estimate the average retention rate of these medications. **(Chapter 5)**
4. To calculate the proportion of patients with neuropsychiatric comorbidities associated with ASD diagnosis. (**Chapter 5)**
5. To investigate the risk of incident seizure associated with antipsychotic medication use in individuals with ASD, using between groups and within-individual analyses. (**Chapters 6 and 7)**.
6. To compare the risk of cardiovascular adverse events, including arrhythmia, heart failure and myocardial infarction between individuals with ASD who were prescribed antipsychotic medication and those who were prescribed other psychotropic medication. (**Chapter 8**).

The following diagram provides an overview of the studies accomplished during this project to attain the objectives mentioned above.

Figure 2.1: Overview of the studies conducted in this project



*__ASD__: Autism spectrum disorder

**__DUS__: Drug utilisation study

***__SCCS__: Self-controlled case series.

Chapter Three: Safety and Tolerability of Antipsychotic Medications in Individuals with Autism Spectrum Disorder: A Systematic Review and Meta-Analysis

The systematic review and meta-analysis presented in this chapter provide an overview of the published literature investigating the safety of antipsychotic medication use in individuals with ASD. This review was published as a journal article in the Pediatric Drugs journal in May 2019[86].

The chapter starts with an introduction that provides background information covering ASD and its management. This is followed by a methodology section describing the search strategy employed to conduct this review and retrieve the literature, data extraction and synthesis process. The chapter continues with the narrative presentation of summarised results and meta-analyses of: AEs prevalence, the RR of developing AEs, mean weight changes and mean serum prolactin changes observed with antipsychotics treatment. Lastly, an update of the systematic review after January 15th 2018 is presented, followed by a discussion and summary of the main findings.

3.1. Introduction

Autism spectrum disorder (ASD) is a persistent neurodevelopmental condition characterised by social communication impairment and stereotyped repetitive pattern of behaviours.

A systematic review of worldwide prevalence studies of ASD from 1990 to 2010 estimated the global burden of ASD to be 52 million cases, equal to 7.6 per 1000 persons in 2010[21]. ASD appears to affect males more than females, with an estimated male to female ratio of approximately 3:1[24]. The lifetime cost of supporting an individual with ASD with intellectual disability was estimated to be £1.5 million in the UK and $2.4 million in the US[87].

Currently, there is no treatment to cure ASD. Symptom management is required to improve the quality of life of affected individuals. Both pharmacological and

non-pharmacological interventions are available for people with ASD. Non-pharmacological therapy includes psychological, educational, behavioural and cognitive therapies. Pharmacotherapy is reserved to treat some of the more challenging issues, such as irritability, aggression and self-injury[88].

Individuals with ASD may have other comorbid conditions, such as attention deficit hyperactivity disorder, depression, epilepsy and schizophrenia. Psychotropic medication, such as antipsychotics, antidepressants, antiepileptic drugs and stimulants have been used for ASD patients with associated comorbidities [89]. There is limited evidence to guide psychotropic medication use in the ASD population; however, a study conducted within the UK population has identified that psychotropic drugs were prescribed to 29% of ASD individuals[22]. International studies have reported that most prescribed drugs identified were sleep medication, psychostimulants and antipsychotics[90, 91].

Antipsychotic medication (first-generation and second-generation) is used for the treatment of behavioural problems in individuals with ASD[88]. Several randomised controlled trials (RCTs) have evaluated the efficacy of antipsychotics in improving some of the issues associated with ASD[74, 82, 92-94]. However, evidence of antipsychotic safety is limited and much of the evidence is drawn from case reports rather than high-quality clinical trials or even well-designed observational studies.

Adverse events associated with antipsychotic use are common and include, but are not limited to, metabolic adverse events, such as weight gain, diabetes mellitus and hyperprolactinaemia[95, 96], and movement disorders such as tardive dyskinesia, tremor and dystonia[96, 97]. Potentially serious adverse events such as

seizures are rare and potentially fatal adverse events such as rhabdomyolysis or neuroleptic malignant syndrome (NMS), have been reported[98-100].

3.2. Aim

This systematic review and meta-analysis aimed to summarise the published evidence of the adverse events (AEs) associated with antipsychotics use in patients with ASD.

3.3. Objectives

The specific objectives of this systematic review and meta-analysis were:

1. To identify the AEs reported with the use of antipsychotic medication in individuals with ASD.
2. To estimate the prevalence of these AEs.
3. To estimate the relative risk of AEs associated with the use of antipsychotic medication in individuals with ASD.

3.4. Method

3.4.1. Search terms

A systematic search was developed based on the Participant-Intervention-Comparison-Outcome-Study Design (PICOS) framework[101]. This allows for the identification of clinically relevant evidence in the literature and the formulation of the research questions. The keywords used for this systematic search with their justifications are shown in **Table 3.1**.

The keywords for this search were inserted into the databases and relevant Medical Subject Heading (MeSH) terms and free texts were identified from the search, as shown below. These MeSH terms and free texts were then included within the search strategy to guarantee that all the required terms were included

for the review. Truncation marks * were used to ensure that the search included all possible roots of the free text search.

Table 3.1: Keywords for the systematic review and meta-analyses

No.	Keywords	Boolean connection	Justification
1	Safety	1 AND 2 AND 3	The focus of this review is on the safety and tolerability of the antipsychotic medication use.
2	Antipsychotic		The intervention of this review will be the use of antipsychotic medication in the treatment of ASD. The comparator may be looking at one antipsychotic medication with another, or a different form of treatment such as psychotherapy or comparing the use of antipsychotic medication to placebo.
3	Autism spectrum disorder		The aim is to examine the population individuals with autism spectrum disorder. This will exclude other mental health disorders from the search.

3.4.2. Electronic database search

The most commonly used and recommended databases by the Centre for Reviews and Dissemination (CRD) for searching for articles and papers related to health care for systematic reviews of adverse events are the Medical Literature Analysis and Retrieval System Online (MEDLINE) and Excerpta Medica database (EMBASE)[102]. The MEDLINE database has over 26 million records and EMBASE has over 32 million records; a coverage overlap ranging from 34% to 70% were reported for these two databases[103]. The MeSH terms can be used as descriptors in extracting and expanding the search to all relevant terms[104]. PsycINFO is a database that deals primarily in the psychology field and contains over 3.5 million records.

These databases were searched using MeSH terms and free text shown in **Appendix 1**, in addition to the Cochrane Library. The literature search was completed on January 15th, 2018. Also, the bibliographies of the most relevant systematic reviews were scanned for possible additional references of interest with regard to the inclusion criteria. The review is reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines[105]. **See Appendix 1** for the complete systematic search strategy.

3.4.3. Inclusion and exclusion criteria

Studies were included if:

- They were RCTs or observational studies.
- They were conducted with participants diagnosed with ASD according to the Diagnostic and Statistical Manual of Mental Disorders, fourth or fifth revision (DSM-IV, DSM-5) or the International Statistical Classification of Diseases and Related Health Problems, tenth revision (ICD-10).
- The intervention of interest was antipsychotic medication (first or second) generation in any dose or frequency.
- The intervention could be compared with placebo, other medications, non-pharmacological therapy, or without comparison.
- They reported adverse events as the primary or secondary outcome.
- They were published in English as a full-text paper.

Exclusion criteria were:

- Studies published as case reports, case series, narrative reviews, commentaries, editorials, book chapters, grey literature or other summaries.
- Studies carried out on animals.

3.4.4. Studies selection process

First, the review author (BA) ran the search and removed duplicates. Then, two reviewers (BA and ZW) independently screened the titles, abstracts and full texts of the retrieved papers. Full-text exclusion was based on the inclusion/exclusion criteria and inconsistent decisions were resolved through consensus.

3.5. Data extraction and management

3.5.1. Data extraction

Studies meeting the eligibility criteria were extracted independently by two reviewers (BA and PM) using a pre-designed extraction form. The following information was extracted: research design, location and setting, participants, intervention, outcome measures and quality assessments (Table 3.2). Any discrepancies between the two reviewers were resolved through discussion. Kappa statistics were calculated to assess the agreements between the two reviewers on the included studies. Kappa values ranged between zero and one: zero reflects complete inter-rater disagreement and one reflects complete inter-rater agreement. The agreement can range between fair agreement, good agreement and excellent agreement if the kappa values were 0.40-0.59, 0.60-0.74 or ≥0.75, respectively[106].

Table 3.2: Data extraction form for the systematic review and meta-analyses

Characteristics	Information extracted
Research Design	Study design
	Publication year
	Length of follow-up
Location and setting	Study location (country)
	Healthcare setting
Participants	Mean Age (year)
	Sex (male %)
	Sample size (n - total, intervention group, control group)
Intervention	Medication
Outcome measures	Reported adverse events (%)
Risk of Bias	Cochrane tool for RCT and modified NOS for observational studies.

RCT; randomised control trial, NOS; Newcastle-Ottawa.

3.5.2. Assessment of risk of bias in included studies

Two reviewers (BA and PM) independently evaluated the risk of bias in each RCT using the Cochrane Collaboration tool for RCTs, which considers the following six domains: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, and selective reporting. A judgment of “high,” “low,” or “unclear” risk of bias is made for each paper. A study is considered to have a high risk of bias if one or more key domains are at high risk. A study is considered to have a low risk of bias if all key domains are at low risk. Otherwise, the study is regarded as having an unclear risk of bias[107].

The modified Newcastle-Ottawa scale (NOS) has been used for the assessment of the methodological quality and bias of the observational studies as recommended by The Cochrane Handbook for Systematic Reviews of Interventions[108] . It consists of five domains of evaluation**:** methods for selecting study participants (i.e. selection bias), methods to control for confounding (i.e. performance bias), statistical methods (i.e. detection bias), methods of measuring outcome variables (i.e. information bias) and subject follow-up[109]. Each domain ranges between zero (high risk of bias) and three (low risk of bias). Based on the reviewers’ judgment, the included observational studies were classified as high, moderate or low risk of bias if the total scores were 0-1, >1 and <2, or 2-3, respectively.

Any discrepancy in bias assessment was resolved by discussion and group consensus among the reviewers. A kappa value was calculated to assess the agreement between the two reviewers on the quality assessment of the included papers (tables of the quality assessment of the included studies are provided in **Appendix 2**).

3.5.3. Data synthesis

Study results were summarised by reporting the adverse events as percentages; a systematic narrative synthesis was provided with information presented in the text, tables and graphs to summarise and explain the characteristics and findings of the included studies.

Meta-analyses were performed under the DerSimonian-Laird random-effects model to estimate the RR with 95% confidence intervals (CIs) for the risk of adverse events in RCTs and pooled prevalence of adverse events across observational studies. RCTs were selected which provided enough information to calculate the RR, i.e. the number of patients who had AEs in both intervention and placebo groups and the number of patients who did not have AEs. Observational studies which reported the number of patients who had AEs and the total sample size number were included in the meta-analysis of the estimated pooled prevalence of AEs. To measure the degree of statistical heterogeneity between studies, I^2 was used, which rates the heterogeneity between the studies in percentages from 0 to 100%, where I^2 value <25% indicated low, 25–75% moderate, and >75% high heterogeneity[110]. To explore possible sources of heterogeneity, subgroup analyses were performed by medication. The results are presented using forest plots. All analyses were conducted using STATA, v14.1.

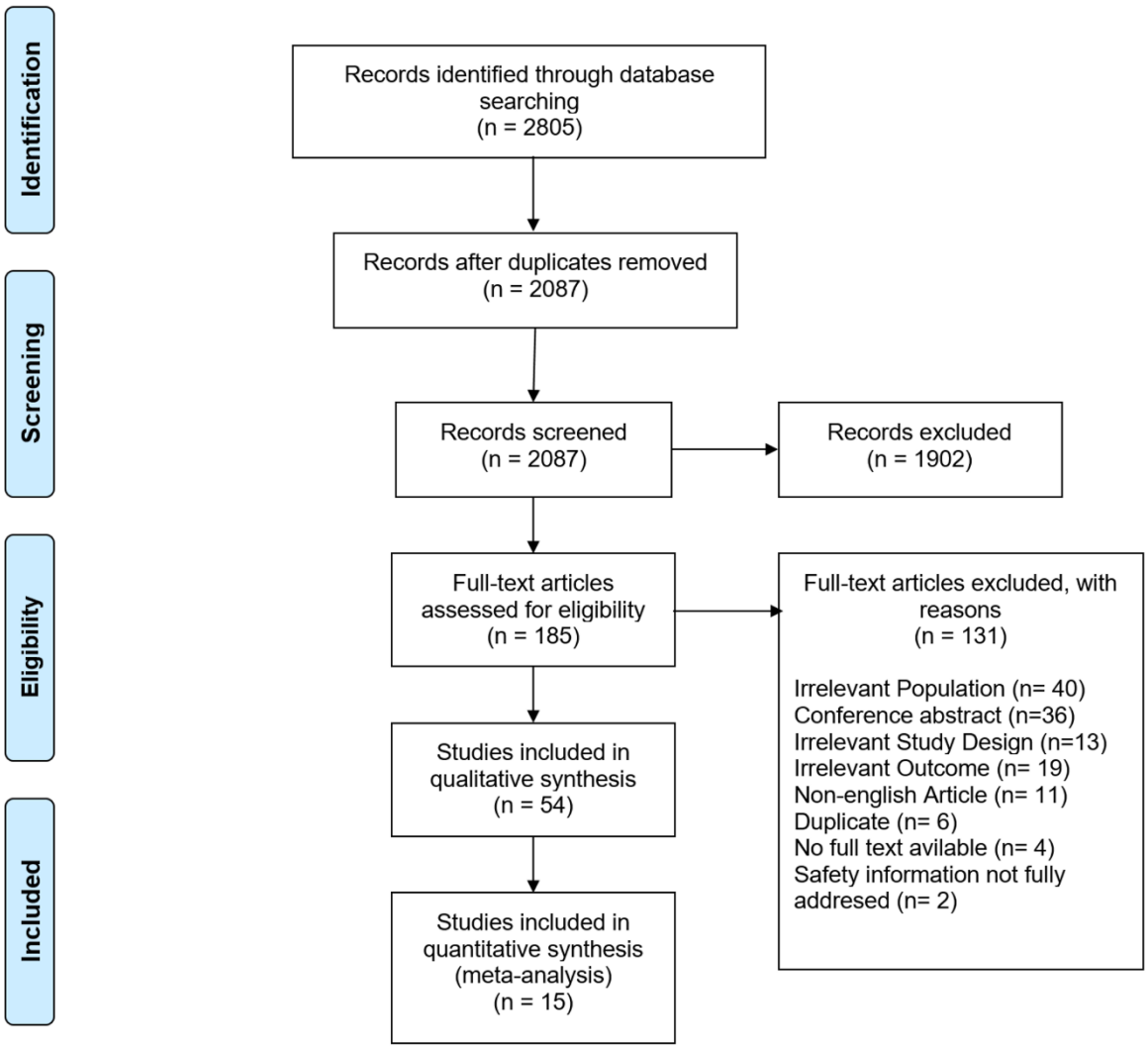
Publication bias was assessed for both included observational studies and RCTs using Funnel plots; Begg's test and Egger's test were used to test the significance of the publication bias.

3.6. Results

3.6.1. Results of the search

Two thousand eight hundreds and five citations were identified in the databases search (**Figure 3.1**); 2620 citations were removed after identification of duplicates or after the screening of titles and abstracts. One hundred and eighty-five full-text citations were assessed for eligibility. From those, 54 citations met the inclusion criteria and provided the data for the meta-analysis and narrative review. The kappa value of full-text screening was 0.72 (95% CI: 0.54-0.88) which indicates good agreement.

Figure 3.1: PRISMA flow diagram of study selection process



3.6.2 Included studies

From the 54 included studies (**Table 3.3 and 3.4**), 14 were observational and 40 were RCT studies involving 3216 participants in total. Of the 3216 participants, 2034 participated in the RCTs, while 1182 were in the observational studies. Males comprised 70% or more of the participants in most of the included studies. The overall mean age of the participants was 9.6 years. The sample size of the included studies ranged between 6 and 330 participants in RCTs and between 6 and 203 participants for observational studies. The shortest duration of follow-up was six weeks and the longest duration was approximately five and a half years in two studies; one of these was an open-label study and the other was a prospective cohort study. Detailed descriptions of the included studies can be found in **Table 3.3 and Table 3.4**. Most of the participants were medication-free for at least one week before the studies started; in some studies, anticonvulsants used for the treatment of a seizure disorder were permitted if the dose had been stable for at least four weeks and the patient was seizure-free for at least six months. Stimulants were permitted in some studies for the management of ADHD if there was no change in the dose.

From the included RCTs, 18 studies were blinded trials and 22 were open-label trials. Most of the observational studies were composed of a treatment group only, with no control group; only one observational study was a retrospective cohort study comparing the effect of risperidone and aripiprazole on body mass index (BMI) change[111]. Fifty-one studies examined the effect of second-generation antipsychotics (mainly risperidone and aripiprazole), while two studies examined the effect of a first-generation antipsychotic (haloperidol) and one study examined the effect of 14 different first-generation and second-generation antipsychotics[85]

Table 3.3: **Characteristics of included RCTs in the systematic review and meta-analyses.**

Author (Year)	Country	Sample size	Study design	Treatment duration	Sex male%	Mean Age (year)	Treatment regimen	Method used to report the adverse events
Findling, RL. et al.[112] (1997)	United states	6	Open-Label	8-week	100%	7	Risperidone	Medical records
McDougle, CJ. et al.[113] (1997)	United states	18	Open-Label	12-week	83%	10.2 ± 3.7	Risperidone	Medical records
McDougle, CJ. et al.[114] (1998)	United states	31	Double-Blind, Placebo-Controlled	12-week	71%	28.1± 3.7	Risperidone	Medical records
Nicolson, R. et al.[115] (1998)	Canada	10	Open-label	12-week	100%	7.2 ± 2.2	Risperidone	Medical records
Masi, G. et al.[116] (2001)	Italy	10	Open-label	16-week	70%	4.5	Risperidone	Parent reported/ medical records
Masi, G. et al.[117] (2001)	Italy	24	Open-label	16-week	76%	4.6 ± 8	Risperidone	Parent reported/ medical records
Masi, G. et al.[118] (2001)	Italy	25	Open-label	10-week	88%	4.1	Risperidone	Medical records
Remington, G. et al.[119] (2001)	Canada	36	Double-Blind, Placebo-Controlled, Crossover Study	7-week	83%	16.3	Haloperidol	Medical records
Kemner, C. et al.[120] (2002)	Netherlands	23	Open-Label	12-week	97%	11.2	Olanzapine	Parent reported/ medical records
Malone, RP. et al.[121] (2002)	United states	22	Open-label	1-month	82%	7.1	Risperidone	Parent reported/ medical records

Author (Year)	Country	Sample size	Study design	Treatment duration	Sex male%	Mean Age (year)	Treatment regimen	Method used to report the adverse events
McCracken, JT. et al.[66] (2002)	United states	101	RCT double blind	8-week	81%	8.8 ± 2.6	Risperidone	Parent or primary caretaker reported
Gagliano, A. et al.[68] (2004)	Italy	20	Open-label	24-week	70%	6 ± 2.4	Risperidone	Parent reported/ medical records
Shea, S. et al.[122] (2004)	Canada	79	Randomized, double-blind, parallel-group	8-week	77%	7.5	Risperidone	Parent reported/ medical records
McCracken, et al.[69] (2005)	United states	63	Open-label extension	16-week	78%	8.6 ± 2.8	Risperidone	Parent reported/ medical records
Troost, PW. et al.[70] (2005)	United states	26,24	Open-label	24-week	92%	9.4	Risperidone	Medical records
Hollander, E. et al.[94] (2006)	United states	11	Randomised Double-Blind Placebo-Controlled	8-week	82%	9	Olanzapine	Parent reported/ medical records
Luby, J. et al.[71] (2006)	United states	23	Randomized placebo-controlled study	6-month	74%	4	Risperidone	Parent reported
Nagaraj, R. et al.[72] (2006)	India	39	Randomised Double-Blind Placebo-Controlled	6-month	87%	58 month	Risperidone	Parent reported
Anderson, GM. et al.[73] (2007)	United states	101	Randomised Double-Blind Placebo-Controlled	8-week	81%	8.8 ± 2.6	Risperidone	Medical records
Malone, RP. et al.[123] (2007)	United states	12	Open-Label Pilot Study	6-week	80%	14.5 ± 1.8	Ziprasidone	Medical records

Author (Year)	Country	Sample size	Study design	Treatment duration	Sex male%	Mean Age (year)	Treatment regimen	Method used to report the adverse events
Pandina, GJ. et al.[74] (2007)	Canada	55	Double-Blind Placebo-Controlled	8-week	49%	7.4 ± 2.4	Risperidone	Parents reported /Medical records
Troost, PW. et al.[75] (2007)	Netherlands	25	Placebo-controlled discontinuation study	24-week	92%	8.6 ± 2.2	Risperidone	Medical records
Capone, GT. et al.[124] (2008)	United states	23	Open-label study	14±1-week	87%	7.8 ± 2.6	Risperidone	Telephone follow up with families
Gencer, O. et al.[125] (2008)	Turkey	28	Open-label continuation study of RCT	12-week	79%	10.9±2.9 / 10.2±2.8	Haloperidol, Risperidone	Parents reported/Hospital records
Marcus, RN. et al.[126] (2009)	United states	218	Randomized, double-blind, placebo-controlled	8-week	89%	9.7	Aripiprazole	Hospital records
Owen, R. et al.[127] (2009)	United states	98	Double-blind, randomized, placebo-controlled,	8-week	88%	9.3	Aripiprazole	Hospital records
Stigler, KA. et al.[128] (2009)	United states	25	Prospective, open-label	14-week	76%	8.6	Aripiprazole	Caregiver Reported
Hellings, JA. et al.[76] (2010)	United states	19	Additional open label study	40–272 weeks	58%	23.7	Risperidone	Medical records
Marcus, RN. et al.[129] (2011)	United states	330	Open label	52-week	87%	9.6 ±3	Aripiprazole	Hospital records
Stigler, KA. et al.[93] (2012)	United states	25	Open-label study	8-week	84%	15.3	Paliperidone	Caregiver-reported

Author (Year)	Country	Sample size	Study design	Treatment duration	Sex male%	Mean Age (year)	Treatment regimen	Method used to report the adverse events
Kent, JM. et al.[78] (2013)	United states	96	Randomized double-blind placebo controlled fixed-dose	6-week	88%	9 ± 3.1	Risperidone	Parents reported/Hospital records
Kent, JM. et al.[77] (2013)	United states	79	Open-label extension	26-week	89%	9.2 ± 3.1	Risperidone	Parents reported/Hospital records
Findling, RL. et al.[80] (2014)	United states	157 85	Phase 1: single-blind phase (stabilisation phase) Phase 2: double-blind (randomisation phase)	13-26 weeks 16-week	- 80%	NA 10.4±2.8	Aripiprazole	Patient reported
Ghanizadeh, A. et al.[81] (2014)	Iran	59	Randomised double blind clinical trial	2-month	81%	9.6 ± 3.3 9.5 ± 4.6	Aripiprazole vs Risperidone	Medical records
Loebel, A. et al.[92] (2016)	United states	150	Randomized, double-blind, fixed-dose, placebo-controlled study	6-week	81%	10.5 ±3	Lurasidone	Medical records
Scahill, L. et al.[79] (2016)	United States	124	Randomized trial of risperidone only versus risperidone plus parent training	24-week	85%	6.9 ± 2.35	Risperidone	Medical records
Vo, LC. et al.[130] (2016)	United states	101	RCT double blind	8-week	81%	8.8 ± 2.6	Risperidone	Medical records

Author (Year)	Country	Sample size	Study design	Treatment duration	Sex male%	Mean Age (year)	Treatment regimen	Method used to report the adverse events
Ichikawa, H. et al.[82] (2017)	Japan	92	Randomized, double-blind, placebo-controlled	8-week	82%	10.1±3.2	Aripiprazole	Parents reported/ medical records
Nikvarz, N. et al.[131] (2017)	Iran	30	Randomized open-label trial	8-week	77%	6.7 ± 3.2	Risperidone vs Memantine	Patients/ parents reported
Ichikawa, H. et al.[132] (2018)	Japan	86	Open-label extension	99±55 weeks	80%	10±3	Aripiprazole	Parents reported/medical records

RCTs, randomised control trials

NA, not available.

Table 3.4: **Characteristics of included observational studies in the systematic review and meta-analyses.**

Author (Year)	Country	Sample size	Study design	Length of follow up	Sex male%	Mean Age (year)	Treatment regimen	Method used to report the adverse events
Masi, G. et al.[133] (2003)	Italy	53	Prospective observational study	7.9 ± 6.8 months (range, 1-32 months)	85%	4.6 ± 0.7	Risperidone	Medical records
Corson, AH et al.[134] (2004)	United states	20	Retrospective observational study	59.8 ±55.1 weeks (range, 4-180 weeks)	80%	12.1 ± 6.7	Quetiapine	Medical records
Masi, G. et al.[135] (2009)	Italy	34	Retrospective observational study	Mean 7.0 ±3.6 months (range 4–12 months)	68%	10.2 ± 3.3	Aripiprazole	Medical records
Beherec, L. et al.[136] (2011)	France	6	Retrospective observational analysis	(Range, 8-12 months)	33%	23.2 ± 6.9	Clozapine	Medical records
Boon-Yasidhi, V. et al.[137] (2014)	Thailand	45	Cross-sectional observational study	36.8 ± 27.8 months	78%	8.1 ± 2.9	Risperidone	Medical records/ parents reported
Wink, LK. et al.[111] (2014)	United states	142	Retrospective observational study	Risperidone, 2.37 ± 2.55 years Aripiprazole, 1.47 ±1.21 years	82%	Risperidone gp 8.4 ± 3.5, Aripiprazole gp 9.7 ± 3.4	Risperidone	Medical records

Author (Year)	Country	Sample size	Study design	Length of follow up	Sex male%	Mean Age (year)	Treatment regimen	Method used to report the adverse events
Aman, M. et al.[138] (2015)	United states	84	Prospective observational cohort study	21 month	80%	8.8 ± 2.6	Risperidone	Medical records/ parents reported
Hellings, JA. et al.[139] (2015)	United states	34	A prospective cross-sectional/Retrospective chart review	4.2 years (range, 0.8–13 years)	74%	23.4	Loxapine	Medical records
Hongkaew, Y. et al.[140] (2015)	Thailand	147	Retrospective cross-sectional observational study	46.06 ±32.23 months	86%	9.5 ±3.7	Risperidone	Medical records
Ngamsamut, N. et al.[141] (2016)	Thailand	103	Observational cohort study	48.93 months	87%	9.6 ± 3.7	Risperidone	Medical records
Nuntamool, N. et al.[142] (2017)	Thailand	82	Prospective cohort/cross-sectional observational study	67.9 months (IQR: 52.53–90.93)	90%	Median age 11 (9-14)	Risperidone	Medical records
Srisawasdi, P. et al.[143] (2017)	Thailand	168	A cross-sectional observational study	60.7 months	89%	10	Risperidone	Medical records
Vanwong, N. et al.[144] (2017)	Thailand	203	Observational cohort study	61.27 months.	86%	NA	Risperidone	Medical records
Wink, LK. et al.[85] (2017)	United states	61	Retrospective observational study	509± 533 days	87%	15.1 ± 10.9	14 different antipsychotic medications	Medical records/ parents reported

NA, not available.

3.6.3. Excluded studies

The majority of excluded studies were carried out on psychiatric patients in general (i.e. the population included multiple mental health diagnoses, e.g. ADHD, schizophrenia, mood disorders and psychosis), in addition to those with ASD. Extraction of distinct safety information related to the ASD population in these studies was not feasible. Thirty-six excluded citations were conference abstracts and 13 were for study design irrelevant to the inclusion criteria: for example, reviews, case reports and letters to editors. Nine studies did not meet the eligibility criteria because they used the DSM-III criteria for ASD diagnosis.

3.6.4. Quality assessment

The included RCTs were assessed using the Cochrane Collaboration tool for assessing the risk of bias. Four RCTs were considered as low risk of bias in all six domains[72, 78, 92, 127]. Twenty-two studies were considered as high risk of bias in the study performance domain due to the open-label design[68-70, 75-77, 93, 112, 113, 115-118, 120, 121, 123-125, 128, 129, 131, 132]. According to the selection bias domain, 13 studies were judged as having an unclear risk of bias because the random sequence generation and allocation concealment were not clearly described[66, 73, 74, 79-82, 94, 119, 122, 126, 130]. One included study was judged to have a high risk of bias due to the lack of blinding of the outcome assessment[71].

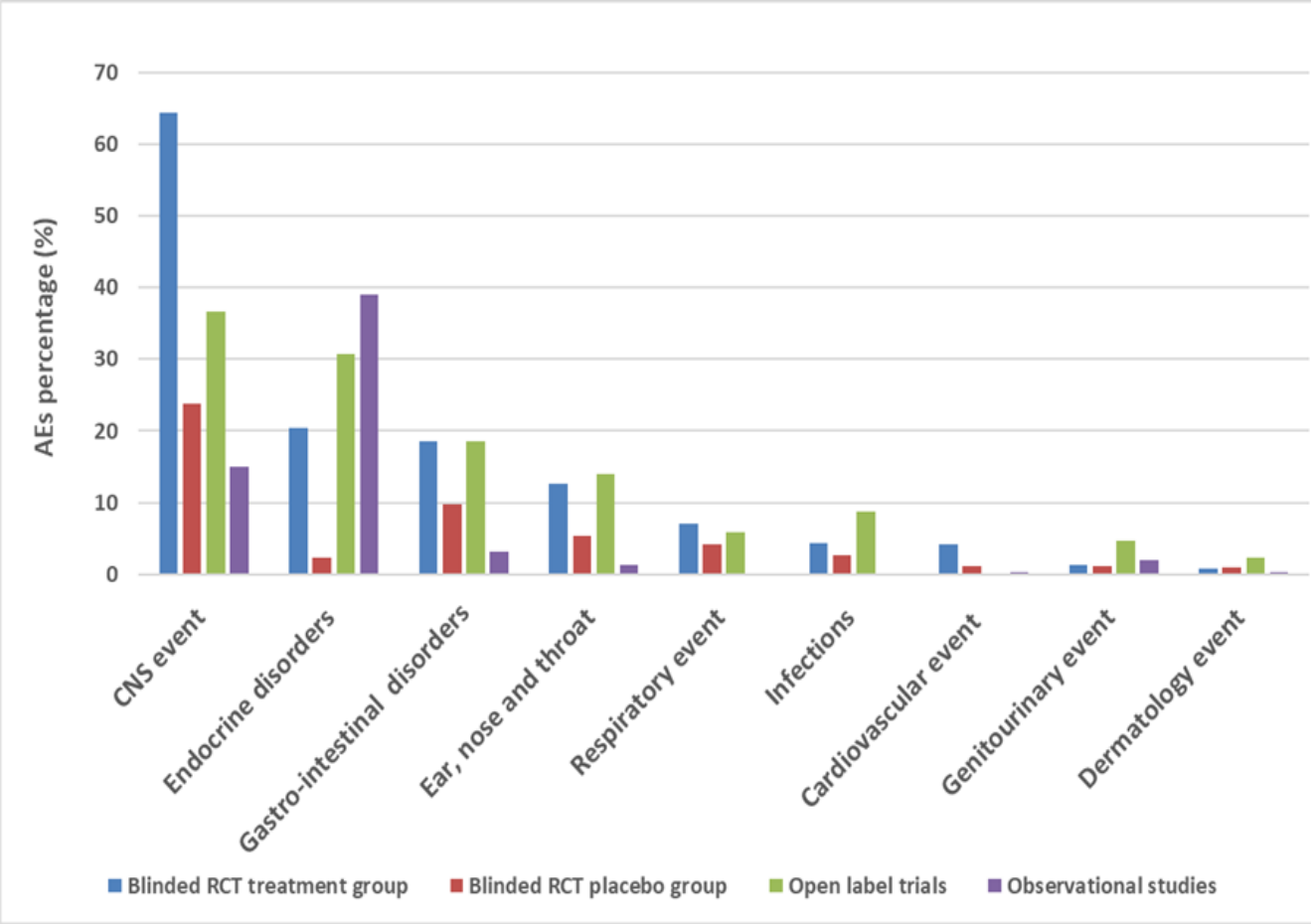
For observational studies, eight studies were judged to have a low risk of bias[85, 135, 138-143]. Six studies fell under the moderate risk of bias category[111, 133, 134, 136, 137, 144]. The agreement between the two reviewers on the quality assessment of the included papers was good (kappa value =0.63, 95%CI: -0.025 - 1.000).

The papers included in the meta-analyses were either with a low or moderate risk of bias; none of the papers with a high risk of bias was included. The details of the quality assessment are shown in **Appendix 2**.

3.6.5. Adverse events occurrence based on body systems classification

A total of 127 AEs were identified in the included studies. Central nervous system (CNS) events were the most frequent AEs identified in the RCTs included, followed by endocrine disorders and gastrointestinal disorders, respectively (**Figure 3.2**). In the observational studies endocrine disorders were the most frequent AEs identified, followed by CNS events and then gastrointestinal disorders.

Figure 3.2: Most frequent adverse events (AEs)



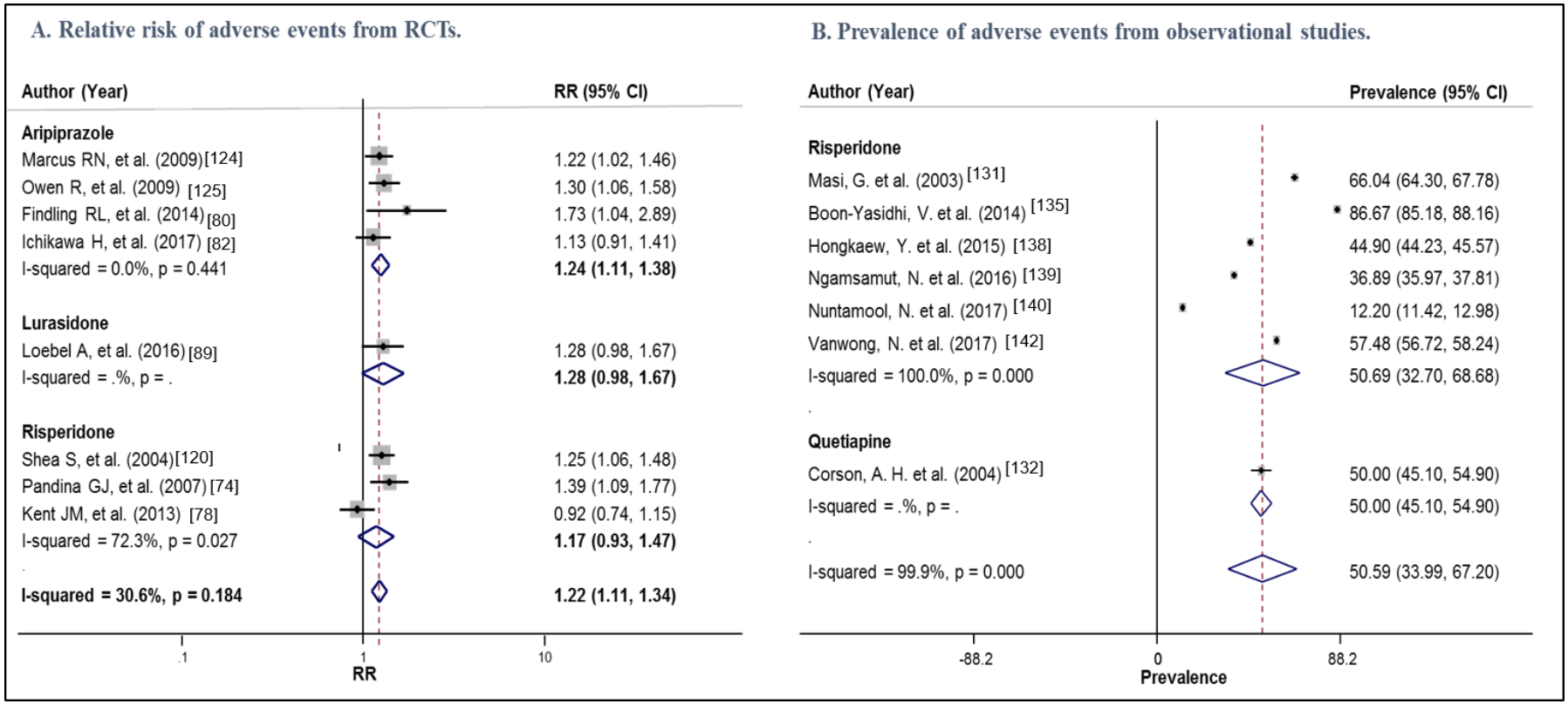
RCT, randomised control trial; CNS, central nervous system

3.6.6. Adverse events relative risk and prevalence

From the eight randomised placebo-controlled blinded studies which were included in the meta-analysis to estimate the RR of AEs associated with antipsychotic use, antipsychotic treatment increased the risk of developing AEs by 22% compared to placebo (RR= 1.22, 95% CI: 1.11-1.34, I^2= 30.6%, p= 0.184) (**Figure 3.3 (A)**).

Seven observational studies reported the total number of participants who had AEs and were included in a meta-analysis to estimate the pooled prevalence of AEs, which was 50.5% (95% CI: 33-67). However, there was significant heterogeneity in the results of the articles (I^2 = 99.9%) (**Figure 3.3 (B)**).

Figure 3.3: The forest plots of meta-analysis of RR and prevalence



RR, relative risk; RCTs, randomised control trials; CI, confidence interval

The dotted line in figure 3.3A and 3.3B refers to the pooled relative risk of adverse events and the pooled prevalence of adverse events, respectively

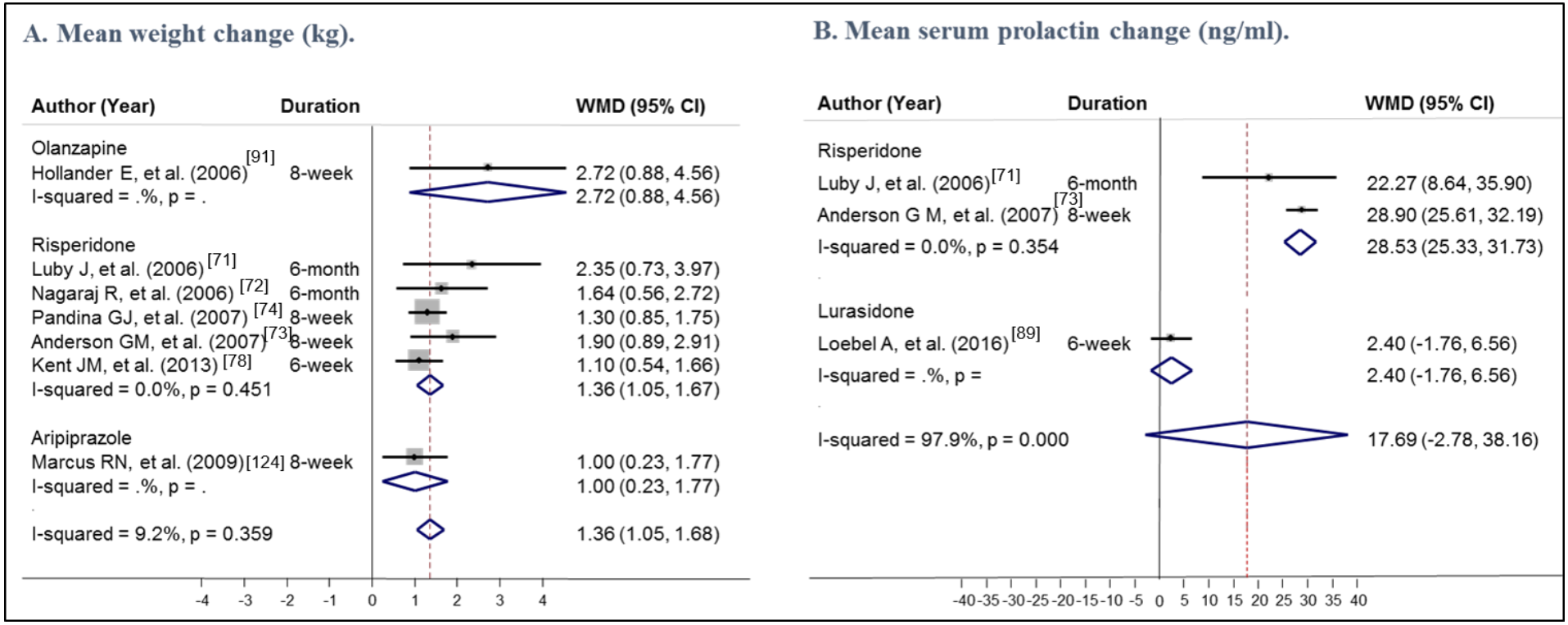
3.6.7. CNS adverse events

A wide range of CNS AEs was reported. Appetite increase was the most frequently reported, followed by sedation, somnolence and headache. Extrapyramidal symptoms, including tremor, akathisia and tardive dyskinesia were also reported frequently. Some AEs were infrequently reported but could, potentially, be serious. Examples included seizure, reported by two patients, intentional self-injury and suicidal ideation, each of which were reported once[81, 92, 127, 128]. Moreover, CNS AEs caused many participants to drop out of the study or discontinue the use of antipsychotic medication[65, 74, 75, 93, 119, 126, 127, 129, 135].

3.6.8. Endocrine adverse events

Weight gain and hyperprolactinemia were prominently reported. The result from the meta-analysis of seven RCTs demonstrated that antipsychotic medication was associated with an increase in the mean weight by 1.4 kg compared to the placebo (I^2 = 9.2%, p = 0.359). Weight was reported as one of the leading causes of study discontinuation for many participants[70, 75, 127, 129, 132, 134]. Hyperglycaemia, hyperleptinemia and increased insulin resistance were prominently reported endocrine disorders. The mean serum prolactin increased by 17.7 ng/ml compared to the placebo (I^2 = 97.9%, p <0.001). The forest plots of the meta-analysis of mean weight change and mean serum prolactin change are shown in **Figure 3.4**.

Figure 3.4: The forest plots of meta-analysis of mean weight change and mean serum prolactin change



Kg; kilogram, WMD; weighted mean difference

The dotted line in figure 3.4A and 3.4B refers to the pooled estimate of mean weight change and mean serum prolactin change, respectively

3.6.9. Cardiovascular system and other adverse events

Cardiovascular AEs were identified less frequently. A change in heart rate and prolonged QT interval were reported in 10 participants in RCTs looking for cardiac conduction effects of risperidone in children with ASD[130].

The other main AEs were: vomiting, constipation, upper respiratory tract infection, nasopharyngitis, coughing, enuresis and fatigue.

3.6.10. Publication bias

The publication bias assessment of the included studies in the meta-analysis of the RR resulted in a symmetric funnel plot. In addition, there was no evidence of publication bias from the Begg's test and Egger's test (P-value =0.54 and 0.47, respectively). Similar findings were identified for the observational studies included in the meta-analysis of the prevalence of AEs. (**Appendix 3**)

3.7. Systematic review update

For the purpose of this thesis, an update of the systematic review search was conducted on November 18th 2020. This update includes the literature that met the inclusion criteria of this systematic review and published after January 15th 2018. A similar search strategy was applied by searching the same electronic databases to retrieve the most recent studies in this area.

3.7.1. Systematic review update results

Five additional studies meeting the inclusion criteria of the original systematic review were identified. Of these, two studies were interventional trials and three studies were of an observational study design. The first study was an open label-design investigating the effect of aripiprazole treatment for irritability in children and adolescents with autistic disorder. Sixty-seven patients were treated with aripiprazole for 12 weeks[145]. The most common AE reported was weight gain,

followed by somnolence, sedation, nasopharyngitis and pyrexia. The second study was a double blinded RCT comparing aripiprazole and risperidone treatment for the management of irritability in children and adolescents with ASD[146]. In this study, 61 patients with ASD were randomised to either aripiprazole or risperidone for a 10-week period, with 31 patients completing an optional 12-week blinded extension period. During the 10-week trial period, 26% of patients taking aripiprazole experienced more than a 7% increase in their baseline weight. Among patients on risperidone, 70% experienced significant weight gain, which led to discontinuation of the treatment in two patients. During the optional 12-week extension phase, one patient taking aripiprazole terminated early due to enuresis. Among patients taking risperidone, four terminated early due to increased aggression, tachycardia, and two patients due to excessive weight gain.

Of the three recently published observational studies, one study assessed the pharmacogenetics of risperidone-induced insulin resistance in children and adolescents with ASD[147]. This study was a retrospective study of 89 patients on risperidone treatment for more than four weeks. Of the total patients, 5% presented with hyperglycaemia and 16% had insulin resistance. Another study investigated the effect of risperidone concentration on the weight change, metabolic, endocrine, extrapyramidal and cardiac side effects[148]. Forty-two children and adolescents were included in this 24-week prospective observational trial. The findings of this study showed that higher risperidone sum trough concentrations predicted higher body mass index z-scores, sedation and higher prolactin levels. No association was found between sum trough concentrations and EPS, triglycerides, total cholesterol, HDL cholesterol, LDL cholesterol, glucose, haemoglobin A_{1C} (HBA_{1C}), or QTc interval. The last study

identified in the updated search was a retrospective observational study comparing olanzapine and aripiprazole or rispiridone[149]. One-hundred and two patients with ASD were treated with one of these medications for at least eight weeks and were followed retrospectively. The most common AEs reported in this study were weight gain and sedation, which were more frequent in patients who received olanzapine. The AEs reported in the literature published after January 15th 2018 were similar to those summarised in the original systematic review. No serious AEs were reported in these studies. **Tables 3.5 and 3.6** illustrate the characteristics of recently published studies.

Of the two recent interventional studies, one of them was considered as high risk of bias due to the open label design of the study[145]. The other study considered as low risk of bias in most of the quality assessment bias; however, there was no description of randomisation and allocation which lead to unclear risk of selection bias[146]. The overall risk of bias was low among the added observational studies[147-149]. Quality assessment tables can be found in **Appendix 2**.

Table 3.5: Characteristics RCTs published after January 15th 2018

Author (Year)	Country	Sample size	Study design	Treatment duration	Sex male %	Mean Age (year)	Treatment regimen	Method used to report the adverse events
Kim, HW. et al.[145] (2018)	Asian multinational	67	Open-Label	12-week	78%	10.0 ± 3.1	Aripiprazole	Medical records
DeVane, CL. et al.[146] (2019)	United states	61	Randomised, double-Blind, parallel-group	10-week and 12-week extension	79%	8.5 (6.0-15.1) 8.3 (6.3-17.5)	Aripiprazole vs Risperidone	Medical records

RCTs, randomised control trials

Table 3.6: Characteristics observational studies published after January 15th 2018

Author (Year)	Country	Sample size	Study design	Length of follow up	Sex male %	Mean Age (year)	Treatment regimen	Method used to report the adverse events
Sukasem, C. et al.[147] (2018)	Thailand	89	Retrospective observational study	63.92 months (range, 40.40-83.49)	91%	10.0 (8.9-13.4)	Risperidone	Medical records
Kloosterboer, SM et al.[148] (2020)	Netherlands	42	Prospective observational study	24-week	76%	9.7 ± 5.3	Risperidone	Medical records
Tural, HS. et al.[149] (2020)	Turkey	102	Retrospective observational study	8-week	86%	12.07 ± 3.3 12.45 ± 3.6 11.55 ± 3.6	Olanzapine vs Risperidone and Aripiprazole	Medical records

3.8. Discussion

3.8.1. Main findings

This is an extensive systematic review and meta-analysis to evaluate the safety of and tolerability of antipsychotic medication in individuals with ASD. The meta-analysis from eight RCTs has demonstrated that the RR of developing AEs was 22% higher with antipsychotics than with placebo. The overall RR was similar to the RR stratified by the drug. The meta-analysis of seven observational studies resulted in an estimated overall AE prevalence of 50%. However, this estimated prevalence might be imprecise because of high heterogeneity and a small number of included studies. The heterogeneity could be due to the different geographic locations of the included studies, the drug type and the variability of follow-up periods, which ranged from one to 68 months.

The most frequently reported AEs identified in this review were: weight gain, enuresis, somnolence, increased appetite and extrapyramidal symptoms. These findings are similar to those that have been identified by a systematic review of antipsychotic use for challenging behaviours in people with learning disabilities[150].

The majority of the articles reported weight gain. Both short-term and long-term studies reported a greater mean weight increase with risperidone than with placebo[71-74, 78]. It is noted that long-term therapy was associated with more weight gain compared with short-term therapy. Furthermore, weight gain led to study discontinuation for many participants. Psychiatrists are encouraged to consider weight gain evaluation in individuals on antipsychotic therapy. Although hyperprolactinemia was one of the frequently identified AEs, elevated serum prolactin was not reported in any of the studies on aripiprazole. This finding is

consistent with what has been published previously regarding the relationship between hyperprolactinemia and aripiprazole compared to other antipsychotic therapy[151]. There were reports of elevated prolactin with risperidone being decreased by the addition of aripiprazole[152, 153].

NMS is an uncommon but potentially fatal AE that may occur with antipsychotic treatment. In this systematic review, no cases of NMS were identified, most probably because there are no published observational studies or RCTs investigating the association between the use of antipsychotic medication in individuals diagnosed with ASD and the risk of developing NMS. Furthermore, this serious adverse event appears to be rare. The implication is that very large numbers would be required to yield valid frequency data.

Within this systematic review, some serious AEs were infrequently reported, including cardiac events and seizures. There is a lack of evidence regarding the association between the use of antipsychotic medication in a population with ASD and the risk of these adverse events. Therefore, this PhD project aimed to fill this gap in the knowledge. In the subsequent chapters of this thesis, different observational studies that examine the hypothesis that patients with ASD who are exposed to antipsychotic medications are at greater risk of developing seizures and cardiac problems will be presented.

3.8.2. Strengths and limitations

This is the first systematic review to assess the safety of both first-generation and second-generation antipsychotics in individuals with ASD. It provides an evidence-based overview of the prevalence and type of AEs associated with antipsychotic medication use in people with ASD. The publications included in this review were identified through electronic searches from four different

databases using a comprehensive search strategy to provide the best chance of identifying all relevant citations. In addition, this review follows the standard methodology of systematic review and meta-analysis which is recommended by the Cochrane and PRISMA checklists[101, 105] .

The potential limitations of this systematic review include the following: i) one of the major limitations in most of the included RCTs studies was that the safety of the antipsychotic medication was a secondary outcome and the primary outcome was its efficacy. This reflects on the quality and completeness of safety data. ii) the quality of some of the included studies was questionable. First, most of the observational studies were composed of one group (intervention arm), which did not allow us to draw any comparisons. Second, almost half of the RCTs included were open-label studies, which increases the risk of bias in outcome measurements. Third, the sample sizes were very small in many reviewed studies, and could be unrepresentative: eight studies had a sample size of fewer than 20 participants. However, these studies were included due to the lack of well-designed clinical trials investigating the safety of antipsychotics in the ASD population. Fourth, even though the agreement between the two reviewers on the quality of the included papers was good, there was a wide CI; hence, this value may not provide enough information to make a decision and should be interpreted with caution. iii) the overall I^2 values were markedly high for the meta-analysis of AEs prevalence and the mean serum prolactin change: 99% and 97%, respectively. This indicates high heterogeneity between the studies included in the meta-analysis. iv) although no evidence of publication bias was identified by the Begg's test and Egger's test, these tests could be underpowered due to the small number of studies included in the analysis. v) only studies published in English were included in this review; this may lead to language bias. However,

Moher et al. found that the exclusion of trials published in a language other than English had no significant effect on meta-analyses results[154]. Furthermore, over the past two decades, the number of RCTs published in a language other than English has been declining, which may diminish the extent of language bias introduced[155].

This systematic review highlighted that the majority of published studies on antipsychotic medication use in populations with ASD, which have reported an associated AEs. Currently, the available evidence on the association between antipsychotic use in individuals with ASD and the risk of developing AEs is limited. The findings of this review highlight the need for well-designed safety and tolerability studies to investigate the association between antipsychotics in individuals with ASD and adverse events.

3.9. summary

- A total of 54 studies were included in this systematic review; of these, 14 were observational studies and 40 studies were RCTs.
- The estimated pooled RR of AEs associated with antipsychotic use was 1.22, 95% CI: 1.11-1.34 (I^2= 30.6%).
- The estimated pooled prevalence of AEs was 50.5%, 95% CI: 33-67 (I^2 = 99.9%).
- CNS and endocrine disorders were the most commonly reported AEs.
- Antipsychotic medication was associated with a 1.4 kg increase in mean weight compared to placebo (I^2 = 9.2%, p = 0.359). The mean serum prolactin associated with antipsychotic medication use increased by 17.7 ng/ml compared to the placebo (I^2 = 97.9%, p <0.001).

- CNS adverse events and weight gain caused many participants to drop out from the study or discontinue the use of antipsychotic medication.
- Five studies published after January 15th 2018 were identified; the reported AEs in these studies were consistent with what was presented in the original systematic review.

Chapter Four: Data Source

This chapter provides an overview of the IQVIA Medical Research Data (IMRD-UK) database, which has been used as the source of data to conduct the analyses of the studies in Chapters Five, Six, Seven and Eight. The chapter will give a general overview of the health care structure in the UK. This will be followed by an overview of the primary care databases available in the UK. Then, the IMRD-UK database will be described in-depth, including validity and generalisability, structure and content, information recording and strengths and limitations.

4.1. Healthcare structure in the UK

The healthcare system in the UK consists of a public and private health care sector. The National Health Service (NHS) was established in 1946 and is responsible for the public healthcare sector of the UK[156]. Public healthcare is provided to all permanent residents in the UK, free at the point of delivery, and is funded by general taxation. Approximately 8.5% of the UK's Gross Domestic Product (GPD) is spent on healthcare, of which 7.3% is spent on public health and 1.2% on private[157].

The healthcare in the UK is divided into primary care, secondary care and tertiary care. The majority of healthcare is delivered through the primary care sector. It is often the first point of contact for people in need of healthcare, and it is provided by professionals such as general practitioners (GPs), dentists and pharmacists. Secondary care is hospital-based care, specialist clinics or community-based care accessed by either elective care through GP referrals or by emergency care. Tertiary care refers to highly specialised healthcare services, such as neurology, organ transplants and oncology.

4.2. Primary care databases in the UK

There are three major primary care health electronic databases in the UK: The Clinical Practice Research Datalink (CPRD), formerly known as the General Practice Research Database (GPRD); the IQVIA Medical Research Database (IMRD-UK), known previously as The Health Improvement Network (THIN), and QResearch. The Prescribing Analysis and Cost database and the Quality Management and Analysis System are other primary care databases; however, the data contained in these databases are not based on individual patient-level records. For all three major primary care databases, anonymised patient information on symptoms, diseases and other medical conditions is recorded using the Read code system.

Electronic health care databases have been widely used as data sources for scientific research. From 1995 to 2015, the publication output of research that has used primary care databases in the UK to extract and analyse data from electronic health records has increased at a yearly rate of 18.6%[158]. Over a ten-year period (from 2004 to 2013), CPRD, IMRD-UK and QResearch collectively produced 1,296 publications[159]. The CPRD has been mostly used by research conducted in pharmaco-epidemiology and drug safety and was sourced for 63.6% of these publications. The IMRD-UK database was sourced for 30.4% of the total publications, and the area of research derived from IMRD-UK was similar to that of the CPRD. Papers derived from the QResearch database amounted to 5.9% of the publications, and most of these papers were about general and internal medicine speciality areas. **Table 4.1** provides a simple comparison between these three databases.

GPs may contribute patient-level data to more than one database, which results in overlapping data within them. A cross-sectional study aimed at assessing the proportion of overlapping patients between the CPRD and IMRD-UK among patients initiating saxagliptin using demographic and pharmacy variables found that over 60% of the identified patients were included in both databases[160]. Another study was conducted to compare the estimates of disease burden between the CPRD and IMRD-U from 1998 to 2006[161]. This study found comparable results of venous leg ulceration burden produced by data collected from 2000 to 2006

Table 4.1: Comparison between major primary care databases in the UK

Database	Establishment	Coverage	Linkage to HES[3]	Funder
CPRD[1162]	Has provided longitudinal anonymised patient-level data from 1987	More than 1,900 practices contribute to the CPRD and provide data of 50 million patients (15 million of them are currently active)	√	Funded by the NHS National Institute for Health Research (NIHR) and the Medicines and Healthcare products Regulatory Agency (MHRA).
IMRD-UK[2163, 164]	Patient-level records have been available since 1987	Includes non-identified electronic patient health record data from over 18 million patients collected from over 550 practices	√	IQVIA
QReseach[165]	Provides historical patient-level records dating back to1989	Data in QResearch come from 2,530 practices and provide information about more than 35 million patients	√	Self-funded

[1] Clinical Practice Research Datalink (CPRD)

[2] IQVIA Medical Research Database (IMRD)

[3] Hospital Episode Statistics (HES)

4.3. Database in this thesis

Both the CPRD and IMRD-UK are representative of the UK population and can be used as a data source to answer the questions of this thesis. As mentioned before, they are widely used for pharmaco-epidemiological studies and provide comparable estimates of disease burden. Access to the CPRD dataset requires protocol approval by the MHRA and is subject to fees. In 2003, the South East Multicentre Research Ethics Committee (MREC) approved data collection for THIN. No separate ethical approval is required for studies using anonymised data from THIN; however, the study protocol must be reviewed by an independent Scientific Review Committee (SRC) to guarantee appropriate data handling. The School of Pharmacy (SoP) at UCL has a license to access IMRD-UK. Through this license, an IMRD-UK dataset can be requested for academic research purposes after obtaining ethical approval from the SRC.

Like most ongoing data analyses projects at UCL SoP, IMRD-UK was selected to be the source of data for the studies carried out during this project. First, a drug utilisation study (DUS) using data on ASD diagnosis and medication prescribing patterns over a period of eight years was conducted. This was followed by three analytical studies to assess the safety of psychotropic medication use in individuals with ASD by extracting exposure and outcome data of a large ASD cohort. The methodology, population and results of these studies will be described in subsequent chapters.

4.4. IMRD-UK

In 2016, Quintiles and IMS Health, Inc. were merged to form IQVIA, a multinational human data science company. IQVIA is one of the world's largest contract research organizations (CRO). These longitudinal medical data provide patient-level information for more than 800 million non-identifiable patients worldwide[166]. The IQVIA medical research database (IMRD) incorporates data from THIN, a UK primary care database which is currently known as IMRD-UK.

4.4.1. Validity and generalisability

Data from IMRD-UK are validated for pharmaco-epidemiological research[164]. IMRD-UK contains data that is derived exclusively from Vision software developed by In Practice Systems Ltd (INPS) to manage patient data by GPs in the UK[159]. Vision/INPS is a problem-oriented medical record (POMR) software which encourages the data entry to be linked to a previously entered condition instead of creating multiple separate entries for each patient[167]. This approach decreases the variability in data coding for each patient and enhances the quality of the data[167]. Furthermore, patient data in IMRD-UK are classified using different patient flags: flag A and C indicate data integrity and acceptable patient records.

The completeness and accuracy of data recording in UK primary care are influenced by the Quality and Outcomes Framework (QOF)[168]. The QOF is a UK national incentive-based system introduced in 2004 to improve the quality of chronic disease management in primary care[169]. QOF condition prevalence, deaths and demographic data from IMRD-UK were compared with national statistical and QOF 2006/2007 data. This comparison confirmed the generalisability of data derived from the IMRD-UK concerning the UK population[170].

4.4.2. Structure and content

Data from IMRD-UK are organised by general practice and each practice file is divided into four main files linked by a practice ID. Patient information within these files is linked by a patient ID. The *Patient* file contains information on patient characteristics, such as sex and year of birth. Registration details are also presented in this file to determine person-time in the database. In the *Medical* file, there are multiple records of symptoms, diagnoses and interventions recorded by the GP or transcribed from discharge summaries following hospital stays or from letters sent by specialists. Data on detailed medication prescriptions, including formulation, strength, dose and quantity prescribed, are available in the *Therapy* file. Lastly, data on immunisations and clinical measurements (test results) can be obtained from the *Additional Health Data* (AHD) file.

4.4.3. Information recording in IMRD-UK

Anonymised patient information in IMRD-UK is recorded as coded data using Read codes for clinical information such as symptoms and diagnoses. The Read code is a hierarchical classification system of clinical terms which has been in use in the NHS since 1985. It was created to allow health care providers to record patients' medical conditions. Data on medication prescriptions in the *Therapy* file are presented as drug codes corresponding to British National Formulary (BNF) codes, which are based on BNF chapters. AHD codes are used to record other clinical measurements of the patients.

The Read codes are updated quarterly for clinical terms, and monthly for drugs[171]. A medical dictionary for Read codes and a drug dictionary for drug

codes are available for researchers to develop relevant code lists. A code list is a comprehensive set of condition-specific medical or drug codes which can be used by researchers to extract data which helps to identify cases, exposures or covariates of interest.

4.4.4. Strengths and limitations

IMRD-UK has several strengths: 1) data on the IMRD-UK are regularly updated and are representative of the UK population[170]; 2) data recoded are real world data, representing real primary care; 3) unlike conventional data collection, a large sample size can be obtained for pharmaco-epidemiological studies through reduced time and costs; 4) IMRD-UK data have been recently linked to Hospital Episode Statistics (HES) data, which expands the utility of IMRD-UK by providing data from the secondary care settings; 5) IMRD-UK provides longitudinal data dating back to 1987, which is useful for research that requires long follow-up periods, and 6) information on the socioeconomic status of patients can be linked to their postcode. Postcode variable indicators (PVI), such as the Townsend score of deprivation, and rurality indicators, are also recorded in IMRD-UK.

However, there are some limitations in the IMRD-UK that may affect the ability to answer some research questions: 1) data derived from IMRD-UK are recorded for primary care purposes and not for research purposes; therefore, the chance of missing data exists; 2) data on medication prescribing are not directly linked to the indications, and information on medication administration or adherence are not provided; 3) ethnicity recording in IMRD-UK is poor and unrepresentative of the UK population; 4) there might be some underestimation of the medication prescription rate due to the lack of information on off-label or

controlled medication prescribing. According to NICE guidelines, off-label use of medication is when it is prescribed in a different way than that stated in its licence: for example, using it for different indications, or for different group of patients or changing the dose or means of administration. The Misuse of Drugs Act 1971 has defined and regulates the use of controlled drugs; they are closely regulated because they are susceptible to being misused and can cause harm. Both the off-label controlled drugs can be re-prescribed by GPs; however, they might only be initiated by specialists, and finally 5) although IMRD-UK data have been linked to HES data, this linkage took place in September 2017. Therefore, secondary care data are only available since then and not before.

Chapter Five: Psychotropic Medication Prescribing for Neuropsychiatric Comorbidities in Individuals Diagnosed with Autism Spectrum Disorder (ASD) in the UK: Drug Utilisation Study (DUS)

In this chapter, the results of a descriptive study performed to describe the incidence/prevalence of ASD over a period of eight years and its management in the UK are presented. First, the population included in this study is defined. This is followed by an explanation of the definition of ASD incidence and prevalence: the neuropsychiatric comorbidities of interest and the psychotropic medication classes described in the study. Lastly, the results of the analyses are presented and the chapter ends with a discussion and summary of the main findings.

The findings from the study in this chapter have been published in the Journal of Autism and Developmental Disorders in Nov 2019, under the title: "Psychotropic Medication Prescribing for Neuropsychiatric Comorbidities in Individuals Diagnosed with Autism Spectrum Disorder (ASD) in the UK"[172].

5.1. Introduction

Prior to this study, a study (published in 2014) was carried out within a population diagnosed with ASD in the UK, using the same data source used in this research[22]. This study gave a comprehensive description of ASD in children, adolescents and young adults aged <25 years for the period from 1992-2008. Murray at al. reported a 65-fold increase in ASD prevalence from 1992 to 2008[22]. The study presented in this chapter describes ASD incidence/prevalence in the UK and its management over the period from 2009 to 2016, including a broader population of all age groups.

Psychotropic medications, such as antipsychotics, antidepressants, antiepileptic drugs and stimulants, have been used for ASD patients with associated comorbid conditions[89]. There is, however, limited evidence to guide psychotropic medication prescribing in the ASD population. As briefly mentioned in Chapter One, risperidone is the only antipsychotic medication approved for the

management of behavioural disorders in children and adolescents associated with ASD diagnosis in the UK. Risperidone was approved in 2007 for the management of behavioural disturbance in children and adolescents with autism and conduct disorder by the EMA and the MHRA of the United Kingdom[63, 64]. Both risperidone and aripiprazole are approved by the FDA for the management of irritability in children and adolescents with ASD autism[61, 62].

The findings of the study presented in this chapter will enable a detailed understanding of how medications are being used in patients with ASD so that safety and efficacy studies can be planned for this specific population. A specific research objective of this study was to investigate whether the approval of risperidone for the treatment of ASD symptoms has affected the pharmacotherapy prescribing pattern within a population with ASD. An additional objective of this study was to examine the duration of treatment for different psychotropic drug classes over the study period using survival analysis.

5.2. Objectives

The specific objectives of this DUS were:

1. To assess the incidence and prevalence of ASD diagnoses per calendar year from 2009 to 2016, stratified by age groups and gender.
2. To describe neuropsychiatric comorbidities associated with ASD.
3. To investigate the pattern of psychotropic medication prescribing in a population with ASD, stratified by medication class and individual drug.
4. To examine the retention rate of each psychotropic medication class.

5.3. Methods

5.3.1. Study design

The study presented in this chapter is an observational descriptive study conducted to provide an up-to-date overview of the ASD disease and related medication prescribing in the UK.

5.3.2. Data source

Data for this study were provided by the IQVIA Medical Research Data (IMRD-UK) database (see Chapter Four).

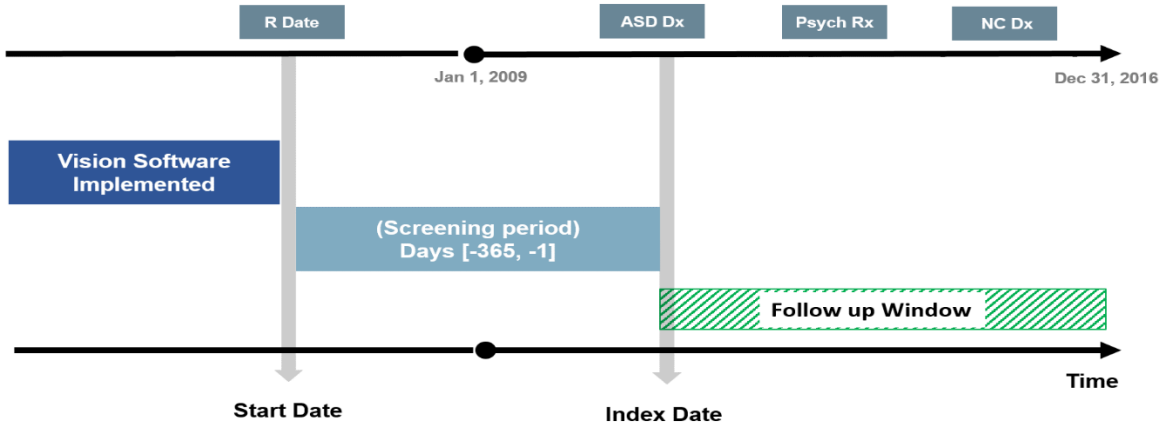
5.3.3. Ethical approval

Ethical approval for this fully anonymised study was obtained from the Scientific Review Committee (SRC) which was established to review research using the IMRD-UK database (ref: 18THIN010), **see Appendix 4**.

5.3.4. Population

In this study, patients from all age groups who had a record of ASD diagnosis between 1st of January 2009 and 31st of December 2016 were identified. The start date for each patient was the latter of the patient's registration at the general practice date or the date at which the GP started to use Vision software (a computerised clinical management system). To confirm that the first record of the ASD diagnosis was truly the first diagnosis date, only patients who had a twelve-month screening period from the start date to the first ASD record were included (**see Figure 5.1**). The index date for each patient was the date of the first-recorded ASD diagnosis following the patient's start date. Age at first ASD diagnosis was defined as the time between the birth year and the diagnosis year. The patients were followed from their index date to the end of the study period.

Figure 5.1: Follow-up period of drug utilisation study



a. Vision Software is a computerised clinical management system used by general practices to record patient information.
b. Start Date is the latest of either the date of the patient's registration at the general practice or the date that the general practice began using Vision software.

R Date = date of patient's registration in the GP.
ASD Dx = Autism spectrum disorder diagnosis.
Psych Rx = Psychotropic medication prescription.
NC Dx = Neuropsychiatric comorbidity diagnosis.

5.3.5. Incident/prevalent cases definition

ASD Read codes were used to identify ASD cases; the Read codes list for ASD diagnosis used in this PhD project was validated by Fombonne et al.[173] (**see Appendix 5**). This list has been used in other published studies carried out using UK primary care databases[174, 175]. Additionally, the IMRD-UK database was searched to update the ASD Read code list and one Read code that had not been used in previous studies was added. This read code was (Eu84z11) and the description of this code is (autistic spectrum disorder).

In order to provide consistent information with what was provided by the Murray et al. study on ASD incidence and prevalence, a similar definition of incident and prevalent cases of ASD were applied. The ASD incident patients were defined as 1) patients who had a first diagnosis of ASD following the first-year screening period; 2) patients with an ASD diagnosis aged < 2 years during the 12-month screening period (ASD is usually diagnosed at age two or older; if the patient had a record under two years of age, they were counted as an incident case). The prevalent patients were defined as all patients who had a record of ASD diagnosis in each particular year regardless of whether it was the first diagnosis recorded or not. Considering the fact that ASD is a lifelong condition, if the patients had the diagnosis previously they would be counted as prevalent cases later. For example, if a patient was diagnosed with ASD in 2009 and not re-diagnosed in the years after, he would be counted as an incident case only in 2009 and as a prevalent case in 2009 onward as long as he exists in the database.

5.3.6. Neuropsychiatric comorbidities

A number of neuropsychiatric conditions were identified based on data from the National Institute for Health and Care Excellence (NICE) guideline on the

management of ASD in individuals under 19 years of age[7] and a literature review[22, 29]. The neuropsychiatric comorbidities recorded on or after the index date were identified and the proportions of the ASD cohort who developed these comorbidities were calculated.

The neuropsychiatric conditions included were: ADHD, anxiety, behavioural/conduct disorders, intellectual disabilities, sleep disorders, depression, epilepsy, schizophrenia and tic disorders. The Read code lists used to identify these comorbidities were obtained from the official website of the University of Cambridge[176] and published studies[22, 177-179] (**Appendix 6**). The descriptions of the codes have been reviewed by Professor Frank Besag, Consultant Neuropsychiatrist in Bedford and London.

5.3.7. Psychotropic medication

The records of the following psychotropic medication classes identified from the literature review of published studies with similar objectives were extracted: stimulants, antidepressants, antipsychotics, antiepileptic medication, anxiolytics and hypnotics. Drug code lists for each psychotropic medication class were used to identify the records of psychotropic medications prescriptions; medication lists for each class were obtained from Chapter 4 of the British National Formulary (BNF)[40] (**see Appendix 7&8**).

The prescriptions for the study drugs of each patient recorded on or after their index date were identified and the annual proportions of the ASD cohort prescribed drug treatment were calculated by drug category and by individual drug.

5.3.8. statistical analysis

5.3.8.1. Incidence/prevalence

Descriptive statistics were used to describe the patients' demographic characteristics. The annual incidence/prevalence of ASD was calculated by gender and according to the following age groups: children at age 2 years or younger, 3–5-year olds (young children), 6–12-year olds (children), 13–17-year olds (adolescents), 18–24-year olds (young adults), 25-64-year olds (adults) and ≥ 65-year olds (elderly). The annual incidence/ prevalence per 1,000 persons was calculated according to the following equation:

Annual incidence:

$$Incidence\ of\ ASD\ at\ year\ x = \frac{All\ patients\ with\ incidence\ of\ ASD\ in\ year\ x}{The\ total\ number\ of\ individuals\ in\ IMRD - UK\ mid - year\ population\ in\ year\ x}\ X\ 1000$$

In epidemiology, the incidence rate of a condition is defined as the number of new cases diagnosed with this condition in year(x) divided by the number of the population at risk (total population in year(x) - prevalent cases in year(x)). In the equation above, the denominator is the total number of individuals present in the database in year(x) including prevalent cases in that given year. This is because in this study, a huge database that contains data on millions of people is used. Therefore; the number of people with ASD diagnosis relative to the total population in each year is negligible and does not affect the incidence rate estimation [22, 180-182].

Annual prevalence:

$$Prevalence\ of\ ASD\ at\ year\ X = \frac{All\ prevalent\ patients\ in\ active\ follow-up\ of\ year\ x}{The\ total\ number\ of\ individuals\ in\ IMRD-UK\ mid-year\ population\ in\ year\ x}\ X\ 1000$$

5.3.8.2. *Comorbidities*

The percentage of the ASD cohort having other neuropsychiatric diagnoses was calculated by dividing the number of patients having a record of each diagnosis over the total ASD cohort multiplied by 100.

5.3.8.3. *Drug utilisation*

The annual proportion of ASD patients treated with psychotropic drugs was calculated by dividing the number of treated patients in each class in a year by the ASD prevalent cases in the same year multiplied by 100. A secondary analysis was performed by excluding patients with only one psychotropic drug prescription. The Kaplan-Meier survival analysis was used to estimate the average retention rate of psychotropic drugs in this cohort. Analyses were performed using the Statistical Analysis System (SAS) version 9.4.

5.4. Results

5.4.1. Descriptive results

Over the study period, there were 20,194 patients with at least one recorded diagnosis of ASD: 78% of them were male. The mean age of the first recorded diagnosis among females was 14.03 (SD 11.9) years and 11.5 (SD 10.7) years among males. Further details of the study cohort are provided in **Table 5.1**.

Table 5.1: Patients characteristics in the drug utilisation study

Cohort characteristics	All	Male	Female
Number of subjects (%) with at least one diagnosis of ASD	20194 (100%)	15923 (78.9%)	4271 (21.1%)
Age at first recorded diagnosis of ASD (%)			
0-2	369 (1.8%)	307 (1.5%)	62 (0.3%)
3-5	5094 (25.2%)	4225 (20.9%)	869 (4.3%)
6-12	8601 (42.5%)	7021 (34.7%)	1580 (7.8%)
13-18	3263 (16.1%)	2325 (11.5%)	938 (4.6%)
19-24	858 (4.2%)	609 (3.0%)	249 (1.2%)
25-64	1944 (9.6%)	1389 (6.8%)	555 (2.6%)
≥65	65 (0.3%)	47 (0.2%)	18 (0.09%)
Neuropsychiatric comorbidities (%)			
Behavioural/conduct disorders	6208 (30.7)	5023 (24.9)	1185 (5.8)
Anxiety	3077 (15.2)	2085 (10.3)	992 (4.9)
Attention deficit hyperactivity disorder (ADHD)	2897 (14.3)	2454 (12.1)	443 (2.2)
Depression	2234 (11.0)	1459 (7.2)	775 (3.8)
Intellectual disabilities	2093 (10.3)	1591 (7.8)	502 (2.5)
Epilepsy	909 (4.5)	652 (3.2)	257 (1.3)
Sleep disorders	879 (4.3)	682 (3.4)	197 (0.9)
Tic disorders	411 (2.0)	359 (1.8)	52 (0.2)
Schizophrenia	152 (0.7)	117 (0.5)	35 (0.2)
Psychotropic medication prescribing (%)			
Hypnotic	1894 (9.3)	1510 (7.4)	384 (1.9)
Antidepressant	1836 (9.0)	1218 (6.0)	618 (3.0)
Stimulant	1163 (5.7)	1015 (5.0)	148 (0.7)
Antipsychotic	814 (4.0)	614 (3.0)	200 (1.0)
Antiepileptic	585 (2.8)	418 (2.0)	167 (0.8)
Anxiolytic	237 (1.1)	162 (0.8)	75 0.3)

5.4.2. Incidence/ prevalence of ASD diagnosis

The incidence of ASD rose 2.9-fold during the period 2009 to 2016: from 0.226 per 1000 persons (95% CI, 0.226–0.227) to 0.647 per 1000 persons (95% CI, 0.646–0.648). The incidence rate increased 5.1-fold among females and 2.5-fold among males. During the study period, the incidence of ASD was the highest in 2016 among young children aged from 3 to 5, at 4.505 per 1000 persons (95% CI, 4.493–4.517). The annual ASD incidence is shown in **Figures 5.2 and 5.3**.

Figure 5.2: ASD annual incidence

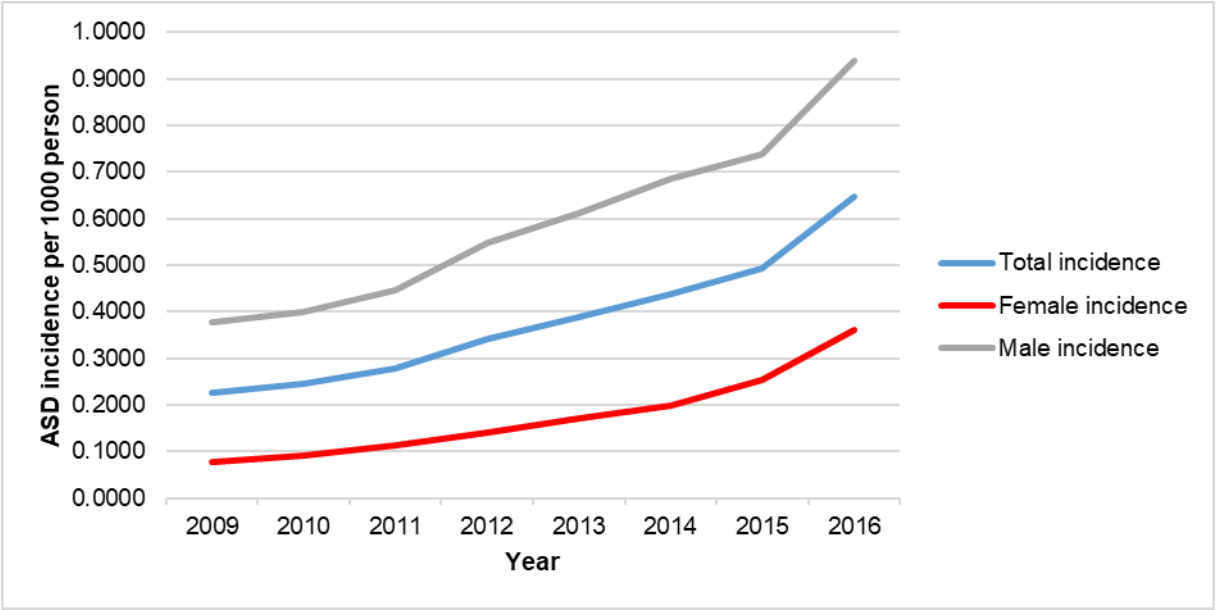
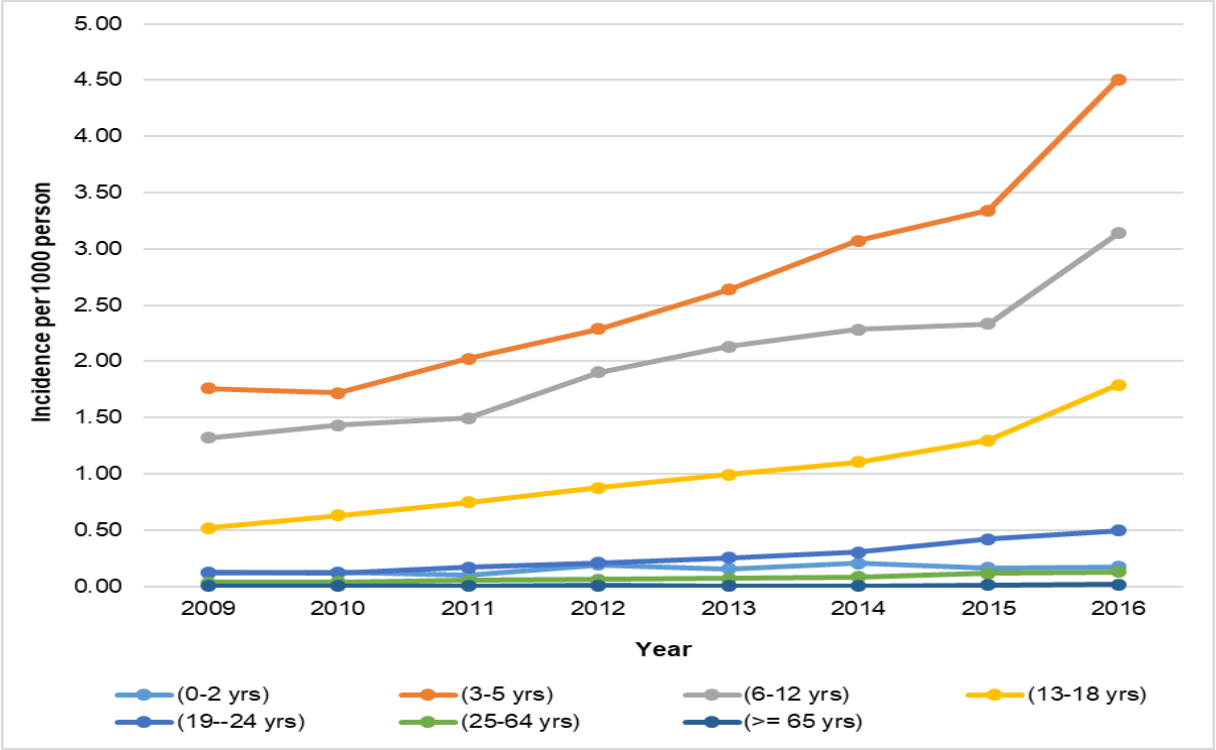


Figure 5.3: ASD annual incidence stratified by age groups



Over the study period, the prevalence of ASD increased 3.3-fold from 1.095 per 1000 persons (95% CI, 1.094–1.096) in 2009 to 3.555 per 1000 persons (95% CI, 3.553–3.557) in 2016. Generally, the prevalence of ASD was higher among males than females. In 2016, the ASD prevalence was 1.576 per 1000 persons (95% CI, 1.574–1.577) and 5.576 per 1000 persons (95% CI, 5.573–5.580) in females and males, respectively. The prevalence of ASD was highest in individuals in the age groups of 6 to 12 years (children) and 13 to 18 years (adolescents). In 2016, the prevalence of ASD was 16.092 (95% CI, 16.077–16.107) per 1000 persons in children and 15.694 per 1000 persons (95% CI, 15.678–15.710) in adolescents. **Figures 5.4 and 5.5** show the detailed annual prevalence of ASD.

Figure 5.4: ASD annual prevalence

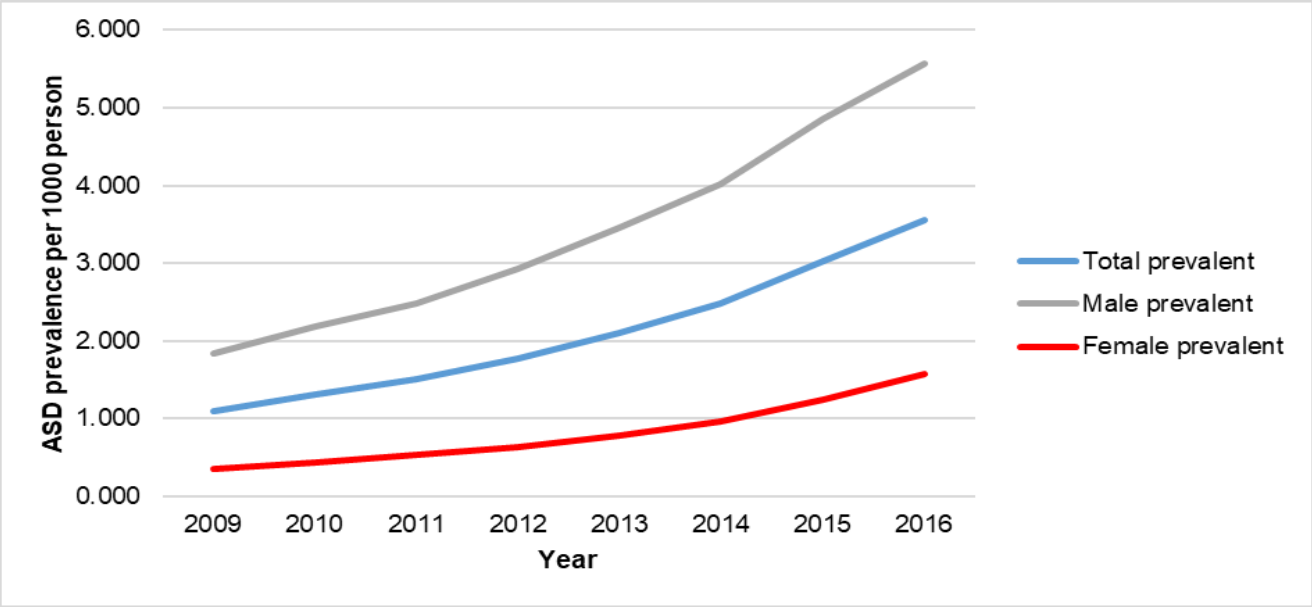
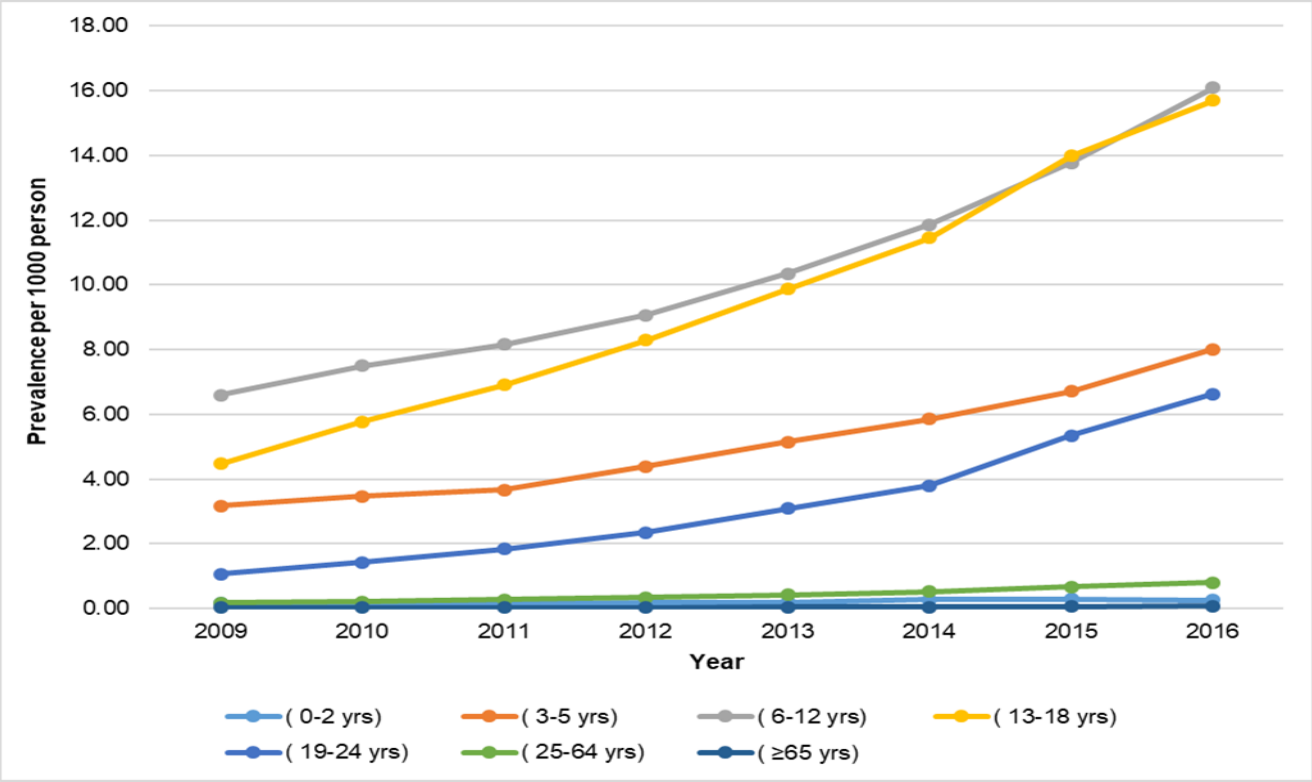


Figure 5.5: ASD annual prevalence stratified by age groups



5.4.3. Neuropsychiatric comorbidities

Of the total ASD cohort, 57.3% of the patients had at least one neuropsychiatric comorbidity. The three most common neuropsychiatric diagnoses accompanying ASD were behavioural/conduct disorders at 30.7% (95% CI, 30.1-31.3), anxiety at 15.2% (95% CI, 14.7-15.7) and ADHD at 14.3% (95% CI, 13.8-14.8). The percentage of diagnoses was higher in males than females for ADHD (15.4% and 10.3%) and behavioural/conduct disorders (31.5% and 27.7%). However, the proportion of patients with anxiety was greater among females, at 23.2%, compared to 13.1% in males. Almost twice as many females (18.1%) than males (9.1%) were diagnosed with depression. For the remaining neuropsychiatric diagnoses, the proportions were similar for both males and females. **Table 5.1** provides a full description of the numbers of neuropsychiatric diagnoses.

5.4.4. Psychotropic medication prescribing

Within the total cohort, 6529 patients (33.4%) received at least one psychotropic prescription; overall, 270,391 psychotropic prescriptions were issued. The prescribing rate was significantly greater among females (37.2% of the female cohort) compared to males (31.0% of the male cohort), $p < 0.0001$. Among the males, the three most commonly prescribed psychotropic drugs were hypnotics (in 30.5% of treated males), antidepressants (24.6%) and stimulants (20.5%). Whereas in the females, the three most commonly prescribed psychotropic drugs were antidepressants (38.8%), hypnotics (24.1%) and antipsychotics (12.5%).

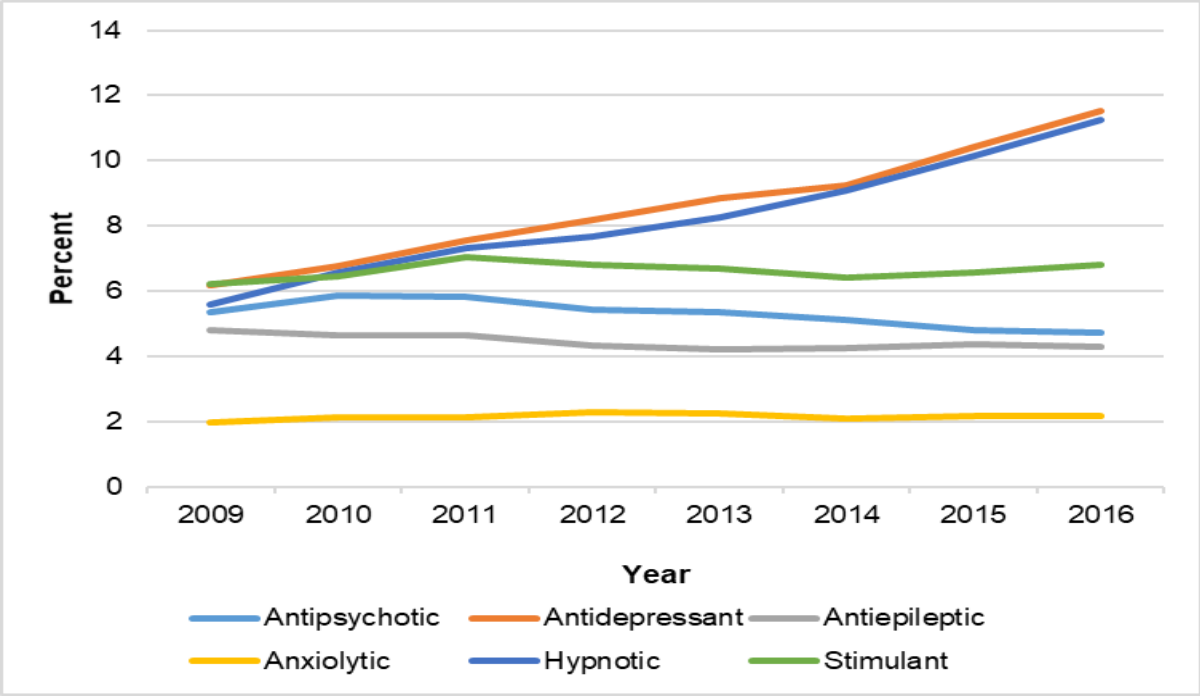
The highest numbers of prescriptions issued throughout the study period were for methylphenidate (46,393 prescriptions were identified, which comprised 17.1% of all psychotropic drug prescriptions), followed by melatonin (38,520 prescriptions, 14.2%) and risperidone (19,800 prescriptions, 7.3%). Valproic acid

was the most frequently prescribed antiepileptic drug (17,271 prescriptions, 6.3%). The most commonly prescribed antidepressants were fluoxetine (15,252 prescriptions, 5.6%) and sertraline (14,997 prescriptions, 5.5%).

The percentage of patients prescribed both antidepressant and hypnotic drugs approximately doubled over the period from 2009 to 2016: from 6.2% (95% CI, 5.6-6.8) to 11.5% (95% CI, 10.9-12.1) and from 5.5% (95% CI, 5.0-6.2) to 11.2% (95% CI, 10.6-11.8), respectively. For the remaining psychotropic drug classes, the percentage of patients prescribed these medications remained relatively steady over the study period. A secondary analysis conducted by excluding patients with only one prescription for each drug class resulted in similar findings to those of the primary analysis.

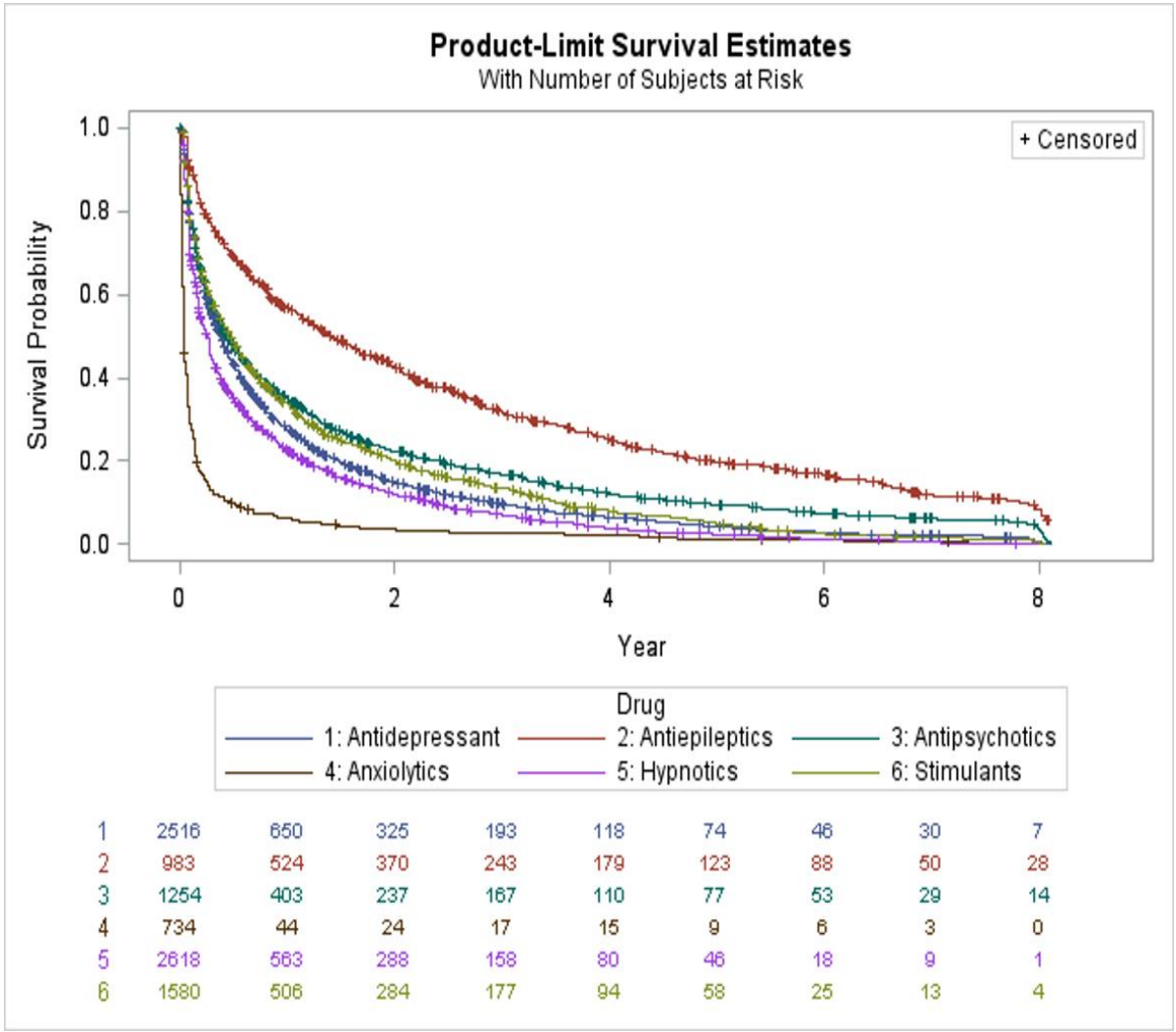
The most commonly prescribed psychotropic drug classes in patients with other neuropsychiatric comorbidities were antidepressants (14.3%) and hypnotics (10.5%). Among ASD patients on antipsychotics, more than half (53.3%) were diagnosed with behavioural/conduct disorders and 34.9% as having anxiety, whereas 8.1% were diagnosed with no additional neuropsychiatric comorbidities identified. Among the patients with ASD but no comorbid neuropsychiatric diagnoses, 87.6% of them were not on any psychotropic therapy; of the remaining 12.4%, 7.7% were prescribed hypnotics and 2% were on antidepressants. In those who had neuropsychiatric comorbidities, 52.8% were not on psychotropic therapy, although almost 60% of these patients had behavioural/conduct disorders. **Figure 5.5** shows the annual percentage of those prescribed psychotropic drugs in the total ASD cohort.

Figure 5.6: Annual percentage of psychotropic drug users per ASD cohort



Kaplan-Meier survival curves demonstrated that approximately one-third of those prescribed antipsychotic drugs, 403 patients of 1254 (32.1%), were on continuous antipsychotic therapy for more than one year, and 6.1% (77 patients) continued for up to five years. Furthermore, 29.9% (190 of 634) remained on risperidone therapy for more than one year, and 31.5% of those prescribed aripiprazole remained on the treatment for more than one year. For antidepressants, almost a quarter of the patients (25.8%; 650 of 2516 patients) continued on therapy for more than a year, while 2.9% of them remained on antidepressants for more than five years. Of patients prescribed fluoxetine, 25% remained on the treatment for more than one year. More than half of the patients prescribed antiepileptic medication continued on therapy for one year, and 12.5% of them continued for more than five years. The majority of ASD patients prescribed anxiolytic medication (94%) had stopped the treatment after one year. For patients treated with hypnotics and stimulants, 21.5% and 32% continued treatment for up to one year, respectively. The detailed survival analysis for psychotropic drugs identified in this study is illustrated in **Figure 5.7**.

Figure 5.7: Survival analysis curves for psychotropic drug



5.6. Discussion

5.6.1. Main findings

The incidence and prevalence of ASD have increased markedly over recent years. This probably reflects the current broader diagnostic criteria for ASD and increasing awareness of the condition. In this study, the incidence and prevalence of ASD increased 2.9-fold and 3.3-fold respectively, from 2009 to 2016. During the study period, the greatest prevalence of ASD was seen in children (6–12-year-olds), followed by adolescents (13–18-year-olds) and then young children (3–5-year-olds).

Nearly half of the ASD patients identified in this study had at least one comorbid neuropsychiatric diagnosis, and 25.1% of the total cohort had a record of two or more neuropsychiatric comorbid diagnoses. Psychotropic medication was prescribed to 12.4% of individuals with ASD but without a record of comorbid neuropsychiatric conditions, which may suggest either the under-recording of the neuropsychiatric diagnoses or the use of psychotropic drugs to treat other issues.

One-third of the identified cases with ASD were on psychotropic medication. Of the treated cohort, 12.4% were prescribed antipsychotic drugs. of the antipsychotics prescription issued, 50.7% was for risperidone and 49.3% was for other antipsychotic medication; the latter could be having been "off-label". This suggests that the guidance on psychotropic prescribing in children with ASD needs to be reviewed.

5.6.2. Comparison with previous studies

Similar trends were observed in the study by Murray et al. which covered the period from 1992 to 2008[22]. However, the increase in the incidence and prevalence of ASD from 1992 to 2008 were much higher in Murray's study (23.7-

and 64.6-fold) compared to the findings from this study. This could be because, by 2009, when the study period started, the broader diagnostic criteria of ASD were already well established and the level of parental and societal awareness of the condition had increased. In the US, the prevalence of ASD in 2014 in children aged 8 years was 16.8 per 1000 children[183]. This was comparable to the findings from this study in 2014: the prevalence was 11.870 per 1000 in children aged 6–12 (95% CI, 11.859–11.881). A 3.7:1 male to female ratio of ASD prevalence was identified in this study. This is similar to what was found in a prevalence study conducted in Canada over the period 2004 to 2015[184].

Compared to the prevalence estimated in this study using the IMRD-UK database for children of school age in 2009 (6.6/1000), higher prevalence rates were observed in 2006 in South Thames (11.6/1000)[185] and in 2003–2004 in Cambridgeshire (15.7/1000)[186] according to school-based population studies. These data suggest that prevalence estimates based on data extracted from registries (administrative prevalence) are on average lower than estimates coming from epidemiological studies based on direct population screening (epidemiological prevalence). This discrepancy in the prevalence rate could be attributed to the undiagnosed autism cases that were detected during screening. These cases are expected to be less severe than most of the cases recorded in the registries which require clinical care.

Although in this study there were no restrictions on age, the findings regarding psychotropic drug prescribing were consistent with the findings of Murray et al.[22], in which, of the total cohort, 28.7% were on psychotropic therapy, compared with 32.3% in this study. In both studies, the prescribing rate was higher among females than males. Furthermore, over the two study periods, from 1992 to 2008 and from 2009 to 2016, the three most commonly prescribed drugs remained the

same: methylphenidate, risperidone and melatonin. This prescribing pattern corresponds with the most common comorbid neuropsychiatric diagnoses which were recognised: 14.3% of the total cohort were found to have a record of an ADHD diagnosis and 30.7% had a record of behavioural disorders. Nevertheless, the percentage of patients recorded as having a sleep disorder (4.3%) was less than what was expected, based on the high rate of hypnotic drug prescribing (24.1% of treated females and 30.5% of treated males), which may be due to the under-recording of sleep disorder diagnoses. In studies that have specifically examined sleep disorders in children with ASD, the rate is usually very high compared to typically developing children, ranging from 40% to 80%[187]. In this study, some of the patients may have unrecorded comorbidities or comorbidities that were not identified (per protocol) in this cohort.

Aripiprazole and risperidone are antipsychotic drugs shown to be effective in the management of behavioural symptoms in children and adolescents with ASD[61, 127]. In two multinational studies investigating the treatment pattern of ASD, risperidone was the most commonly prescribed drug in most of the countries involved[90, 91]. The rate of psychotropic drug prescribing was higher in the US compared to the UK (approximately two-thirds of the total ASD cohort had at least one psychotropic drug prescription compared to one-third of this cohort)[188, 189]. In the US, both risperidone and aripiprazole are approved for the management of behavioural disorders accompanying autism in children, while in the UK, risperidone is the only antipsychotic drug which has been approved for the same indication. Although aripiprazole has not yet been approved in the UK for the treatment of behavioural disorders associated with ASD, in this cohort, almost 2% of psychotropic medication prescriptions were for aripiprazole (5241 aripiprazole prescriptions were issued). Moreover, 31.5% of patients treated with

aripiprazole remained on the drug for more than one year. A study conducted in a secondary care setting in the UK found that over a 6-year observation period, 10% of 3482 children with ASD and aged below 18 were on antipsychotic therapy: 55% (*n* = 191) on risperidone and 32% (*n* = 112) on aripiprazole[190].

5.6.3. Strengths & weaknesses

This study has extended the previous findings of research in this area by 1) providing the most recent and comprehensive description of ASD in the UK, 2) analysing a broader cohort, including patients with ASD of all age groups, and 3) using survival analysis to examine the duration of treatment for different psychotropic drug classes over the study period.

As mentioned in Chapter Four, although the information provided by the IMRD-UK database is generalisable to the UK population, it only includes information for patients in primary care. Prescriptions produced by non-primary care settings, such as hospital discharge prescriptions and prescriptions provided by specialised centres, are not recorded in IMRD-UK. Prescriptions for some off-label drugs and controlled drugs such as benzodiazepines may not be recorded either. This may lead to an underestimation of prescription rates. Furthermore, the database does not directly link prescriptions for drugs with their indication for use (whether this use is licensed or unlicensed). Because of this, it is not possible to determine whether recorded drugs were being prescribed to treat neuropsychiatric comorbidities of ASD. Finally, information on patient compliance and adherence to the prescribed medication cannot be obtained from the database; hence, we are not certain if the patients prescribed any of the drugs were taking them correctly, if at all.

5.7. Summary

- Over the study period, 20,194 patients with at least one recorded diagnosis of ASD were identified.
- The highest incidence of ASD was in 2016 among young children aged from 3 to 5, at 4.505 per 1000 persons (95% CI, 4.493–4.517).
- The prevalence of autism has increased 3.3-fold from 1.095 per 1000 persons (95% CI, 1.094–1.096) in 2009 to 3.555 per 1000 persons (95% CI, 3.553–3.557) in 2016.
- More than 50% of the identified cohort had at least one neuropsychiatric comorbidity diagnosis in addition to autism, and the most common neuropsychiatric diagnoses accompanying ASD was behavioural/conduct disorders at 30.7% (95% CI, 30.1-31.3).
- Approximately one-third of the identified patients were prescribed at least one psychotropic medication. Of the psychotropic medication prescriptions issued, 7.3% was for risperidone. Of the antipsychotic medication prescribed patient, 49.3% of the prescriptions were for antipsychotic medication other than risperidone.

Chapter Six: The Risk of Incident Seizure Among Antipsychotic Medication Users in Individuals Diagnosed with Autism Spectrum Disorder (ASD): Cohort Study

The studies presented in this chapter and the following two chapters (Chapters Seven and Eight) represent the main goal of this thesis which was to investigate the association between antipsychotic medication exposure and risk of developing certain adverse events in populations with ASD. In this chapter and in Chapter Seven, incident seizure was the adverse event of interest. In Chapter Eight, the adverse events studied are cardiac adverse events.

This chapter describes a cohort study performed to assess the relationship between the use of antipsychotic medication and the risk of incident seizure. The chapter starts with an introduction that highlights the importance of performing this study followed by a detailed description of the applied methodology. The chapter continues with a presentation of the results of the analyses and ends with a discussion and summary of the main findings.

6.1 Introduction

Antipsychotics have commonly been used in the management of disruptive behaviours in individuals with autism[50, 191]. The efficacy of antipsychotic medication in the management of behavioural disorder associated with ASD has been reported in several RCTs[82, 192-195]. Risperidone and aripiprazole are antipsychotic medication approved in the USA by the Food and Drug Administration (FDA) for the treatment of irritability associated with autistic disorder in children[196, 197]. In the UK, risperidone has been approved for the management of behavioural disturbance in children and adolescents associated with autism and conduct disorder[63]. However, many other antipsychotic medications are prescribed. The DUS presented in Chapter Five found that antipsychotics were prescribed to approximately 12.4% of the treated cohort: 50.7% of the issued prescriptions were for risperidone and 49.3% for other antipsychotics[172].

Several published papers have described the adverse events reported with the use of these agents. Metabolic adverse events, such as weight gain and hyperprolactinemia, have been reported frequently[95]. Extrapyramidal symptoms (EPS), such as tardive dyskinesia (TD), have also been reported, particularly with the typical antipsychotics[50, 198].

Seizure is a serious CNS adverse event. Both first-generation and second-generation antipsychotics can lower the seizure threshold, increasing the chances of seizure occurrence[199, 200]. The situation is complicated by the fact that autism itself and intellectual disability, which is common in people with autism, are risk factors for seizures[201, 202]. However, as highlighted in a previous review[203], most of the literature in this area consists of case reports. In the systematic review presented in **Chapter Three**, seizure events were infrequently reported by patients with ASD receiving antipsychotic medication. However, in some of the included studies, patients were on anti-seizure medications simultaneously with the antipsychotic medication (section 3.4.2.). This may explain the reason for reduced seizure events reported by the participants. It has been noticed that there is a lack of well-designed analytical studies of the risk of seizures with antipsychotic medication, particularly in populations with ASD. The study presented in this chapter aimed to fill the gap in the knowledge concerning the association between antipsychotic medication use and the risk of developing seizures in a population with ASD.

6.2. Objectives

The specific objective of this cohort study was:

1. To calculate the incidence rates of incident seizure, in antipsychotic medication users and in other psychotropic medication users comprising antidepressants, stimulants or non-benzodiazepine hypnotics and anxiolytics, in a population with ASD.
2. To compare the HR of incident seizure between antipsychotic medication users and the users of other psychotropic medication specified above, in a population with ASD.

6.3. Methods

6.3.1. Study design

This study is an observational retrospective cohort study. Although observational studies have been commonly used to investigate suspected adverse drug reactions in post-marketing drug evaluation, there are some challenges in designing these studies to avoid introducing bias to the estimated results. In RCT, treatment allocation is by random, which means that all the patients have an equal chance of receiving a drug, while in the practice treatment allocation is often influenced by patient characteristics (covariates). Therefore, allocating treatment groups using data from healthcare electronic databases which were collected during routine practice and comparing these group directly may produce biased results as these results could be influenced by underlying patients' characteristics rather than the effect of the treatment.

The propensity score (the probability of a patient receiving a drug) becomes a keystone of covariates adjustment in observational studies evaluating causal inference in routine healthcare[204]. This method facilitates the measurement of

differences in outcomes between the treatment and comparison groups in a way similar to RCT studies[205]. The propensity score (PS) is estimated based on the observed patient's characteristics (covariates). Following the PS estimation, covariates are adjusted by conditioning on the propensity scores. This can be applied using different techniques including: matching, stratification, adjustment, and inverse probability of treatment weighting using the PS[206]. Each one of these methods has its pros and cons; the selection of the appropriate method depends on the design of the study. In this study, PS fine-stratification weighting, a new approach of PS weighting, was used to adjust for potential confounders to have comparable groups.

Another challenge that faces the researcher in designing observational studies particularly when the data collection process is designed to be retrospectively, is the missing data. Missing data are commonly classified into three types: 1) missing completely at random (MCAR), which indicates that the probability of an observation being missing does not depend on the value of any variables under study; 2) missing at random (MAR), which indicates the probability of missing depend only on the subset of complete cases; 3) missing not at random (MNAR), which indicates the probability that a missing value is associated with the missing variable itself and with other variables.

Some studies deal with missing data by conducting complete case analysis, in which only observations with complete data are included in the analysis. This approach may affect the precision of the results and introduce bias if the missing data are not MCAR. Another way to deal with missing data is by single imputation (SI). In SI, the missing value is replaced by either the mean value or another appropriate value to create a complete data set. SI method may result in underestimation of the variance and potentially biased estimates. Multiple

imputation is a statistical method generated to address missing data based on the assumption that data are MAR. In multiple imputation, each missing value is replaced with a set of plausible values that represent the uncertainty about the right value to impute. These multiple imputed data sets are then analysed and combining the results from these analyses[207]. There are some considerations to be taken into account to ensure the validity of the multiple imputation and avoid introducing biased results. If the proportion of the missing data is large and exceeds 40%, this will violate the validity of the multiple imputation technique[208].

6.3.2. Data source

Data for this study were provided by the IQVIA Medical Research Data (IMRD-UK) database (see Chapter Four).

6.3.3. Ethical approval

Ethical approval for the fully anonymised studies presented in this chapter and in Chapters Seven and Eight was obtained from the SRC, which was established to review research using the IMRD-UK database (ref: 18THIN044), **see Appendix 9**.

6.3.4. Participants, exposure and outcomes

Diagnostic Read codes (**see Appendix 5**) were used to identify patients aged two years and older with the first-recorded diagnosis of ASD between 1st of January 1996 to 26th September 2017. The start date of each patient was defined as the latter of the following: the date of the patient's registration at the general practice, the date that the general practice began using Vision software (a clinical management system) or their second birthday. Patients were included if they received at least one prescription of the study medications, which included the following classes of psychotropic medication: antipsychotics, antidepressants,

stimulants and non-benzodiazepine hypnotics and anxiolytics. Medication lists for each class were obtained from Chapter 4 of the BNF (**see Appendix 7**). Anti-seizure medications (ASMs), (formerly known as antiepileptic drugs) and also benzodiazepines that are not necessarily listed as ASMs were not included because of the likely effect on the outcome of interest (seizures). Drug codes of the preceding psychotropic medications were extracted to identify medication exposure. Patients were considered eligible for inclusion in the study only if they had a screening period of at least six months available from their start date to the date of first prescription that followed the ASD diagnosis. This date was considered to be the index date for each patient, except for those patients whose start date equalled their second birthday, for whom no screening period was required.

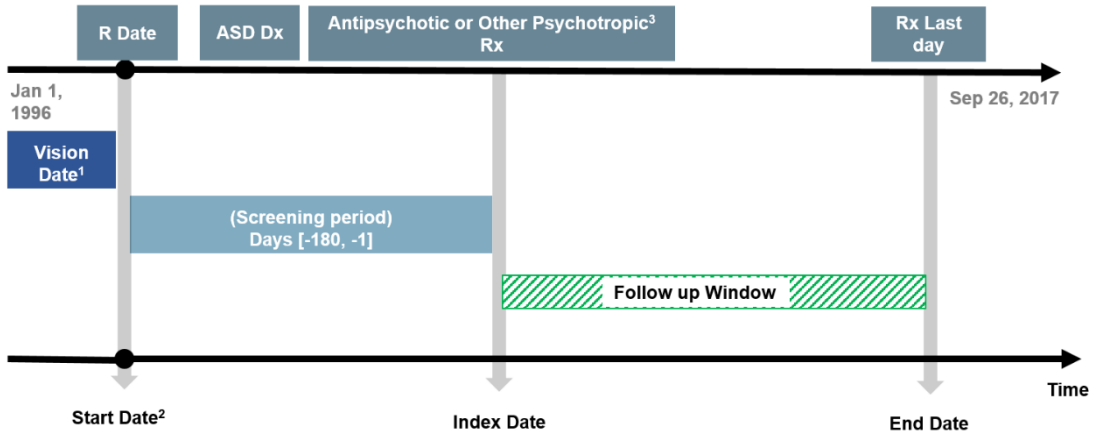
The exposure group was comprised of patients who had been prescribed antipsychotics after a diagnosis of ASD. Patients prescribed other psychotropic medications, including antidepressants, stimulants, or non-benzodiazepine hypnotics and anxiolytics were included in the comparison group. Patients who had a record of epilepsy or seizure before the index date were excluded from the analysis. Some patients were exposed to both antipsychotics and other psychotropic medication. The follow-up time of patients using 'other psychotropic medication' was censored once they received a prescription for an antipsychotic agent. A new follow-up period for them started on the first day of the antipsychotics prescription (**see Figure 6.1**).

In this cohort, for each patient, the start of the follow-up date was the index date. In the main analysis, the end of the follow-up date was defined as the earliest of the following: occurrence of the outcome date, the medication of interest had been switched or discontinued, death, date of last data collection or the end date

of the study. **Figure 6.1** illustrates the follow-up period for each observation during the cohort main analysis.

The outcome of this study was incident seizure. The seizure diagnosis was identified by the Read codes list obtained from a previous study on incident seizure using a UK general practice database[209] (**see Appendix 10**). Fever or febrile seizures were not included in the outcome definition.

Figure 6.1: Observation follow-up period in the cohort study



[1]Vision Date is the date of implementing Vision software which is a computerised clinical management system used by the general practices to record patient information.

[2]Start Date is the latest of either the date of the individual patient registration at the general practice, Vision date, second birthday or the date of the study start Jan 1, 1996.

[3]Psychotropic medication classes included were: antidepressants, stimulants and non-benzodiazepine hypnotics and anxiolytics.

[4]The follow-up time of patients using 'other psychotropic medication' was censored once they received a prescription for an antipsychotic agent. A new follow-up period for them started on the first day of the antipsychotics prescription.

R Date = date of patient's registration in the GP.
ASD Dx = Autism spectrum disorder diagnosis.
Rx = Drug prescription.

6.3.5. Statistical analysis

6.3.5.1. Sample size calculation

Sample size calculation was done based on the incidence rate of seizure in the general population to determine the number of patients needed to provide 80% power of detecting a relative risk of 2 with a 95% confidence interval. The incidence rate of seizure in the general population was 58.8 per 10,000 PY[210], implying a total of 8,072 patients are required to be included in this cohort study to provide an acceptable statistical power.

6.3.5.2. Propensity Score Fine-Stratification Weighting

Confounding can occur in observational studies when the baseline covariates that predict the exposure are independently related to the outcome. Hence, any marginal association between the exposure and outcome can be attributed to the confounder. PS methods depend on a model of the conditional probability of exposure given the confounders[206]. PS fine-stratification weighting with 50 strata was applied to adjust for potential confounders. Unlike conventional PS weighting, such as Inverse Probability of Treatment Weighting (IPTW), PS fine-stratification does not depend directly on PS to calculate the observation weight; instead it uses PS to create fine strata. In each stratum, weights for the exposed group are set to 1 and comparison patients are reweighted based on the number of exposed patients residing within their stratum. Therefore, extreme weights resulting from PS that are close to 0 or 1 are unlikely[211].

Standardised mean differences (SMD) were used to examine the balance of covariates between the exposure groups (**see Table 6.1**). An SMD greater than 0.1 indicates evidence of imbalance between treated and control groups [212]. Hazard ratios (HR) of seizure events were estimated using a Cox proportional

hazard model. To adjust for the potential clustering effect of patients contributing to both antipsychotics and other psychotropic groups which may leads to a loss of independence of observations, robust standard error was applied [213].

6.3.5.3. Covariates

Recent studies have suggested including all the covariates that are related to the outcome (i.e. the risk factors) in the PS model. They found that this could increase the precision of an estimated exposure effect[214] Also, it has been shown that including covariates that are related to the exposure and unrelated to the outcome can decrease the efficiency of an estimated exposure effect[215]. Therefore, several covariates related to seizure were incorporated in the PS fine-stratification model namely age[216], gender[217], smoking and problematic alcohol drinking[218]. In addition, certain medical conditions potentially related to seizure were added to the adjustment model, including neuropsychiatric comorbidities, diabetes[219], hypertension and stroke[220]. Data on concomitant medication use that may be related to seizure was obtained for each patient for the following drugs/drug classes: non-steroidal anti-inflammatory drugs (NSAID)[221], antidiabetic medication including: sulfonylurea[222] and glutathione[223], antihistamine[224], tramadol[225], cytostatic drugs[226] and immunomodulators[227]. In both groups of the cohort study, patients may have had concomitant prescriptions for ASMs; therefore, the use of these medications was adjusted for in the PS model.

6.3.5.4. Missing data

The multiple imputation technique was planned to handle the missing data of smoking, assuming that the missing data were missing at random. However, in the cohort identified in this study, 42.3% of the patients had missing smoking records. Therefore, performing multiple imputation to impute missing smoking

records would be invalid. It has been found that 95% of the missing smoking data involved patients aged ≤ 18-years old, and 75% of the missing smoking records involved patients aged ≤ 12-years old. This was anticipated since children and adolescents make up the majority of the population with ASD. Since 2007, in the UK, it has been illegal to sell tobacco products to people aged under the age of 18. A Smoking, Drinking and Drug Use among Young People survey (SDD) conducted by the NHS every two years, found that in 2016, 19% of 11-15-year-old pupils (secondary school) had smoked at least once. Only 3% of those who had done so were considered regular smoker[228]. In this study, patients with missing smoking records were assumed to be non-smokers.

6.3.5.5. Sensitivity analyses

Two sensitivity analyses were applied to examine the validity of the main analysis. The purpose of these analyses was to investigate the effect of different follow-up periods on the resulting HR. In the sensitivity analyses, the definition of the end of follow-up date was changed to the following: 1) the earliest of the occurrence of the outcome date, death, the patient left the practice or the end date of the study; 2) the earliest of the occurrence of the outcome date, death, the patient left the practice or the end date of the study, 90 days after the first continuous medication exposure (the grace period). The grace period was added to allow for the residual effect of the medication or the possibility of persistence of administration using a residual supply of medication that had resulted from patient non-adherence. All analyses were performed using SAS software, version 9.4.

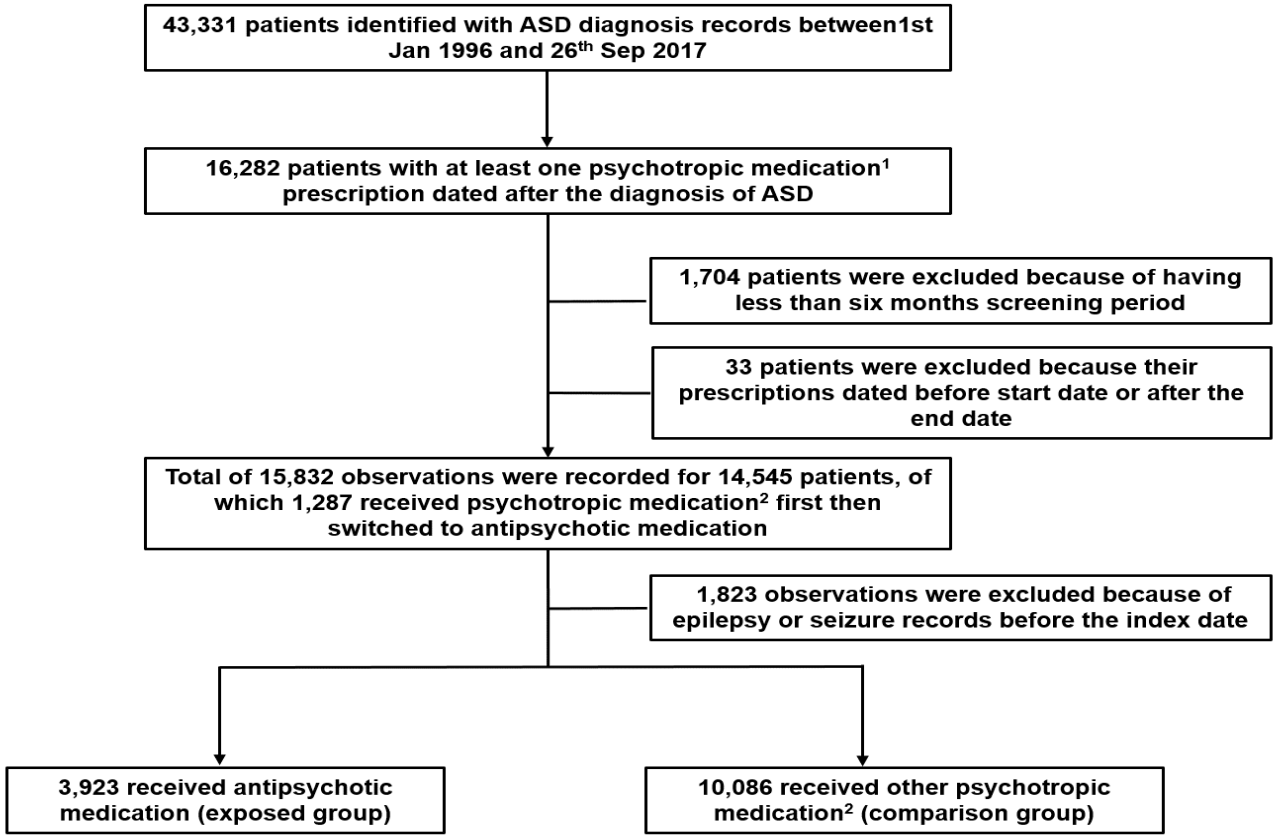
6.4. Results

6.4.1 Descriptive results

During the study period, a total of 16,282 patients with ASD who had received at least one medication prescription of the study medications was identified. Of these, 14,009 observations met the inclusion criteria and were included in the cohort analysis. Based on the sample size calculation, a sample size composed of 8,072 patients was required to have an 80% statistical power with a 95% confidence interval, which mean that the obtained sample size was more than enough to fulfil this requirement. **Figure 6.2** is a flowchart illustrating the patient selection process. Three thousand nine hundred and twenty-three observations of patients receiving antipsychotic prescriptions were identified and allocated to the exposed group: 10,086 observations of patients were identified as being on other psychotropic medication and they were considered to be the unexposed group. The mean age of the participants at the index date was 25.7 years (SD 14.0) for the exposed group, and the mean follow-up was 2.2 years (SD 2.6). For the comparison group, the mean age was 18.1 years (SD 12.2) and the mean follow-up was 3.0 years (SD 3.4). The age difference between the two groups is probably due to stimulants being prescribed at a younger age[229].

The ratio of male to female patients in both the exposed and unexposed groups was approximately 3:1. The average age of seizure onset in the exposed group was 25.9 years (SD 14.5); in the comparison group, the average age of the onset of seizure was 19.7 years (SD 12.2). In the PS-weighted model, all covariates were balanced between the two study groups, with an SMD of less than 0.1. **Table 6.1** lists the crude and weighted baseline clinical characteristics of the exposed and unexposed groups at the index date, with a standardised mean difference.

Figure 6.2: Flow chart for patients' inclusion



[1]In this step psychotropic medication classes included were: antipsychotics, antidepressants, anxiolytics, stimulants, and hypnotics, not including benzodiazepine.

[2]In this step psychotropic medication classes included were: antidepressants, stimulants and non-benzodiazepine hypnotics and anxiolytics.

Table 6.1: Patients' characteristics baseline in the cohort study

Characteristic, no (%)	Crude		SMD	Weighted		SMD
	Antipsychotic	Other psychotropic[1]		Antipsychotic	Other psychotropic[1]	
Age, mean (SD)	25.7 (14)	18.1 (12.2)	0.582	25.7 (14)	26.7 (17.5)	-0.061
Gender						
Female	906 (23.1)	2,391 (23.7)	-0.014	906 (23.1)	2,353 (23.4)	-0.006
Male	3,017 (76.9)	7,695 (76.3)	0.014	3,011 (76.9)	7,712 (76.6)	0.006
Smoking status						
Non-smoker	3,105 (79.1)	8,470 (84)	-0.125	3,100 (79.1)	7,724 (76.7)	0.058
Current smoker	553 (14.1)	957 (9.5)	0.143	552 (14.1)	1,508 (15)	-0.025
Ex-smoker	265 (6.8)	659 (6.5)	0.009	265 (6.8)	832 (8.3)	-0.057
Alcohol status						
Non-problematic drinker	3,720 (94.8)	9,724 (96.4)	-0.078	3,714 (94.8)	9,460 (94)	0.036
Problematic drinker	203 (5.2)	362 (3.6)	0.078	203 (5.2)	605 (6)	-0.036
Comorbidities						
Neuropsychiatric comorbidities (+)	3,346 (85.3)	7,554 (74.9)	0.263	3,340 (85.3)	8,635 (85.8)	-0.015
Diabetes (+)	94 (2.4)	114 (1.1)	0.096	94 (2.4)	276 (2.7)	-0.022
Hypertension (+)	1,079 (27.5)	2,860 (28.4)	-0.019	1,079 (27.5)	3,088 (30.7)	-0.069
Stroke (+)	8 (0.2)	10 (0.1)	0.027	8 (0.2)	21 (0.2)	0
Medication use						
Non-user of antidiabetic medication[2]	3,884 (99)	10,057 (99.7)	-0.089	3,878 (99)	9,941 (98.8)	0.023
Current user of antidiabetic medication	30 (0.8)	20 (0.2)	0.082	30 (0.8)	109 (1.1)	-0.033
Ex-user of antidiabetic medication	9 (0.2)	9 (0.1)	0.035	9 (0.2)	15 (0.2)	0.018
Non- user of Antihistamine	2,421 (61.7)	6,080 (60.3)	0.029	2,417 (61.7)	6,120 (60.8)	0.018
Current user of Antihistamine	804 (20.5)	1,761 (17.5)	0.077	802 (20.5)	2,084 (20.7)	-0.006

Characteristic, no (%)	Crude		SMD	Weighted		SMD
	Antipsychotic	Other psychotropic[1]		Antipsychotic	Other psychotropic[1]	
Ex-user of Antihistamine	698 (17.8)	2,245 (22.3)	-0.112	698 (17.8)	1,861 (18.5)	-0.017
Non- user of Tramadol	3,857 (98.3)	9,883 (98)	0.025	3,851 (98.3)	9,846 (97.8)	0.035
Current user of Tramadol	27 (0.7)	88 (0.9)	-0.021	27 (0.7)	82 (0.8)	-0.014
Ex- user of Tramadol	39 (1)	115 (1.1)	-0.014	39 (1)	137 (1.4)	-0.034
Non-user of NSAID	2,852 (72.7)	6,855 (68)	0.104	2,846 (72.7)	7,188 (71.4)	0.028
Current user of NSAID	454 (11.6)	1,192 (11.8)	-0.008	454 (11.6)	1,247 (12.4)	-0.025
Ex- user of NSAID	617 (15.7)	2,039 (20.2)	-0.117	617 (15.8)	1,629 (16.2)	-0.012
Non- user of cytostatic	3,903 (99.5)	10,049 (99.6)	-0.022	3,897 (99.5)	10,015 (99.5)	-0.002
Current user of cytostatic	14 (0.4)	19 (0.2)	0.032	14 (0.4)	34 (0.3)	0.003
Ex- user of cytostatic	6 (0.2)	18 (0.2)	-0.006	6 (0.2)	15 (0.2)	0
Non- user of immunomodulator	3 910 (99.7)	10,053 (99.7)	-0.001	3,904 (99.7)	10,009 (99.4)	0.034
Current user of immunomodulator	7 (0.2)	22 (0.2)	-0.009	7 (0.2)	18 (0.2)	0
Ex-user of immunomodulator	6 (0.2)	11 (0.1)	0.012	6 (0.2)	38 (0.4)	-0.043
Non- user of antiepileptic		9,872 (97.9)	-0.356	3,503 (89.4)	9,137 (90.8)	-0.045
Current user of antiepileptic	400 (10.2)	196 (1.9)	0.351	394 (10.1)	884 (8.8)	0.044
Ex-user of antiepileptic	20 (0.5)	18 (0.2)	0.057	20 (0.5)	44 (0.4)	0.01
Non- user of benzodiazepine	3,423 (87.3)	9,750 (96.7)	-0.352	3,422 (87.4)	8,775 (87.2)	0.005
Current user of benzodiazepine	451 (11.5)	272 (2.7)	0.348	446 (11.4)	1,135 (11.3)	0.003
Ex-user of benzodiazepine	49 (1.2)	64 (0.6)	0.064	49 (1.3)	154 (1.5)	-0.024

SMD standardised mean difference, SD standard deviation, NSAID non-steroidal anti-inflammatory drug.

[1]Psychotropic medication classes included were: antidepressants, stimulants and non-benzodiazepine hypnotics and anxiolytics.

[2]Antidiabetic medication included: glutathione and sulfonylurea

6.4.2 Risk of incident seizure

The crude incidence rate of seizure was 54 per 10,000 person-years (PY) among 3,923 patients in the exposed group, and 36 per 10,000 PY among 10,086 patients in the comparison group. The PS-weighted HR of the incident seizure was 1.28, 95% CI: 0.74-2.19, indicating no evidence of an increased risk of incident seizure associated with antipsychotic exposure compared to other psychotropic medication in a population with ASD.

6.4.3 Sensitivity analyses results

Sensitivity analyses results were consistent with the main analysis. The HRs of the incident seizure were 1.40, 95% CI: 0.85-2.30 and 1.36 (0.72-2.57) during different follow-up periods. **Table 6.2** shows the results of the crude and weighted Cox proportional hazard model.

Table 6.2: Results of the cohort analyses

	Patients (n)	Patient-years	Events (n)	Crude HR (95% CI)	Weighted HR (95%CI)
Main analysis **1. Follow up end by earlier of: outcome date, medication has been switched or discontinued, death, patient left practice or study end date.**					
Antipsychotic	3,923	11,914	65	1.59 (1.15-2.22)	1.28 (0.74-2.19)
Psychotropic[1]	10,086	22,577	82	1.0	1.0
Sensitivity analyses **1. Follow up end by earlier of: outcome date, death, patient left practice or study end date.**					
Antipsychotic	3,923	15,238	77	1.70 (1.26-2.30)	1.40 (0.85-2.30)
Psychotropic[1]	10,086	30,306	94	1.0	1.0
2. Follow up end by earlier of: outcome date, death, patient left practice, study end date or 90 days after first continuous exposure.					
Antipsychotic	3,923	8,988	52	1.80(1.23-2.65)	1.36 (0.72-2.57)
Psychotropic[1]	10,086	15,601	55	1.0	1.0

[1]Psychotropic medication classes included were: antidepressants, stimulants and non-benzodiazepine hypnotics and anxiolytics.

6.5. Discussion

6.5.1. Main findings

Based on the PS-weighted cohort results, no evidence of an increased risk of incident seizure associated with antipsychotic exposure compared with the use of other psychotropic medication: HR 1.28 (0.74-2.19) was found.

6.5.2. Comparison with previous studies

The likelihood of the association between antipsychotics and seizures has been investigated in patients with schizophrenia, mood disorders and dementia. A nested case-control study conducted in the UK using the CPRD found that the prescription of haloperidol, prochlorperazine or trifluoperazine was associated with an increased risk of seizures: the adjusted odds ratio (OR) was 2.51, 95% CI: 1.51-4.18 compared with non-users[230]. However, considering the study design used in the previous study, the estimated risk could be inflated[231]. In this study, the risk of seizure between different antipsychotic medication was not compared. A study with data from the National Health Insurance Research Database (NHIRD) compared the risk of seizure among first and second-generation antipsychotics in patients diagnosed with schizophrenia and mood disorders[232]. This study showed no evidence of a higher risk of seizure associated with first-generation antipsychotics compared to second-generation antipsychotics: HR 1.34, 95% CI: 0.99-1.81; P = 0.06[232]. When compared to risperidone, clozapine (HR 3.06, 95% CI: 1.40-6.71); thioridazine (HR 2.90, 95% CI: 1.65-5.10); chlorprothixene (HR 2.60, 95% CI: 1.04-6.49) and haloperidol (HR 2.34, 95% CI: 1.48-3.71) all had a higher risk of antipsychotic-related seizure, while aripiprazole had a potentially lower risk of seizure: HR 0.41, 95% CI: 0.17-1.00; P = 0.05 [232]. However, the results of the previous study could have been affected by confounding by indication rather than reflect the actual effect of the

medication on the risk of seizure. In this cohort study, most of the prescriptions of antipsychotics were for second-generation antipsychotics (82.4%) and 45% of the prescriptions were for risperidone. Other reports have suggested that low-dose antipsychotic medication, as used to treat anxiety and/or behavioural problems in young people with ASD, might not be associated with an increased risk of seizures but this leaves the possibility that higher antipsychotic doses, such as those used to treat psychosis or bipolar disorder, might be associated with an increased seizure risk.

6.5.3. Strengths & weaknesses

To date, this is the first analytical study investigating the association between antipsychotic agents and incident seizure in a population with ASD. The source of the data used in this research is a large primary care database representative of the UK population. The cohort study was used to estimate the HR of the incident seizure associated with antipsychotic exposure compared with other psychotropic medication. Both the number of ASD subjects identified and the number eligible for this study (14,009 observations) were large; they were followed for an average of more than two years. The PS fine-stratification model that was used adjusts the variability between the study groups. PS fine-stratification is a newer approach of the standard PS weighting; this model provides smaller relative bias in estimates of cases of low exposure prevalence[211].

IMRD-UK is a primary care database; therefore, only medication prescriptions provided by primary care general practitioners are recorded. Other prescriptions, for example, medication prescribed in secondary care settings or hospital discharge medications are not recorded. Similarly, with the seizure diagnosis records, there could have been seizure events in hospital emergency

departments that were not linked to the patients' files in the general practice. This could have led to the number of cases being underestimated. Also, the database does not provide information on treatment compliance or dispensing of prescriptions; therefore, we are not certain that all the medications prescribed were administered by the patients. Another potential weak point of the study is that 10% of the total patients included in this cohort had only one prescription of the study medication. In this study, the medication dose was not taken into account. There is considerable evidence from the literature that, for medications that are associated with increased seizure risk, the risk is very much related to medication dose[233-235]. The results of this research apply only to individuals with ASD with no history of epilepsy or seizure, and of antipsychotics in general; the analysis was not stratified by type of antipsychotic medication.

6.6. Summary

- During the study period, 14,009 observations met the inclusion criteria and were included in the cohort analysis. Of these, 3,923 patients were on antipsychotic medication and assigned to the exposed group, and 10,086 were on other psychotropic medication and assigned to the comparison group.
- At the first date of medication exposure, the mean age of the participants was 25.7 years (SD 14.0) for the exposed group, and the mean follow-up was 2.2 years (SD 2.6). For the comparison group, the mean age was 18.1 years (SD 12.2) and the mean follow-up was 3.0 years (SD 3.4).
- Seizure incidence rates were 54 per 10,000 PY in 3,923 patients using antipsychotic medication and 36 per 10,000 PY in 10,086 patients using other psychotropic medication.
- There is no evidence of an increased risk of incident seizure associated with antipsychotic exposure compared to other psychotropic medication in a population with ASD: the HR was 1.28, 95% CI: 0.74-2.19.

Chapter Seven: The Risk of Incident Seizure Among Antipsychotic Medication Users in Individuals Diagnosed with Autism Spectrum Disorder (ASD): A Self-controlled Case Series Study

The cohort study presented in the previous chapter shows no evidence of an increased risk of incident seizure associated with antipsychotic medication use compared to other psychotropic medication. To further investigate the association between antipsychotic medication and seizure, which is the main focus of this thesis, a different analytical study design (a self-controlled case series) was employed in which the within-person risk of incident seizure during exposed periods with the risk of incident seizure during unexposed periods was compared. Unlike the previous cohort study which compare the risk of seizure between antipsychotic and other psychotropic medication, the self-controlled case series (SCCS) design investigated the association between antipsychotic medication use and seizure from a different angle. It provided an estimation of when the risk of seizure was higher (i.e. during which period of antipsychotic medication use). Moreover, this study design eliminated the effect of both measured and unmeasured time invariant confounding variables between groups: i.e. sex. Whereas, in the cohort study, we were able to control the effect of measured confounders only. Therefore, this SCCS helped us to determine whether the results of the previous cohort study were influenced by a variation between patients using and not using antipsychotic medication. Using more than one study design in addressing the clinical question has been acknowledged as good practice as it can provide a comprehensive assessment from different directions.

The chapter starts with the objectives of conducting this study followed by a detailed methodology section which describes the SCCS as well as the assumptions that need to be met to conduct a valid self-controlled case series analysis. Next, the chapter continues with the results of the analyses, followed by a discussion section in which a comparison of the SCCS results and cohort study is presented, along with a discussion of the strengths and weaknesses of the

SCCS study design. Highlights of the main findings are provided at the end of the chapter in the summary section.

7.1 Introduction

Refer to Chapter Six, **section 6.1**.

7.2. Objectives

The specific objective of this SCCS study was similar to the main objective as presented in the previous chapter:

1. To estimate the relative risk of incident seizure associated with antipsychotic medication; by comparing the incidence of seizure during antipsychotics exposure periods to non-exposure periods, within patients diagnosed with ASD.

An additional objective was:

2. To examine whether the findings from the cohort study in the previous chapter are influenced by variations between patients by comparing its results with the results from the SCCS analyses in this chapter.

7.3. Methods

7.3.1. Study design

The study presented in this chapter is an observational SCCS design study. SCCS analyses have been proposed for investigating the association between intermittent exposure and acute outcome. It was developed in the early 1990s by Professor Farringdon to investigate the safety of the Mumps, Measles and Rubella (MMR) vaccine[236]. This method combines the features of the simple cohort design and the economy of the case-control method[237, 238]. In this design, only data from cases in which the comparisons are made within individuals who

experience both the event and the exposure of interest are used. Relative incidence is estimated in different exposure intervals relative to a control period. As the study design is based on within-person comparisons rather than between-person comparisons, only a small sample size is needed to conduct the analysis. Furthermore, this study design overcomes the potential effect of time-fixed confounders, such as gender and genetic factors; as the comparison is carried out by using each individual participant as their own control ("self-control") instead of comparing different groups of participants. Time-varying confounders such as: age and seasonal variations, can be adjusted. This method has been widely used in pharmaco-epidemiological research investigating the potential benefits and harms associated with the use of drugs[239-245].

As part of the study, two independent SCCS analyses were performed to estimate the incidence rate ratio (IRR) of seizure during predefined risk periods. The risk of seizure during different exposure windows was compared to the risk in non-exposed observation periods (exposure windows are defined in **section 7.3.4.**) within each patient. In the main SCCS analysis, the exposure of interest was the use of antipsychotic medication, which is the main focus of this PhD project. Psychotropic medication other than antipsychotic or ASM was the exposure medication as a sensitivity SCCS analysis. This sensitivity analysis was carried out to compare the results of the two SCCS and the results of the cohort study presented in **Chapter Six**.

Additional SCCS analysis was undertaken as a negative control outcome sensitivity analysis, whereby the exposure was antipsychotic medication and the outcome was otitis media. A negative control outcome is a tool that is commonly applied in observational studies to examine the validity of the causal inferences[246]. It helps to detect selection and measurement bias in

epidemiological studies[247]. The concept of this approach relies on looking for an association that cannot plausibly be hypothesised. The negative control outcome must share a common source of correlated measurement error with the true outcome[247]. Otitis media is an acute recurrent event; the occurrence of this event has never been linked with the use of antipsychotic medication. Therefore, it was selected as the negative control outcome to validate the causal interpretations of the antipsychotics and incident seizure SCCS.

7.3.2. Assumptions

As for other epidemiological study designs, the SCCS design requires certain assumptions that should be met to provide valid and unbiased estimates. Two key validity elements must be fulfilled for the self-controlled design to be valid[248]. First, the exposure should be transient or intermittent. The second validity element is about the outcome which should be an acute event; however, any event for which it is possible to assign a date of onset, such as date of hospital admission or diagnosis, should be suitable for study.

Several other assumptions need to be met to conduct a well-designed SCCS study [249]:

1. The SCCS method is suitable for independent recurrent events. It may also be applied to rare non-recurrent events. If the events are recurrent and the occurrence of one event increases the probability of subsequent events, care needs to be taken to only consider the first recorded event[250]. The recurring event has to be rare, i.e. have a low incidence in the general population. Seizure is a recurrent event and the first seizure could lead to multiple seizure events; therefore, only the first (incident) seizure was included in the analysis.

2. The occurrence of an event must not alter the probability of subsequent exposure i.e. exposure is contra-indicated after a medical event. A seizure event is not considered to be a contraindication for antipsychotic prescribing. However, it could affect the clinicians' decision on prescribing such medication. Therefore, a 14-day pre-exposure period (pre-risk period) was included to consider the likelihood that the occurrence of seizure may affect the chance of antipsychotic treatment[249]. Not allowing for this period of low incidence would inflate the relative incidences in the post exposure risk periods[251]. Testing whether the relative incidence associated with this additional pre-risk period is significantly different from other risk periods allows us to know if the exposure is event-dependent.
3. Finally, the occurrence of the outcome must not lead to the censoring of the observation i.e. when the outcome of interest is likely to increase the short-term death rate. Extension of the standard SCCS method can be applied to help detect event-related mortality[252]. Another simple way to deal with this situation is by comparing the results from fitting SCCS models to all cases and excluding those who died, particularly if the event mortality is low[251]. Major differences in the results between the two analyses would suggest assumption's violation by event-related observation period censoring. A seizure episode could be serious and lead to death (although this would be a very unlikely event) which, subsequently, would end the observation. Although this would be an exceptionally rare event, a sensitivity analysis by excluding patients who had died during the study period was conducted.

7.3.3. Data source

IQVIA Medical Research Data (IMRD-UK) was the data source used for this study (see Chapter Four).

7.3.4. Ethical approval

The ethical approval for this study was obtained from the SRC, see **Section 6.3.3.**

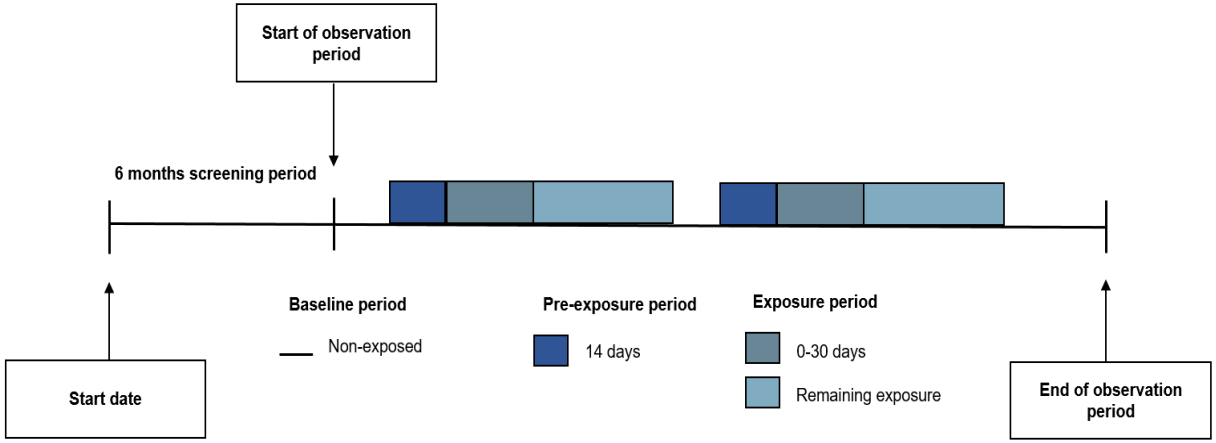
7.3.5. Participants, exposure and outcomes

Data of patients with the first-recorded diagnosis of ASD between 1st of January 1996 to 26th September 2017 were extracted using ASD diagnostic Read codes. In the main SCCS analysis, the data of the patients who had both an incident seizure and exposure to antipsychotics were extracted. In the SCCS investigating the association between psychotropic medication other than antipsychotic medication or ant-seizure medication, the data of patients who had been exposed to these medications and developed incident seizure were extracted. In the negative control SCCS sensitivity analysis, patients with ASD who had been exposed to antipsychotic medication and developed otitis media were included in the analysis. Only patients with a record of incident otitis media were included in the analysis; patients with otitis media records before the observation period were excluded.

Similar definitions of start date and screening period in the previous cohort study were applied. The observation start date was defined as the first day after the end of the six-month screening period. The ASD diagnosis date was recorded before or after the observation start, provided that it preceded or was on the date of the first medication exposure. Patients who had a record of epilepsy or seizure before the start of the observation were excluded from the analysis. For each participant, the observation period was divided into an un-exposure period – the

“baseline period” - including periods before and after medication exposure. The risk period was further divided into the 14 days before medication exposure (the pre-exposure period) and two exposure windows: the first 30 days of medication exposure, and the subsequent medication exposure. As some participants had multiple intermittent medication exposures within their observation time, each continuous exposure was divided into three distinct risk windows. **Figure 7.1** illustrates the observation period timeline for each participant during the SCCS analysis.

Figure 7.1: SCCS observation period in the self-controlled case series analyses



7.3.6. Statistical analysis

7.3.6.1. Primary analyses

As stated, one of the main advantages of the SCCS design is that it eliminates the effect of time-fixed confounders. However, time-variant confounders such as age need to be adjusted. To adjust for age, each individual's observation period should be split into age groups. Specification of piecewise constant age groups can be challenging; misspecification of the age groups can produce biased estimates. Therefore, a semi-parametric SCCS model was applied to estimate the risk by comparing the risk of incident seizure in different risk windows to the baseline period. In this model, the age effect does not need to be pre-specified [253]. In SCCS, Conditional Poisson regression provides estimates of relative incidence of adverse events, comparing incidence in exposed periods to unexposed periods, within individuals. This model was fitted to estimate the IRR of seizure, with 95%CIs. All analyses were performed using SAS software, version 9.4 and R software, version 3.2.0.

7.3.6.2. Sensitivity analyses

The following three sensitivity analyses were conducted:

1. For comparison purposes, a second SCCS was conducted in which the exposure was psychotropic medication other than antipsychotic medication or ASMs.
2. As stated in **Section 7.3.1.**, in SCCS, if the occurrence of the outcome leads to censoring of the observation period, this will fail a major assumption of the model. Therefore, a sensitivity analysis was conducted excluding patients who had died during the study period to avoid failing the SCCS assumption.

3. An additional SCCS analysis was carried out using a negative control outcome. Patients with ASD who had been exposed to antipsychotics and developed otitis media were included in the negative control analysis. Patients with otitis media records before the observation period were excluded.

7.4. Results

7.4.1 Descriptive results

One hundred and forty-nine patients were included in the main SCCS analysis. These patients all experienced a seizure event and were prescribed antipsychotic agents. The overall observation period was nearly 1,529 patient-years. Almost 80% of the patients were males, with a mean age of 17.13 years (SD 14.59) at the start of the observation. At the same time, the female patients were younger: the mean age of the females was 12.23 years (SD 10.89). The average length of continuous antipsychotic prescriptions was 49 days, ranging from 1 to 2,553 days.

In the SCCS investigating the association between psychotropic medication other than antipsychotic or anti-seizure and the risk of incident seizure, 305 patients were included in the analysis. The total observation period for the included patients was approximately 3,168 patient-years. Male patients comprised 75% of the total participants with a mean age of 11.27 years (SD 12.55) at the start of the observation. The mean age of female patients was 12.32 years (SD 111.51). The average length of continuous psychotropic prescriptions was 30 days, ranging from 1 to 2,367 days.

In the negative control SCCS sensitivity analysis, 334 patients who were exposed to antipsychotic medication and had experienced otitis media were included. The

mean age of the participants at the start of the observation was 13.44 years (SD 13.77). The average continuous antipsychotic medication prescriptions length was 32 days, ranging between 1 and 3,763 days. **Table 7.1** provides details of the patient characteristics and the observation period in all the SCCS analyses.

Table 7.1: Patients characteristics in the SCCS analyses.

Characteristic	No. of Patients (%)	Age at Observation start, Mean (SD), Y	Length of Prescription, Median (Range) [IQR], d	Risk period (exposure)		Baseline period (no exposure)	
				Events, No.	Total Follow-up Time, Patient-years	Events, No.	Total Follow-up Time, Patient-years
1. Risk of incident seizure associated with antipsychotic exposure.							
All	149 (100)	16.15 (14.03)	49(1-2553)[25-78]	61	479.4	88	1 049.9
Male	119 (79.9)	17.13 (14.59)	50(1-2553)[25-81]	53	408.7	66	795
Female	30 (20.1)	12.23 (10.89)	28(1-471)[15-56]	8	70.7	22	254.9
2. Risk of incident seizure associated with other psychotropic exposure*.							
All	305 (100)	11.52(12.29)	30(1-2367) [15-60]	97	843.5	208	2,325
Male	230 (75.4)	11.27(12.55)	30(1-2367) [15-60]	71	675.1	159	1,752.9
Female	75 (24.6)	12.32 (11.51)	30(1-1841) [27-65]	26	168.4	49	572.1
3. Risk of incident seizure associated with antipsychotic exposure (excluding patients who died within the observation period).							
All	147 (100)	15.90 (13.71)	49(1-2553)[25-78]	60	469.2	87	1,043.4
Male	117 (79.6)	16.84 (14.23)	50(1-2553)[26-81]	52	398.5	65	788.5
Female	30 (20.4)	12.32 (11.51)	28(1-471) [15-56]	8	70.7	22	254.9
4. Risk of otitis media associated with antipsychotic exposure (negative control).							
All	334 (100)	13.44(13.77)	32(1-3763)[16-71]	73	972.4	261	2 691.6
Male	250 (74.8)	12.32 (13.26)	42(1-3763)[21-74]	54	737	196	2 042.3
Female	84 (25.1)	16.78 (14.75)	28(2-3549)[14-60]	19	235.4	65	649.3

*Psychotropic medication classes included were: antidepressants stimulants, anxiolytics and hypnotics, not including benzodiazepine.

7.4.2 Primary results

In the primary SCCS analysis, using a semi-parametric model, the IRR of seizure for the first 30 days of antipsychotic exposure was 1.79 (95% CI: 0.97-3.30), which indicates no strong evidence of an association between exposure to antipsychotics and increased risk of incident seizure.

7.4.3 Results sensitivity analyses

1. During the first month of treatment with psychotropic medication other than antipsychotic or anti-seizure medication, the IRR of seizure was 1.57 (1.03-2.38). This suggests some evidence of a short-term increase in risk of incident seizure associated with psychotropic medication other than antipsychotic or anti-seizure.
2. Two patients died during the study period and were excluded from the sensitivity analysis. The results of the sensitivity analysis were consistent with the primary analysis.
3. During the three defined risk periods of the semi-parametric SCCS analysis for a negative outcome, the IRR indicated no evidence of an association between antipsychotic exposure and increased risk of otitis media. The results of the SCCS analyses are shown in **Table 7.2**.

Table 7.2: Results of semi-parametric SCCS analyses

Risk Window	Events (n)	Patient-years	Adjusted IRR (95% CI)
Primary analysis			
1. Antipsychotic medication exposure and risk of incident seizure.			
Baseline period	88	1,049.9	-
14 days pre antipsychotic exposure	9	57.5	1.66 (0.74-3.71)
First 30 days of antipsychotic exposure	26	156.3	1.79 (0.97-3.30)
Subsequent antipsychotic exposure	26	265.6	1.02 (0.53-1.96)
Sensitivity analyses			
1. Psychotropic medication* exposure and risk of incident seizure.			
Baseline period	208	2,325	-
14 days pre first psychotropic exposure	18	111.1	1.57 (0.91-2.71)
First 30 days of psychotropic exposure	42	275.4	1.57 (1.03-2.38)
Subsequent psychotropic exposure	37	456.94	(0.53-1.32)
2. Antipsychotic medication exposure and risk of incident seizure (excluding patients who died within the observation period).			
Baseline period	87	1,043.4	-
14 days pre antipsychotic exposure	8	55.9	1.52 (0.65-3.58)
First 30 days of antipsychotic exposure	26	152.7	1.79 (0.96-3.35)
Subsequent antipsychotic exposure	26	260.6	1.08 (0.56-2.11)
3. Negative outcome control, antipsychotic medication exposure and risk of incident otitis media.			
Baseline period	261	2 691.6	-
14 days pre first antipsychotic exposure	8	119.5	0.74 (0.32-1.73)
First 30 days of antipsychotic exposure	23	306.1	0.77 (0.42-1.39)
Subsequent antipsychotic exposure	42	546.8	0.75 (0.42-1.34)

*Psychotropic medication classes included were: antidepressants stimulants, anxiolytics and hypnotics, not including benzodiazepine.

7.5. Discussion

7.5.1 Main findings

This research found no evidence of an association between exposure to antipsychotic medication and an increased risk of seizure in individuals with ASD in the defined risk windows. There was some evidence of increased risk of incident seizure during the first month of treatment with other psychotropic medication: IRR = 1.57 (95% CI: 1.03-2.38, P = 0.03). This would suggest that close monitoring for the possible occurrence of seizures should take place, particularly in the first month of non-antipsychotic psychotropic medication treatment.

7.5.2 Comparison with previous cohort study

The findings from the previous cohort study presented in Chapter Six show no evidence of an association between antipsychotic medication exposure and risk of incident seizure compared to other psychotropic medication: HR 1.28, 95% CI: 0.74-2.19. The results from the SCCS analyses presented in this chapter were consistent with findings from the cohort study. However, in the SCCS analyses focused on the risk of incident seizure associated with psychotropic medication exposure, other than antipsychotics, there was some evidence of an increased risk of incident seizure in the first month of treatment. This would suggest that close monitoring for the possible occurrence of seizures should take place, particularly in the first month. The discrepancy between the results of the two SCCS investigating the risk of seizure associated with antipsychotic medication and other psychotropic medication compared to the results of the previous cohort study could be justified by: 1) physicians may tend to prescribe antipsychotic medication for patients with low risk of developing seizure based on their established belief that this medication is likely to induce seizures; 2) it has been

acknowledged that increased seizure risk reported with antipsychotic medication use is related to the medication dose[233-235]. Possibly, the risk of seizure associated with antipsychotics use was not captured in this study because the medication dose was not considered in the analyses.

7.5.3 Strengths & weaknesses

The SCCS design overcomes the effect of time-fixed measured and unmeasured potential confounders between individuals as each participant acts as their own control [251]. As the comparison of the event rate is within-person, a smaller sample size is needed to conduct such a study. In this research, the case definition was very specific and was applied to a limited number of individuals. This sample involved individuals with ASD being treated with antipsychotics and who had experienced an incident seizure. Certain assumptions must be met to conduct a valid SCCS study. If one of these assumptions is not met, this will introduce bias to the estimated relative incidence. In this study, all these assumptions were considered and measurements were taken to avoid the violation of these assumptions. The results of the sensitivity analysis excluding patients who died during the observation period were similar to all the cases analysis. This indicated that the seizure events did not lead to death, which would subsequently have ended the observation; thus, no violation of the SCCS assumptions occurred during this study. This was consistent with the findings of a previous SCCS study which applied the SCCS extension approach to examining the effects of seizure on censoring the observation period[209]. The results of the negative control SCCS sensitivity analyses show that there is no association between antipsychotic medication exposure and otitis media. This indicates that the main SCCS study of the association between antipsychotic medication and incident seizure fitted

appropriately, and no selection or measurement bias was introduced to the results.

One of the limitations of the SCCS design is that it does not give estimates of absolute incidence; it only estimates the relative incidence. However, in the previous cohort study the absolute incidence of seizure was calculated. Similar to the cohort study presented in **Chapter Six**, the results of this study applied to antipsychotic medication in general, without dose or drug type specifications which may in have influenced the estimated results. In this study, drug type/dose stratified risk estimates could potentially result in biased findings affected by inadequate study power resulting from a limited sample size. Therefore, these issues should be assessed further in future studies.

7.6. Summary

- One hundred and forty-nine patients with ASD were on antipsychotic medication and who had experienced incident seizure were included in the primary SCCS analysis. The overall observation period was nearly 1,529 patient-years.
- The mean age of the patients at the start of observation was 16.15 years (SD 14.03). The average length of continuous antipsychotic prescriptions was 49 days, ranging from 1 to 2,553 days.
- The IRR of seizure for the first 30 days of antipsychotic exposure was 1.79, 95% CI: 0.97-3.30, which indicates no strong evidence of an association between exposure to antipsychotics and increased risk of incident seizure
- In the second SCCS, 305 patients with ASD who were prescribed psychotropic medication, other than antipsychotics, and who had a recorded incident seizure were included in the analysis. The total observation period for the included patients was approximately 3,168 patient-years.
- At the start of the observation, the mean age of the patients was 11.52 years (SD 12.29), The average length of continuous psychotropic medication prescriptions was one month, ranging from 1 to 2,367 days.
- In the subsequent SCCS, the IRR of incident seizure was 1.57, 95% CI:1.03-2.38 during the first month of treatment with psychotropic medication, indicating a short-term increased risk of incident seizure at the beginning of psychotropic medication exposure.

Chapter Eight: The Risk of Cardiac Events Among Antipsychotic Medication Users in Individuals Diagnosed with Autism Spectrum Disorder (ASD): Cohort Study

In this chapter, the results of a retrospective cohort study performed to investigate the association between antipsychotic medication exposure and risk of cardiac AEs in a population with ASD are presented. The chapter starts with an introduction describing the importance and the specific objective of conducting this study. This is followed by a methodology section explaining the details of how this study was conducted, including the design of the study, the population and the statistical analyses. This study shares similar statistical methods applied in the cohort study presented in Chapter Six. Therefore; to avoid repetition, some parts in this chapter will refer to certain sections in Chapter Six. The chapter continues with a presentation of the results, and ends with a discussion and summary of the main findings.

8.1. Introduction

Cardiovascular disease (CVD) is a leading cause of death in people with serious mental illness (SMI). People with SMI die on average 25 years earlier than the general population, most often from premature CVD[254, 255]. Antipsychotic medication may contribute to this CVD risk[256-258]; the metabolic abnormalities associated with atypical antipsychotic use, such as weight gain, type 2 diabetes and other metabolic disorders, may increase the risk of developing CVD[259-261]. It has been found that higher doses of antipsychotic medication treatment predicted greater risk of mortality from coronary heart disease and cerebrovascular accident in people with SMI[262].

A systematic review, published in 2011, aimed at determining whether the use of antipsychotic agents is associated with the incidence of myocardial infarction (MI) in adults identified five observational studies with conflicting results [263]. The variable results provided by the identified studies may be attributed to the heterogeneity of these studies in areas such as the sample size, follow-up time

and type of antipsychotics. A more recent systematic review of antipsychotic use and the risk of MI, published in 2016, identified nine observational studies: the results of the meta-analysis of odds ratios (ORs) for developing MI was 1.88, 95% CI: 1.39, 2.54 in antipsychotic users compared with non-users [264]. A recent systematic review and meta-analysis of antipsychotic drug use and risk of stroke and myocardial infarction, published in 2019, has identified ten observational studies on MI risk; most of these studies included a general population and, thus, did not specify the indication for AP drug use [265]. The pooled HR for the cohort studies (1.29, 95% CI: 0.88-1.90) and case-control studies (1.07, 95% CI 0.94-1.23) indicated no association between AP drug use and MI risk. However; substantial methodological and statistical heterogeneity among a relatively small number of studies, in addition to the potential confounding by indication, limits firm conclusions. This is important to note as previous studies have indicated that use of antipsychotics may be associated with an increased risk of coronary artery disease (CAD), stroke, arrhythmia and sudden cardiac death [266-268]. In 2013, a cohort study was performed to assess the potential risk of cardiac mortality in an antipsychotic-exposed population using data from a UK primary care database[269]. The results showed that the relative risks (RRs) compared to psychiatric non-antipsychotics users of cardiac mortality was 1.72 (95% CI: 1.42–2.07); CAD 1.16 (95% CI: 0.94–1.44); and ventricular arrhythmias (VA) was1.16 (95% CI: 1.02–1.31)[269]. The RRs were lower for SGAP versus FGAP, cardiac mortality 0.89 (95% CI: 0.82–0.97); CAD 0.85 (95% CI: 0.76–0.96); and VA 0.93 (95% CI: 0.79–1.10). Another study carried out within the UK population using a within individual study designs (self-controlled case series) found that the IRR of MI during the first month of use of FGAP was 2.82, 95% CI 2.0–3.99, and for SGAP it was 2.5, 95% CI: 1.18–5.32 [270]. According to this study, the proposed

mechanism of the potential antipsychotic-induced risk of CVD could be due to a drug-induced change in heart rate[270].

The results of the systematic literature review, presented in **Chapter Three** showed that AEs are highly prevalent in people with ASD who take antipsychotic medication. However; cardiovascular AEs have been identified less frequently. A change in heart rate and prolonged QT interval were reported in an RCT looking for the cardiac conduction effects of risperidone in children with ASD[130]. Studies investigating the association of antipsychotic medication exposure and the development of cardiac adverse events, particularly in a population with ASD diagnosis, are limited. Previous studies were conducted using populations with SMI exposed to antipsychotic medication. Additionally, in **Chapter Five**, the results of the DUS indicated that almost half of the issued prescriptions of antipsychotic medication were for antipsychotics other than risperidone, the only antipsychotic medication approved in the UK for people with autism. The effect of prescribing such medication on cardiac health for this critical population is unknown. Therefore, the study presented in this chapter is an analytical cohort study aimed at investigating the association between antipsychotic medication use in people with ASD and the risk of cardiac AEs.

8.2. Objectives

The specific objectives of this cohort study were:

1. To calculate the incidence rates of cardiovascular events, including arrhythmia, heart failure and MI, in antipsychotic medication users and in other psychotropic medication users, in a population with ASD.

2. To compare the HR of cardiovascular events between antipsychotic medication users and the users of other psychotropic medication, in a population with ASD.

8.3. Methods

8.3.1. Study design

The study presented in this chapter is an observational retrospective cohort study.

8.3.2. Data source

Data for this study were provided by the IQVIA Medical Research Data (IMRD-UK) database (see Chapter Four).

8.3.3. Ethical approval

The ethical approval for this study was obtained from the SRC: see **Section 6.3.3.**

8.3.4. Participants, exposure and outcomes

Patients aged two years and older with a first-recorded diagnosis of ASD between 1st of January 1996 to 26th September 2017 were identified using ASD Diagnostic Read codes (**see Appendix 5**). For each patient, the start date was defined as the latter of the following: the date of the patient's registration at the general practice or the date that the general practice began using Vision software (a clinical management system), or the second age of birth. The index date was defined as the date of the first psychotropic medication prescription that followed the ASD diagnosis. Patients were included if they had received at least one prescription of the study medications, which included the following classes of psychotropic medication: antipsychotics, antidepressants, stimulants, antiepileptic medication, hypnotics and anxiolytics. Medication lists for each class were obtained from Chapter 4 of the BNF (**see Appendix 7&8**). The drug codes

of the preceding psychotropic medications were extracted to identify medication exposure.

Patients were considered eligible for inclusion in the study only if they had a screening period of at least six months available from their start date to their index date, except for those patients whose start date equalled their second birthday, for whom no screening period was required. The follow-up period for each patient started on the index date and continued until the earliest of the following: the outcome of occurrence date, the date the medication of interest had been switched or discounted, death, the patient left the practice (date of last data collection) or the end date of the study. **Figure 6.1** (**Chapter Six**), illustrates the follow-up period for each observation during the cohort analysis.

Patients who had been prescribed antipsychotic medication after a diagnosis of ASD were included in the exposure group. The comparison group includes patients prescribed other psychotropic medication, including antidepressants, stimulants, antiepileptic medication, hypnotics and anxiolytics. The follow-up time of patients using 'other psychotropic medication' was censored once they received a prescription for an antipsychotic agent. A new follow-up period for them started on the first day of the antipsychotics prescription.

The outcomes of interest in this study were cardiac events including arrhythmia, heart failure and MI. The cardiac events diagnoses were identified by read codes list (**see Appendix 11**). These Read code lists were taken from published studies which identified these outcomes in primary care databases in the UK[271, 272].

8.3.5. Statistical analyses

Similar statistical methods as described in **Section 6.3.5.** were applied. Briefly, HRs of cardiac events were estimated using a Cox proportional hazard model.

Originally, the intention was to calculate the HR associated with antipsychotic medication exposure for each cardiac outcome independently. However; the event rate identified of the cardiac outcomes in the study population was inadequate to produce valid stratified estimates. Therefore; a pooled analysis of the three cardiac outcomes was conducted.

8.3.5.1. Sample size calculation

Based on the incidence rates of cardaic outcomes of interest in the general population, sample size calculation for each outcome was done independently to determine the number of patients required to estimate the risk of each outcome with 80% power of the study and a 95% confidence interval. The incidence rate of arrhythmia was 47.2 per 10,000 PY[273], 56.4 per 10,000 PY[274] for HF and 89.4 per 10,000 PY[275] for MI. To estimate the risk of arrhythmia, 9,942 patients are needed, and a total of 8,358 and 5,206 patients are needed to estimate the risk of HF and MI, respectively.

8.3.5.2. Propensity Score Fine-Stratification Weighting

Propensity score fine stratification weighting model was used to facilitates the comparison between the study groups. This model adjusts for underlying patient's characteristics that could influence the estimated results. The PS fine stratification model is described in **section 6.3.5.**

8.3.5.3. Covariates

As mentioned in Chapter Six, Section 6.3.5.3, the selection of variables to be included in the PS model is dependent on their association to the outcome. Thus, baseline covariates that are potentially related to the cardiac outcomes of interest were incorporated in the PS fine stratification model (**Table 8.1**). These potential confounders include: age, gender, weight expressed as (z-score), smoking and

problematic alcohol consumption[276]. In addition, certain medical conditions were added to the adjustment model, including neuropsychiatric comorbidities, diabetes, dyslipidaemia and hypertension. Data on concomitant medication use were obtained for each patient for the following drugs/drug classes: non-steroidal anti-inflammatory drugs (NSAID)[277], antidiabetic drugs (Sulfonylureas[278] and Glitazones[279]), cardiovascular drugs, cytostatic drugs, and immunomodulatory drugs[280, 281].

The standard deviation scores (SDS) of the weight (Z-score) is a transformed measurement of sex-age-specific weight value. It indicates how far the weight deviates from the population mean and in what direction (positive vs. negative) e.g. a value that is 2 standard deviations above the mean will have a Z-score of +2.0. [282]. Z-score is useful in comparing two groups with different means and/or different standard deviations[282]. Z-score for each patient was calculated using the data of age at index date and the last weight recorded before or on the index date by Least Mean Square growth software (LMS) for participants with age 2-23 years[283]. LMS growth software was developed by Professor Tim Cole and downloaded from http://www.healthforallchildren.co.uk[283]. For patients older than 23 years, the z-score was calculated according to the following equation:

$$Z - score = \frac{Observed\ weight - mean\ weight\ of\ reference\ population}{standard\ deviation\ (SD) of\ reference\ population}$$

The mean weight and standard deviation of the reference population were derived from the Health Survey for England 1993-2017 [284]. For patients with missing weight records, the z-score was estimated to be equal to zero.

8.3.5.4. Sensitivity analyses

Two sensitivity analyses were applied to examine the validity of the main analysis by assigning different follow-up periods. In the first sensitivity analysis, the follow-up period was ended at the earliest date of: occurrence of the outcome, death, the patient left the practice or the end date of the study. In the second sensitivity analysis, a 90 days' grace period was allowed after the first continuous medication exposure. The grace period accounts for the residual effect of the medication or the persistence medication exposure resulted from the remaining medication quantity because of patient non-adherence. The end of follow-up date was defined as the earliest of: the occurrence of the outcome, death, the patient left the practice or the end date of the study, last day of the grace period. All analyses were performed using SAS software, version 9.4.

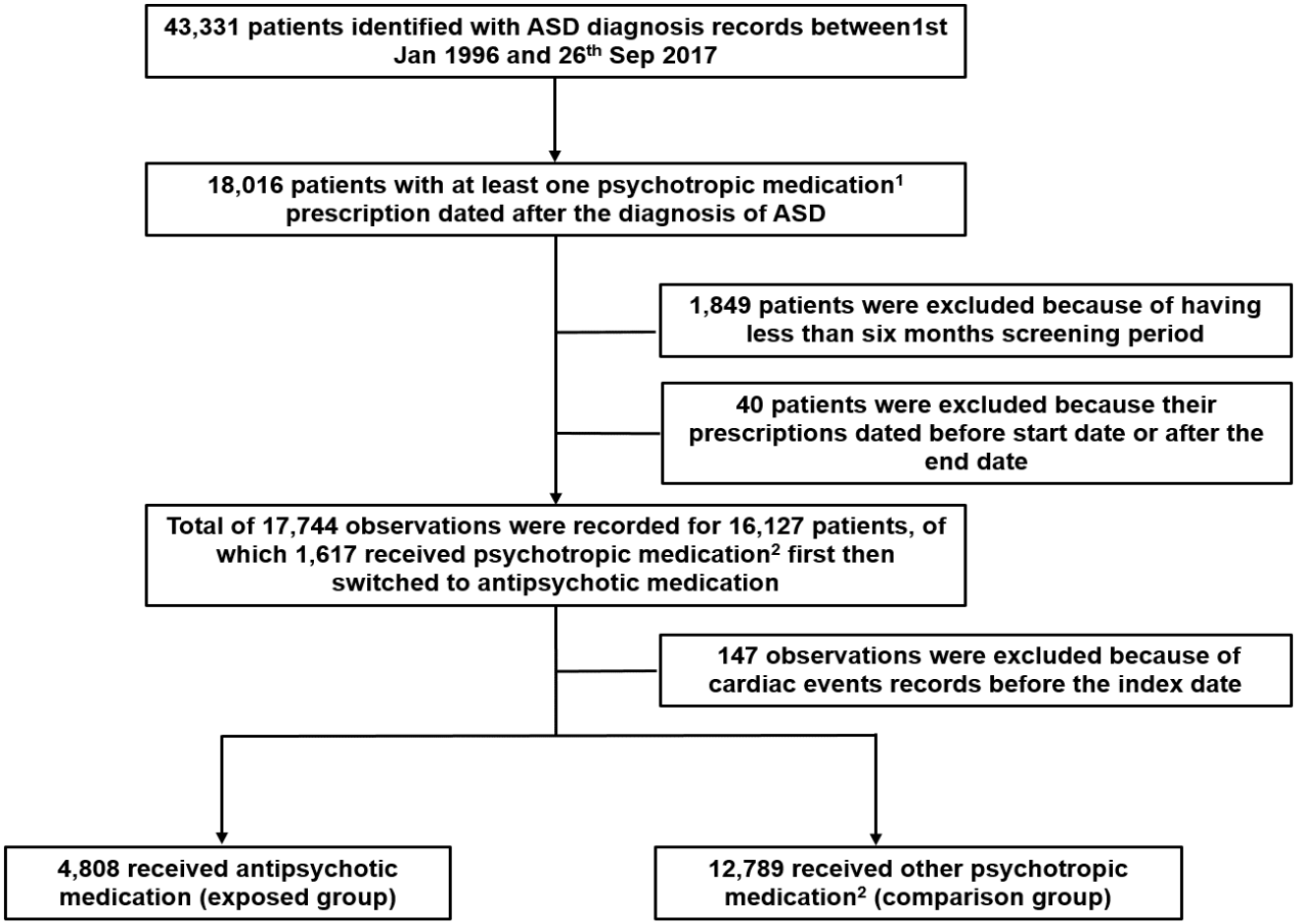
8.4. Results

8.4.1. Descriptive results

From the 1st of January 1996 until the 26th September 2017, 18,016 patients were identified who had a recorded ASD diagnosis and who were prescribed at least one psychotropic medication prescription. Of those, 17,744 observations met the inclusion criteria and were included in the cohort analysis. 4,809 patients were on antipsychotic medication and were assigned to the exposed group and 12,789 patients were on other psychotropic medication and assigned to the comparison group. The patients' inclusion flowchart is illustrated in **Figure 8.1**. The mean age of patients in the exposed group was 26.2 years (SD 13.9) at the date of the first medication prescription. In the comparison group, patients were younger at the first date of medication prescription, the mean age being 18.6 years (SD 12.3). As mentioned in the cohort study presented in Chapter Six, this could be because usually stimulant medication prescribed at a younger age[229]. In both groups, the

ratio of male to female patients was approximately 3:1. In the PS-weighted model, all covariates were balanced between the two study groups, with an SMD of less than 0.1. **Table 8.1** lists the crude and weighted baseline clinical characteristics of the exposed and comparison groups at the index date, with standardised mean differences.

Figure 8.1: Flowchart of patients' inclusion process



[1]In this step psychotropic medication classes included were: antipsychotics, antidepressants, anxiolytics, antiepileptics, stimulants, and hypnotics.

[2]In this step psychotropic medication classes included were: antidepressants, anxiolytics, antiepileptics, stimulants, and hypnotics.

Table 8.1: Patients' characteristics baseline in the cohort study

Characteristic, no (%)	Crude		SMD	Weighted		SMD
	Antipsychotic	Other psychotropic[1]		Antipsychotic	Other psychotropic[1]	
Age, mean (SD)	26.2 (13.9)	18.6 (12.3)	0.583	26.2 (13.9)	26.4 (16.2)	-0.009
Gender						
Female	1,119 (23.3)	3,134 (24.5)	-0.029	1118 (23.3)	2960 (23.4)	-0.002
Male	3,689 (76.7)	9,655 (75.5)	0.029	3689 (76.7)	9713 (76.6)	0.002
SDS_Weight (SD)	-0.3 (13.9)	0.1 (9.6)	-0.030	-0.3 (13.9)	-0.1 (14)	-0.012
Smoking status						
Non-smoker	3,878 (80.7)	10,896 (85.2)	-0.121	3878 (80.7)	10087 (79.6)	0.027
Current smoker	622 (12.9)	1,129 (8.8)	0.132	621 (12.9)	1716 (13.5)	-0.018
Ex-smoker	308 (6.4)	764 (6)	0.018	308 (6.4)	870 (6.9)	-0.018
Alcohol status						
Non-problematic drinker	4,588 (95.4)	1,2369	-0.067	4587 (95.4)	12038 (95)	0.02
Problematic drinker	220 (4.6)	420 (3.3)	0.067	220 (4.6)	635 (5)	-0.02
Comorbidities						
Neuropsychiatric comorbidities (+)	4,218 (87.7)	9,905 (77.4)	0.274	4217 (87.7)	11262 (88.9)	-0.035
Diabetes (+)	119 (2.5)	152 (1.2)	0.096	119 (2.5)	313 (2.5)	0
Hypertension (+)	1231 (25.6)	3141 (24.6)	0.024	1231 (25.6)	3508 (27.7)	-0.047
Dyslipidaemia (+)	60 (1.2)	80 (0.6)	0.065	60 (1.2)	183 (1.4)	-0.017
Medication use						
Non-user of CVD medication	4212 (87.6)	11600 (90.7)	-0.1	4211 (87.6)	11067 (87.3)	0.008
Current user of CVD medication	429 (8.9)	733 (5.7)	0.123	429 (8.9)	1155 (9.1)	-0.007
Ex-user of CVD medication	167 (3.5)	456 (3.6)	-0.005	167 (3.5)	451 (3.6)	-0.004
Non-user of antidiabetic medication[2]	4760 (99)	12752 (99.7)	-0.089	4759 (99)	12563 (99.1)	-0.013
Current user of antidiabetic medication	36 (0.7)	26 (0.2)	0.079	36 (0.7)	81 (0.6)	0.013

Characteristic, no (%)	Crude		SMD	Weighted		SMD
	Antipsychotic	Other psychotropic[1]		Antipsychotic	Other psychotropic[1]	
Ex-user of antidiabetic medication	12 (0.2)	11 (0.1)	0.040	12 (0.2)	29 (0.2)	0.004
Non-user of NSAID	3528 (73.4)	8806 (68.9)	0.1	3528 (73.4)	9219 (72.7)	0.015
Current user of NSAID	556 (11.6)	1541 (12)	-0.015	556 (11.6)	1528 (12.1)	-0.015
Ex- user of NSAID	724 (15.1)	2442 (19.1)	-0.107	723 (15)	1926 (15.2)	-0.004
Non- user of cytostatic	4784 (99.5)	12740 (99.6)	-0.018	4783 (99.5)	12611 (99.5)	-0.002
Current user of cytostatic	17 (0.4)	24 (0.2)	0.032	17 (0.4)	45 (0.4)	0
Ex- user of cytostatic	7 (0.1)	25 (0.2)	-0.012	7 (0.1)	17 (0.1)	0.004
Non- user of immunomodulator	4791 (99.6)	12741 (99.6)	0.004	4790 (99.6)	12621 (99.6)	0.009
Current user of immunomodulator	8 (0.2)	32 (0.3)	-0.018	8 (0.2)	24 (0.2)	-0.006
Ex-user of immunomodulator	9 (0.2)	16 (0.1)	0.016	9 (0.2)	28 (0.2)	-0.007

SMD standardised mean difference, SD standard deviation, SDS standard deviation scores, CVD cardiovascular disease, NSAID Non-steroidal anti-inflammatory drugs.

[1]Psychotropic medication classes included were: antidepressants, antiepileptics, stimulants, hypnotics and anxiolytics.
[2]Antidiabetic medication included: glutathione and sulfonylurea

8.4.2. Primary results

The crude incident rates of each cardiac outcome were calculated. The incident rate of arrhythmia was 7.06 per 10,000 PY in patients with ASD who were prescribed antipsychotic, and 6.95 per 10,000 PY in patients who were prescribed other antipsychtic medication. Whereas the incident rate of heart failure in patients with ASD who were treated with antipsychotic medication was 1.91 per 10,000 PY, and for patients treated with other psychotropic medication, the incident rate was 0.62 per 10,000 PY. The incident rates of MI in both groups were similar to heart failure incident rates. For patients with ASD who were treated with antipsychotic medication, the incident rate was 1.91 per 10,000 PY, and the incident rate among patients who were treated with other psychotropic medications was 0.63 per 10,000 PY.

originally, the plan was to estimate the risk of each cardiac outcome associated with antipsychotic use separately. However, the incidence rate identified within this cohort for each outcome was smaller than the incidence rate in the general population and a larger sample size were required to provide an acceptable statistical power. Hence, the three cardiac outcomes were analysed together (i.e. the occurrence of the outcome was defined as the occurrence of any of the three cardiac outcomes of interest).

The crude incidence rate of all cardiac events in 4,808 patients with ASD who were prescribed antipsychotic medication was 10.93 per 10,000 PY. In 12,789 patients with ASD who were prescribed other psychotropic medication, the incidence rate of cardiac events was 8.23 per 10,000 PY. The primary PS-weighted HR of the cardiac events was 1.27, 95% CI: 0.62-2.62, indicating no evidence of an increased risk of cardiac events associated with antipsychotic exposure compared to other psychotropic medication in a population with ASD.

8.4.3. Sensitivity analyses results

The results of the sensitivity analyses were consistent with the primary analysis: the HRs of cardiac adverse events were 1.60, 95% CI: 0.82-3.16 and 2.08, 95% CI: 0.94-4.61. **Table 8.2** shows the results of the crude and weighted Cox proportional hazard model.

Table 8.2: Results of the cohort analyses

Group	Patients (n)	Patient-years	Events (n)	Crude HR (95% CI)	Weighted HR (95%CI)
Primary analysis **2. Follow up end by earlier of: outcome date, medication has been switched or discontinued, death, patient left practice or study end date.**					
Antipsychotic	4,808	15,547	17	1.26 (0.68-2.33)	1.27 (0.62-2.62)
Psychotropic[1]	12,789	31,585	26	1.0	1.0
Sensitivity analyses **3. Follow up end by earlier of: outcome date, death, patient left practice or study end date.**					
Antipsychotic	4,808	19,464	23	1.76 (1.00-3.10)	1.60 (0.82-3.16)
Psychotropic[1]	12,789	40,667	26	1.0	1.0
4. Follow up end by earlier of: outcome date, death, patient left practice, study end date or 90 days after first continuous exposure.					
Antipsychotic	4,808	11,950	16	1.80(0.90-3.50)	2.08 (0.94-4.61)
Psychotropic[1]	12,789	22,545	16	1.0	1.0

[1]Psychotropic medication classes included were: antidepressants, stimulants, hypnotics and anxiolytics.

8.5. Discussion

8.5.1. Main findings

This study found no evidence of an association between antipsychotic medication use and risk of cardiac events, including arrhythmia, heart failure and MI, compared to the use of other psychotropic medication in individuals with ASD. The PS-weighted HR of cardiac events was 1.27, 95% CI: 0.62-2.62 during the follow-up period. The results of the sensitivity analyses were not significant and consistent with the primary analysis.

8.5.2. Comparison with previous studies

There is limited published evidence on the association between antipsychotic medication exposure and the risk of developing cardiac events in a population diagnosed with ASD. Most of this evidence has arisen from research into the effects of antipsychotic medication use on the change in the QT interval. Two studies (an open-label and an observational study) have reported no change in the corrected QT interval (QTc) after administration of aripiprazole[285] and ziprasidone[286] in 24 and 42 children with ASD, respectively. A double-blinded RCT on the effect of acute treatment with risperidone on cardiac conduction in 65 children with ASD did not identify any cardiac conduction adverse effects of risperidone, and there was no difference in the mean change in the QTc compared to placebo[130]. These findings were supported by a recent observational study which assessed the effect of risperidone serum concentration on effectiveness and side effects in 42 children and adolescents with ASD[287]. The study found no association between risperidone concentration and QTc prolongation. Although the results of those studies appear consistent with the results of the study presented in this chapter, the interpretation of the QTc interval data in those studies was limited by the small sample size. Furthermore, the

cardiac outcomes included in this cohort study were arrhythmia, heart failure and MI, making a direct comparison with the results of the preceding studies inappropriate.

8.5.3. Strengths & weaknesses

To date, this is the largest cohort study to assess the risk of cardiac events associated with antipsychotic treatment in people with ASD. In Chapter Six, the strengths of the study design used are explained in detail. As shown in Chapter Four, the source of data in this study was a large primary care database representative of the UK population.

However, one of the limitations of this database is the potential lack of data on outcomes recorded at secondary or tertiary health care settings. This may lead to an underestimation of outcome counts and, subsequently, outcome misclassification that could potentially bias the estimated results to the null value. Other factors may contribute to the reduced outcome rate in this study. One of these is the young age of the study sample; their mean age was approximately 26 years. Nevertheless, although it is well known that young people are less prone to develop cardiac problems than the elderly, the limited evidence linked between antipsychotics and cardiac problems suggested that young people could have a greater chance of developing cardiac changes than adults[288-290]. Also, despite the approximately long follow-up duration (an average of more than two years in both groups) and the long retention time for antipsychotic medication and other psychotropics observed in the DUS presented in **Chapter Five**, a considerable number of patients had a short-term exposure to medication that might not be sufficient to precipitate cardiac problems. The reduced outcome rate in the study population may have affected the statistical power of the study and a larger sample size could be required to draw firm conclusions on the association

between antipsychotic use in patients with ASD and risk of cardiac events. As a result of the specific case definition and low events rate, the sample size was not large enough to conduct subgroup analyses based on each cardiac outcome or antipsychotic class. As previously stated, the medication type or dose was not considered in the studies conducted in this thesis. The sample size identified was inadequate to conduct a stratified analysis with enough study power. The limitations of the data source used in this study (IMRD-UK) are provided in Chapter Four, section 4.3. Further studies, in larger population samples, are needed to support the results of this study and to confirm the long-term safety of antipsychotic medication use in ASD.

8.6. Summary

- During the 20-year study period, 4,808 patients with ASD and who were prescribed antipsychotic medication were identified and eligible for exposed group. In the comparison group, 12,789 patents prescribed other psychotropic medication were included.
- The mean age for patients at the time of starting antipsychotic treatment was 26.2 years (SD 13.9) and the mean follow-up was 2.4 years (SD 2.8). In the comparison group, the mean age was 18.6 years (SD 12.3) and the mean follow-up was 3.2 years (SD 3.5).
- The incidence rate of cardiac events in exposed patients was 10.93 per 10,000 PY. Among 12,789 patients in the comparison group, the incidence rate of cardiac events was 8.23 per 10,000 PY.
- The PS-weighted HR of the cardiac events was 1.27, 95% CI: 0.62-2.62, indicating no evidence of an increased risk of cardiac events associated with antipsychotic exposure compared to other psychotropic medication in a population with ASD.
- The low number of cardiac events made it difficult to draw any firm conclusions based on each cardiac event or antipsychotic class/drug type.

Chapter Nine: Overall Discussion and Conclusion

This chapter summarises the key findings of the previous chapters presented in this PhD project, in addition to any implications for clinical practice, the strengths and limitations of the research, its contribution to the current knowledge and recommendations for future research.

9.1. Overview of the key findings

This thesis has assessed the use of antipsychotic medication in patients with ASD from clinical and pharmaco-epidemiological perspectives. Different study designs were employed in this PhD project, focussed on a population with ASD:

a) A systematic review to summarise the available literature on the adverse events associated with antipsychotic medication. The findings from this systematic review showed that the risk of adverse events is increased by 22% with the use of antipsychotic medication in a population with ASD. CNS and endocrine disorders such as weight gain were the most predominant adverse events and these led to the discontinuation of therapy in many patients.

b) A drug utilisation study using a UK primary care database (IMRD-UK) to provide an overview of ASD incidence/prevalence in the UK, in addition to pharmacotherapy prescribing patterns and the neuropsychiatric conditions associated with ASD. From 2009 to 2016, the incidence and prevalence of ASD increased 2.9-fold and 3.3-fold respectively. More than half of the ASD population identified had at least one additional neuropsychiatric comorbidity diagnosis and almost one-third of the identified cohort were on psychotropic medication. Up to 49.3% of antipsychotic medication prescriptions were for antipsychotic medication other than risperidone.

c) An analytical retrospective cohort study followed by a self-controlled case series analyses to examine the primary research question of this project: whether

the use of antipsychotic medication is associated with increased risk of incident seizure. The findings from these analytical studies suggested no evidence of an increased risk of incident seizure associated with antipsychotic exposure compared to other psychotropic medication.

d) Another retrospective cohort study to investigate the risk of cardiac adverse events associated with antipsychotic medication treatment, including arrhythmia, heart failure and myocardial infarction. This study indicated no association between antipsychotic medication and the risk of cardiac events.

9.2. Overall discussion

As highlighted in the systematic review and meta-analysis presented in **Chapter Three**, the available evidence that assessed the safety of antipsychotic medication use in a population with ASD is limited. Most of the published literature was on either aripiprazole or risperidone, which are the approved agents to be used for irritability in children and adolescents diagnosed with ASD. There is a lack of well-designed observational studies that have evaluated the association between antipsychotic medication exposure and the risk of developing certain adverse events; most published observational studies focused on weight gain and hyperprolactinemia. Serious adverse events such as cardiac problems and seizure are linked with the use of antipsychotic medication. ASD is a mental health disorder diagnosed usually at an early stage of the patient's life. It has been acknowledged that patients with mental health problems are at increased risk of both seizure and cardiac problems. The proposed mechanism for how antipsychotics could induce seizure is by lowering the seizure threshold. Metabolic abnormalities and changes in heart rate induced by antipsychotic medication are suggested mechanisms of cardiac adverse events reported with antipsychotic use. Before this PhD project, there had been no observational

studies assessing the association between antipsychotic medication use and the risk of developing these specific adverse events in populations with ASD. Thus, this PhD project aimed to fill this gap in the knowledge by conducting different pharmaco-epidemiological studies to investigate the association between antipsychotic medication use with the increased risk of seizure or cardiac adverse events in a population with ASD. A descriptive DUS (**Chapter Five**) was first carried out to provide an overview of the current ASD status in the UK and the prescribing patterns of different psychotropic classes, including antipsychotic medication, in addition to the other neuropsychiatric diagnoses that accompanied ASD. This was followed by two analytical observational studies (**Chapter Six and Seven**) with different designs to assess the risk of seizure associated with antipsychotic medication compared to other psychotropic medication. The risk of cardiac adverse events associated with antipsychotic medication was then examined using an analytical retrospective cohort design (**Chapter Eight**).

The findings from the DUS were generally consistent with findings from other studies conducted in other countries. This study showed a persistent increase in ASD incidence/prevalence over the study period, from 2009 to 2016. However, this increase was less intense than what had been found during the period from 1992 to 2008. The reason behind this difference could be that the social awareness and the broad diagnostic criteria of the condition had already been stabilised a few years before the start of this study. In this DUS study, I was interested in exploring the change in the prescribing pattern of antipsychotic medication in ASD patients after the approval of risperidone in the UK in 2007. Unexpectedly, there was a high percentage of the prescribing of agents other than risperidone. Approximately half of the antipsychotic medication prescriptions

were for risperidone and the remaining prescriptions were for other agents, including aripiprazole.

Despite the large number of published case reports linking antipsychotic medication use with increased risk of seizure, the cohort study conducted in this thesis found no evidence of an increased risk of seizure associated with antipsychotic medication compared to other psychotropics in a population with ASD. This finding could support the clinician decision about antipsychotic medication prescribing for patients with ASD. However, it could be unwise and risky to jump to this conclusion and make this clinical decision based on the findings of one study. Therefore, a self-controlled case series study was conducted to confirm the results of the preceding cohort study and to further investigate the association between antipsychotic use and risk of seizure. The self-controlled study design eliminated the effect of the time-invariant confounders and provided information on which period of the exposure time was associated with an elevated rate of event occurrence. The findings from this study were consistent with the cohort study, but there was evidence of a short-term elevated risk of seizure corresponding to the use of other psychotropic medication.

Like each clinical study, this study has its limitations, which were discussed in detail in different contexts of this thesis. One of these limitations concerns the use of the IMRD-UK database as a source of data. This database does not provide information on patients' adherence to their medications. Patients' non-adherence to medication may lead to what has been called exposure misclassification whereby non-users are misclassified as users [291]. This misclassification could bias the estimates towered the null value and affect the results. To minimise the impact of exposure misclassification on the estimated results, evidence of a

second prescription filled within a fixed period is required to increase the likelihood that patients are taking the medication[292]. Unfortunately, this evidence could not be provided by the database used. Besids, one of the objectives in this study was to examine the short-term risk of seizure during the first month of antipsychotic medication use and it would be unlikely patients would have received a second prescription by then. A secondary analysis conducted within the DUS presented in **Chapter Five** which excluded patients with only one prescription for each drug class resulted in similar findings to those of the primary analysis.

If the chance is offered to repeat this work, I would aim to optimise it by modifying any amendable fault and removing any points of weakness. The weaknesses and limitations of this project are discussed thoroughly in the following section. One main limitation concerns the recording of exposure and outcomes. At the time of this study, the IMRD-UK database used provided patients information of primary care setting only. Replicating the studies using a database that provides patients' records in secondary and tertiary care settings would offer more accurate counts of exposure and outcomes records, and avoid any underestimations. Another point that could be considered to improve the study presented in **Chapter Eight** is to carry it out using multiple databases to provide a big enough sample size that would enable us to draw a firm conclusion on the association between antipsychotic medication and risk of cardiac adverse events. A larger sample size was required to stratify the results by drug type/dose with acceptable statistical power, and this is applied to all the analytical studies carried out in this thesis.

The results of this thesis contribute to medical literature that may lead to better practice in antipsychotic medication prescribing for patients with ASD, especially with the observed prescribing of antipsychotic agents other than risperidone and

their long retention time. Hence, I was eager to disseminate these results and share them with other colleagues in the mental health field. The results of the studies conducted in this PhD project have been presented and discussed with pharmaco-epidemiology and psychopharmacology experts in departmental meetings and international conferences such as the International Congress of the Royal College of Psychiatrists and The International Conference on Pharmaco-epidemiology and Therapeutic Risk Management (ICPE). Also, the work carried out in this thesis has been published in the form of three full papers in scientific medical journals such as the Journal of Autism and Developmental Disorders and Pediatric Drugs journal.

9.3. Implications for clinical practice

The findings from this PhD project have an impact on clinical practice and the healthcare provided to patients with ASD in many aspects. Several recommendations for best antipsychotic medication assessment and treatment practices in patients with ASD are provided based on the findings of the studies conducted within this thesis:

1. As a general principle, certain measurements such as careful diagnostic assessment, attention to comorbid medical conditions, a review of other drugs the patient is being prescribed and the monitoring of improvements are recommended to obtain optimum therapy.

2. Psychosocial intervention is the first line treatment recommended for the management of the core features of ASD. It is recommended to that antipsychotic medication prescribing is reserved for patients who do not benefit from psychosocial intervention alone and who need to manage behavioural disturbance, such as irritability and self-injury.

3. The DUS conducted in this thesis (Chapter Five) revealed that many antipsychotic agents other than risperidone, which is the only approved agent for ASD management, have been prescribed for patients with ASD. These agents might be prescribed as off-label drugs (refer to off-label definition in Ch4 Section 4.4.4). Unlike the licensed medications (aripiprazole and risperidone), the off-label medications have not been studied rigorously and their efficacy and safety are not well established. Therefore, physicians who intend to prescribe antipsychotic medication for patients with ASD are advised to prescribe the approved antipsychotic medication for the management of behavioural disorders associated with the condition.

4. The findings of the systematic review and meta-analysis presented in Chapter Three showed weight gain to be one of the common adverse events reported with the use of antipsychotics. According to the American Academy of Child and Adolescents, healthcare providers should order blood tests to check for diabetes in children and adolescents treated with antipsychotics and who gain a lot of weight.

5. The findings of the systematic review conducted in this thesis concerning the available evidence on the adverse events associated with antipsychotic medication prescribing in ASD patients showed that the short and long-term safety of these medications has not been fully evaluated and, therefore, careful and frequent monitoring of side effects should be performed. Healthcare providers should pay attention to patients with ASD prescribed psychotropic medication, particularly at the initiation of the treatment as the probability of developing adverse events is increased then.

6. Healthcare providers are encouraged to educate the parents and caregivers of patients with ASD about the possible adverse events that could occur with treatment with such medication. A discussion of the risks and benefits of antipsychotic treatment with both the patients and their caregivers is also encouraged. This includes an emphasis on the importance of reporting the occurrence of any adverse events to the healthcare providers.

9.4. Strengths and limitations

This section presents the main strengths and limitations of this PhD project. The strengths and limitations of each study have been presented at the end of each relevant chapter.

The main strength of this PhD project is the originality of the research. To date, this is the first research investigating the association between antipsychotic agents and incident seizure in a population with ASD. Additionally, this PhD project explored the risk of cardiac adverse events, including arrhythmia, heart failure and MI by conducting the largest analytical study addressing this pharmaco-epidemiological question to date. Most of the available evidence on these two exposure-event pairs were case reports or studies with limited sample size, which limits the usefulness of drawing firm conclusions over these concerns. Moreover, the populations used in these studies were not purely ASD-diagnosed patients; they were often drawn from a population with mixed psychiatric diagnoses. The population with ASD is at an increased risk of developing seizure and cardiac adverse events; in addition, children and adolescents represent the majority of this population. It is of the greatest importance to ensure the safety of the use of antipsychotics in this vulnerable population, as a high percentage of

patients with ASD are on continuous treatment with antipsychotic medication for more than one year, reaching up to five years of treatment for some patients.

Different methodological designs were implemented to explore the relationship between antipsychotic medication exposure and risk of incident seizure and to provide a definite answer about this association. Two analytical observational studies were conducted: 1) a cohort study calculated the incidence rate of seizure associated with exposure to antipsychotics; 2) a self-controlled case series analyses which provided the advantage of eliminating between-person variations that could bias the estimated risk.

The source of data used to run the studies conducted within this project is a large UK primary care database (IMRD-UK). A comprehensive description of IMRD-UK is provided in **Chapter Four** in this thesis. Data from IMRD-UK are representative of the UK population and validated for pharmaco-epidemiological research. Ordinarily, the time period required to conduct a prospective cohort study, which involves a large sample size and long follow-up period, is extended and may last for several years to allow for the recruitment of enough participants. However, using this considerable database provides a large enough sample size required to apply the analyses and answer the research question within the time-frame allocated for this PhD project.

The methods of the implemented studies were supported by multiple statistical approaches which were applied to avoid estimating biased results, such as: propensity score fine-stratification weighting, robust standard error and a self-controlled study design. These approaches were described in detail under the methods section of each study. Moreover, the primary analysis for each study

was followed by several sensitivity analyses to examine the validity of the primary analysis.

The main limitations of this PhD project relate to the recording of the exposure and outcomes in the database used in this thesis as it only includes information on patients in primary care. Prescriptions produced by non-primary care settings, such as hospital discharge prescriptions and prescriptions provided by specialised centres, are not recorded in IMRD-UK. Similarly, the outcome diagnosis records; there could have been some events in hospital emergency departments that were not linked to the patients' files in the general practice. These unlinked records may have led to an underestimate of the prescription rates and number of cases. Furthermore, the database does not directly link prescriptions for drugs with their indication for use; therefore, it is not possible to determine whether recorded drugs were being prescribed to treat neuropsychiatric comorbidities of ASD. Moreover, information on patient compliance and adherence to the prescribed medication cannot be obtained from the database; hence, we are not certain if the patients prescribed any of the drugs were taking them as prescribed.

The results of this research applied only to individuals with ASD and to psychotropic drug users in general; therefore, we cannot generalise the findings in the thesis to the general or other psychiatric populations. The analyses undertaken in this thesis were not stratified by type of antipsychotic medication and did not take into account medication dose; this was because of the inadequate sample size identified to produce stratified analyses with sufficient statistical power. There are indications from the literature that certain antipsychotic agents and higher doses of medications are more likely to precipitate seizures.

Finally, in the study presented in Chapter Eight, the low outcome rate in the included sample may have affected the statistical power of the study and a larger sample size could be required to draw firm conclusions on the association between antipsychotic use in patients with ASD and risk of individual cardiac events.

Despite these limitations, the findings from this PhD project were of added value and have contributed to the existing knowledge. These studies were the first to be conducted and to address issues surrounding the use of psychotropic drugs in a population with ASD. In light of the limited clinical guidance of medication use in ASD, this PhD project increases the awareness of the safety of antipsychotic medication use within a population with ASD from clinical and pharmaco-epidemiological perspectives. Further suggested studies concerning these limitations can be found in **Section 9.6.** of this chapter.

9.5. Contribution to the literature

This studies presented in this thesis add to the current literature about the safety of antipsychotic medication use in patients with ASD as follows:

1. The systematic review and meta-analyses presented in Chapter Three summarised the majority of published studies assessing antipsychotic medication use and associated AEs in a population with ASD. I found there was a lack of studies that assessed the relationship between the use of antipsychotic medications and the risk of incident seizure. Studies that assessed the risk of cardiac adverse events with antipsychotics exposure in an ASD population were infrequent and with a limited sample size.
2. The studies presented in Chapters Six, Seven and Eight filled this gap in knowledge through reporting on large analytical studies that were conducted

using different methodological designs and a UK representative database as the data source.

3. The large cohort study presented in Chapter Six is the first analytical study assessing this risk in a population with ASD.
4. The cohort study presented in Chapter Eight is the largest cohort study, set in a population with ASD, which assessed the risk of cardiac adverse events associated with the use of antipsychotic medication. Nevertheless, there is still a need for studies with a larger sample size to draw a definite conclusion on the risk of cardiac events associated with antipsychotic medication exposure in a population with ASD.

9.6. Recommendations for future research

The studies presented in this thesis have filled a gap in the pharmaco-epidemiological area about the use of antipsychotic medication in a population with ASD. Suggestions for future considerations in this area are:

1. Seizure is a recurrent event; the risk of subsequent seizure is increased after the incidence of the first unprovoked seizure. Patients with a history of epilepsy or seizures were excluded from the studies conducted in this thesis to eliminate any bias of the estimated risk of seizure associated with antipsychotic medication exposure. Investigating the risk of seizure in patients with ASD who had a previous history of seizures and were exposed to antipsychotics is a clinically important question to be addressed. Future studies examining the association between antipsychotic medication exposure and the risk of incident seizure in a population with ASD, including patients with a recorded history of seizure or epilepsy, are recommended.

2. The number of patients included in the cohort study conducted in this thesis to examine the association between antipsychotic medication exposure and cardiac adverse events in a population with ASD was insufficient to draw a firm conclusion about this association and to stratify the estimate based on drug type/dose. Therefore, future studies examining the association between antipsychotic medication exposure and the risk of cardiac events in a population with ASD using a larger sample size are needed to provide more detailed conclusions regarding this association.
3. Future studies using a database that provides data recordings from secondary and tertiary healthcare in addition to primary care data, are warranted to ensure the capture of all recorded exposure and outcomes and to avoid the underestimation of prescriptions or events rate.
4. Future studies that stratify the estimated risks based on antipsychotic class and drug type would offer added value to clinical practice and would assist decision-making for physicians. Furthermore, studies providing information on which drug doses could be harmful or potentially associated with an increased risk of seizure or cardiac adverse events for patients would potentially improve patient safety.

9.7. Conclusion

This PhD project is of added value to the pharmaco-epidemiological area of knowledge concerning the use of antipsychotic medication in individuals with ASD. This thesis has investigated the effect of antipsychotic medication treatment and the associated risk of incident seizure and cardiac adverse events using a large primary care database representative of the UK population. Patients with ASD are at a potential increased risk of developing these adverse events. With limited clinical guidance on the use of antipsychotic medication for the

management of behavioural disorders that usually accompany ASD and inadequate safety evidence, healthcare professionals should pay careful attention when prescribing these agents for patients with ASD, many of whom are children and adolescents.

***Table 9.1*: Overall summary of the main findings**

Study (Chapter)	What was unknown	What this study adds	Unanswered questions
Psychotropic medication prescribing for neuropsychiatric comorbidities in individuals diagnosed with autism spectrum disorder (ASD) in the UK: drug utilisation study (DUS) (Chapter 5)	The recent status of ASD incidence/prevalence in the UK and if the pattern of psychotropic medication prescribing had been affected by the approval of risperidone in 2007 in the UK. How long patients with ASD continued on antipsychotic medication treatment.	The ASD incidence and prevalence increased 2.9-fold and 3.3-fold, respectively from 2009 to 2016. 12.4% of the treated cohort were prescribed antipsychotic drugs, of which 50.7% was risperidone and 49.3% was other antipsychotic medications. 32.1% of those prescribed antipsychotic drugs were on continuous antipsychotic therapy for more than one year, and 6.1% continued for up to five years.	Do prescriptions received outside primary care and that are not recorded in a general practice database influence the proportions of medication users?
The risk of incident seizure among antipsychotic medication users in individuals diagnosed with ASD: cohort study (Chapter 6)	If antipsychotic medication treatment is associated with increased risk of incident seizure in a population diagnosed with ASD.	There is no evidence of increased risk of incident seizure associated with antipsychotic medication use compared with other psychotropic medication in a population with ASD.	Do prescriptions received outside primary care that are not recorded in a general practice database influence the risk estimates? Is antipsychotic medication treatment associated with increased risk of incident seizure in a population diagnosed with ASD and who have a history of seizure or epilepsy? Are the findings from this cohort study influenced by variations between patients using and not using antipsychotic medication?

Study (Chapter)	What was unknown	What this study adds	Unanswered questions
The risk of incident seizure among antipsychotic medication users in individuals diagnosed with ASD: a self-controlled case series study (SCCS) (Chapter 7)	If the risk of incident seizure in patients with ASD using antipsychotic medication is influenced by variations between patients using and not using antipsychotic medication.	The results from this SCCS study confirmed the findings of the previous cohort study of no evidence of increased risk of incident seizure associated with antipsychotic medication in a population with ASD, and eliminated the effect of between groups variations.	Do prescriptions received outside primary care that are not recorded in a general practice database influence the risk estimates?
The risk of cardiac events among antipsychotic medication users in individuals diagnosed with ASD: cohort study (Chapter 8)	If antipsychotic medication treatment is associated with increased risk of cardiac adverse events in a population diagnosed with ASD.	There is no evidence of increased risk of cardiac events associated with antipsychotic medication use compared with other psychotropic medication in a population with ASD.	Do prescriptions received outside primary care that are not recorded in a general practice database influence the risk estimates? Will using a larger sample size influence the reported risk estimates?

References

1. Kanner L. Autistic disturbances of affective contact. *Nervous child* 1943; **2**(3)**:** 217-250.

2. Asperger H. Die „Autistischen Psychopathen" im Kindesalter. *Archiv für Psychiatrie und Nervenkrankheiten* 1944; **117**(1)**:** 76-136.

3. McPartland J, Volkmar FR. Autism and related disorders. *Handbook of clinical neurology*, vol. 106. Elsevier2012, pp 407-418.

4. APA. *Diagnostic and statistical manual of mental disorders-IV-text revision* American Psychiatric Pub.2000.

5. WHO. *International statistical classification of diseases and related health problems*, vol. 1. World Health Organization2004.

6. APA. Diagnostic and Statistical Manual of Mental Disorders. 5th Edition edn. American Psychiatric Association: Arlington, 2013.

7. NICE. Autism spectrum disorder in under 19s: recognition, referral and diagnosis. National Institute for Health and Clinical Excellence2011.

8. NICE. Autism spectrum disorder in adults: diagnosis and management. National Institute for Health and Clinical Excellence2012.

9. Brugha TS, McManus S, Bankart J, Scott F, Purdon S, Smith J *et al.* Epidemiology of autism spectrum disorders in adults in the community in England. *Archives of general psychiatry* 2011; **68**(5)**:** 459-465.

10. Lord C, Risi S, DiLavore PS, Shulman C, Thurm A, Pickles A. Autism from 2 to 9 years of age. *Arch Gen Psychiatry* 2006; **63**(6)**:** 694-701.

11. Kleinman JM, Ventola PE, Pandey J, Verbalis AD, Barton M, Hodgson S *et al.* Diagnostic stability in very young children with autism spectrum disorders. *Journal of autism and developmental disorders* 2008; **38**(4)**:** 606-615.

12. Christensen DL, Baio J, Van Naarden Braun K, Bilder D, Charles J, Constantino JN *et al.* Prevalence and Characteristics of Autism Spectrum Disorder Among Children Aged 8 Years--Autism and Developmental Disabilities Monitoring Network, 11 Sites, United States, 2012. *Morbidity and mortality weekly report Surveillance summaries (Washington, DC : 2002)* 2016; **65**(3)**:** 1-23.

13. de Vaan G, Vervloed MP, Hoevenaars-van den Boom M, Antonissen A, Knoors H, Verhoeven L. A critical review of screening and diagnostic instruments for autism spectrum disorders in people with sensory impairments in addition to intellectual

disabilities. *Journal of Mental Health Research in Intellectual Disabilities* 2016; **9**(1-2)**:** 36-59.

14. The UK NSC recommendation on Autism screening in

children,. https://legacyscreening.phe.org.uk/autism, 2011, Accessed Date Accessed 2011 Accessed.

15. National Collaborating Centre for Ws, Children's H. National Institute for Health and Clinical Excellence: Guidance. *Autism: Recognition, Referral and Diagnosis of Children and Young People on the Autism Spectrum*. RCOG Press

Copyright © 2011, National Collaborating Centre for Women's and Children's Health.: London, 2011.

16. Baird G, Douglas HR, Murphy MS. Recognising and diagnosing autism in children and young people: summary of NICE guidance. *BMJ* 2011; **343:** d6360.

17. Ozonoff S, Young GS, Carter A, Messinger D, Yirmiya N, Zwaigenbaum L *et al.* Recurrence risk for autism spectrum disorders: a Baby Siblings Research Consortium study. *Pediatrics* 2011; **128**(3)**:** e488-e495.

18. Durkin MS, Maenner MJ, Newschaffer CJ, Lee LC, Cunniff CM, Daniels JL *et al.* Advanced parental age and the risk of autism spectrum disorder. *American journal of epidemiology* 2008; **168**(11)**:** 1268-1276.

19. Hall SS, Lightbody AA, Reiss AL. Compulsive, self-injurious, and autistic behavior in children and adolescents with fragile X syndrome. *American journal of mental retardation : AJMR* 2008; **113**(1)**:** 44-53.

20. DiGuiseppi C, Hepburn S, Davis JM, Fidler DJ, Hartway S, Lee NR *et al.* Screening for autism spectrum disorders in children with Down syndrome: population prevalence and screening test characteristics. *Journal of developmental and behavioral pediatrics : JDBP* 2010; **31**(3)**:** 181-191.

21. Baxter AJ, Brugha TS, Erskine HE, Scheurer RW, Vos T, Scott JG. The epidemiology and global burden of autism spectrum disorders. *Psychological medicine* 2015; **45**(3)**:** 601-613.

22. Murray ML, Hsia Y, Glaser K, Simonoff E, Murphy DG, Asherson PJ *et al.* Pharmacological treatments prescribed to people with autism spectrum disorder (ASD) in primary health care. *Psychopharmacology (Berl)* 2014; **231**(6)**:** 1011-1021.

23. Matson JL, Kozlowski AM. The increasing prevalence of autism spectrum disorders. *Research in Autism Spectrum Disorders* 2011; **5**(1)**:** 418-425.

24. Loomes R, Hull L, Mandy WPL. What is the male-to-female ratio in autism spectrum disorder? A systematic review and meta-analysis. *Journal of the American Academy of Child & Adolescent Psychiatry* 2017; **56**(6)**:** 466-474.

25. Mandy W, Chilvers R, Chowdhury U, Salter G, Seigal A, Skuse D. Sex differences in autism spectrum disorder: evidence from a large sample of children and adolescents. *Journal of autism and developmental disorders* 2012; **42**(7)**:** 1304-1313.

26. Rivet TT, Matson JL. Review of gender differences in core symptomatology in autism spectrum disorders. *Research in Autism Spectrum Disorders* 2011; **5**(3)**:** 957-976.

27. Autism Developmental Disabilities Monitoring Network Surveillance Year Principal Investigators. Prevalence of autism spectrum disorder among children aged 8 years—autism and developmental disabilities monitoring network, 11 sites, United States, 2010. *Morbidity and Mortality Weekly Report: Surveillance Summaries* 2014; **63**(2)**:** 1-21.

28. Charman T, Pickles A, Simonoff E, Chandler S, Loucas T, Baird G. IQ in children with autism spectrum disorders: data from the Special Needs and Autism Project (SNAP). *Psychological medicine* 2011; **41**(3)**:** 619-627.

29. Simonoff E, Pickles A, Charman T, Chandler S, Loucas T, Baird G. Psychiatric disorders in children with autism spectrum disorders: prevalence, comorbidity, and associated factors in a population-derived sample. *Journal of the American Academy of Child & Adolescent Psychiatry* 2008; **47**(8)**:** 921-929.

30. Weitlauf AS, McPheeters ML, Peters B, Sathe N, Travis R, Aiello R *et al.* Therapies for children with autism spectrum disorder. 2014.

31. National Institute for Health and Care Excellence. Autism spectrum disorder in under 19s: support and management. 2013.

32. Mesibov GB, Shea V, Schopler E. *The TEACCH approach to autism spectrum disorders*. Springer Science & Business Media2005.

33. Prizant BM, Wetherby AM, Rubin E, Laurent AC. The SCERTS Model: A transactional, family-centered approach to enhancing communication and socioemotional abilities of children with autism spectrum disorder. *Infants & Young Children* 2003; **16**(4)**:** 296-316.

34. Ingersoll B. Brief report: Effect of a focused imitation intervention on social functioning in children with autism. *Journal of autism and developmental disorders* 2012; **42**(8)**:** 1768-1773.

35. Rogers SJ, Estes A, Lord C, Vismara L, Winter J, Fitzpatrick A *et al.* Effects of a brief Early Start Denver Model (ESDM)–based parent intervention on toddlers at risk for autism spectrum disorders: A randomized controlled trial. *Journal of the American Academy of Child & Adolescent Psychiatry* 2012; **51**(10)**:** 1052-1065.

36. Crowe B, Salt A. Autism: the management and support of children and young people on the autism spectrum (NICE Clinical Guideline 170). *Archives of disease in childhood Education and practice edition* 2015; **100**(1)**:** 20-23.

37. Meltzer HY. What's atypical about atypical antipsychotic drugs? *Current opinion in pharmacology* 2004; **4**(1)**:** 53-57.

38. Amato D, Vernon AC, Papaleo F. Dopamine, the antipsychotic molecule: a perspective on mechanisms underlying antipsychotic response variability. *Neuroscience & Biobehavioral Reviews* 2018; **85:** 146-159.

39. Sykes DA, Moore H, Stott L, Holliday N, Javitch JA, Lane JR *et al.* Extrapyramidal side effects of antipsychotics are linked to their association kinetics at dopamine D 2 receptors. *Nature communications* 2017; **8**(1)**:** 1-11.

40. British Medical Association RPSoGB. *British national formulary: March 2017 (No. 74)*. Pharmaceutical Pr2009.

41. Jibson MD, Tandon R. New atypical antipsychotic medications. *Journal of Psychiatric Research* 1998; **32**(3)**:** 215-228.

42. Jibson M, Tandon R. The negative symptoms of schizophrenia. *Directions in Psychiatry* 1995; **15:** 1-7.

43. Bilder RM. Neurocognitive impairment in schizophrenia and how it affects treatment options. *The Canadian Journal of Psychiatry* 1997; **42**(3)**:** 255-264.

44. Kane JM. The current status of neuroleptic therapy. *The Journal of clinical psychiatry* 1989.

45. Miyamoto S, Duncan G, Mailman R, Lieberman J. Developing novel antipsychotic drugs: strategies and goals. *Current Opinion in Central and Peripheral Nervous System Investigational Drugs* 2000; **2**(1)**:** 25-39.

46. Miyamoto S, Duncan G, Marx C, Lieberman J. Treatments for schizophrenia: a critical review of pharmacology and mechanisms of action of antipsychotic drugs. *Molecular psychiatry* 2005; **10**(1)**:** 79.

47. Miyamoto S, Wolfgang W. Fleischhacker, and Jeffrey A. Lieberman. *Comprehensive Care of Schizophrenia: A Textbook of Clinical Management* 2012.

48. Alvir JMJ, Lieberman JA, Safferman AZ, Schwimmer JL, Schaaf JA. Clozapine-induced agranulocytosis--incidence and risk factors in the United States. *New England Journal of Medicine* 1993; **329**(3)**:** 162-167.

49. McGuinness S, Johansson R, Lundstrom J, Ross D. Induction of apoptosis by remoxipride metabolites in HL60 and CD34+/CD19− human bone marrow progenitor cells: potential relevance to remoxipride-induced aplastic anemia. *Chemico-biological interactions* 1999; **121**(3)**:** 253-265.

50. Posey DJ, Stigler KA, Erickson CA, McDougle CJ. Antipsychotics in the treatment of autism. *The Journal of clinical investigation* 2008; **118**(1)**:** 6-14.

51. Campbell M, Anderson LT, Meier M, Cohen IL, Small AM, Samit C *et al.* A comparison of haloperidol and behavior therapy and their interaction in autistic children. *Journal of the American Academy of Child & Adolescent Psychiatry* 1978; **17**(4)**:** 640-655.

52. Cohen IL, Campbell M, Posner D, Small AM, Triebel D, Anderson LT. Behavioral effects of haloperidol in young autistic children: An objective analysis using a within-subjects reversal design. *Journal of the American Academy of Child & Adolescent Psychiatry* 1980; **19**(4)**:** 665-677.

53. Anderson LT, Campbell M, Grega D, Perry R, Small A, Green W. Haloperidol in the treatment of infantile autism: effects on learning and behavioral symptoms. *The American journal of psychiatry* 1984.

54. Anderson LT, Campbell M, Adams P, Small AM, Perry R, Shell J. The effects of haloperidol on discrimination learning and behavioral symptoms in autistic children. *Journal of autism and developmental disorders* 1989; **19**(2)**:** 227-239.

55. Perry R, Campbell M, Adams P, Lynch N, Spencer EK, Curren EL *et al.* Long-term efficacy of haloperidol in autistic children: continuous versus discontinuous drug administration. *Journal of the American Academy of Child & Adolescent Psychiatry* 1989; **28**(1)**:** 87-92.

56. Campbell M, Armenteros JL, Malone RP, Adams PB, Eisenberg ZW, Overall JE. Neuroleptic-related dyskinesias in autistic children: a prospective, longitudinal study. *Journal of the American Academy of Child & Adolescent Psychiatry* 1997; **36**(6)**:** 835-843.

57. Zuddas A, Ledda MG, Fratta A, Muglia P, Cianchetti C. Clinical effects of clozapine on autistic disorder. 1996.

58. Chen NC, Bedair HS, McKay B, Bowers Jr MB, Mazure C. Clozapine in the treatment of aggression in an adolescent with autistic disorder. *The Journal of clinical psychiatry* 2001; **62**(6)**:** 479.

59. Gobbi G, Pulvirenti L. Long-term treatment with clozapine in an adult with autistic disorder accompanied by aggressive behaviour. *Journal of Psychiatry and Neuroscience* 2001; **26**(4)**:** 340.

60. Williams AM, Park SH. Seizure associated with clozapine: incidence, etiology, and management. *CNS drugs* 2015; **29**(2)**:** 101-111.

61. Shea S, Turgay A, Carroll A, Schulz M, Orlik H, Smith I *et al.* Risperidone in the treatment of disruptive behavioral symptoms in children with autistic and other pervasive developmental disorders. *Pediatrics* 2004; **114**(5)**:** e634-641.

62. Owen R, Sikich L, Marcus RN, Corey-Lisle P, Manos G, McQuade RD *et al.* Aripiprazole in the treatment of irritability in children and adolescents with autistic disorder. *Pediatrics* 2009; **124**(6)**:** 1533-1540.

63. European Medicines Agency. Assessment of the paediatric needs psychiatry. 2007.

64. World Health Organisation. Application for inclusion to the 19th expert committee on the selection and use of essential medicines: risperidone. 2013.

65. McDougle CJ, Holmes JP, Carlson DC, Pelton GH, Cohen DJ, Price LH. A double-blind, placebo-controlled study of risperidone in adults with autistic disorder and other pervasive developmental disorders. *Archives of general psychiatry* 1998; **55**(7)**:** 633-641.

66. McCracken J, McGough J, Shah B, Cronin P, Hong D, Aman M *et al.* Risperidone in children with autism and serious behavioral problems. *New England journal of medicine*, vol. 3472002, pp 314-321.

67. McDougle C, Scahill L, McCracken J, Aman M, Tierney E, Arnold L *et al.* Research Units on Pediatric Psychopharmacology (RUPP) Autism Network. Background and rationale for an initial controlled study of risperidone. *Child and adolescent psychiatric clinics of North America* 2000; **9**(1)**:** 201-224.

68. Gagliano A, Germano E, Pustorino G, Impallomeni C, D'Arrigo C, Calamoneri F *et al.* Risperidone Treatment of Children with Autistic Disorder: Effectiveness, Tolerability, and Pharmacokinetic Implications. *Journal of Child and Adolescent Psychopharmacology* 2004; **14**(1)**:** 39-47.

69. McCracken. Risperidone treatment of autistic disorder: Longer-term benefits and blinded discontinuation after 6 months. *American Journal of Psychiatry* 2005; **162**(7)**:** 1361-1369.

70. Troost PW, Lahuis BE, Steenhuis M-P, Ketelaars CE, Buitelaar JK, Engeland HV *et al.* Long-term effects of risperidone in children with autism spectrum disorders: A placebo discontinuation study. *Journal of the American Academy of Child & Adolescent Psychiatry* 2005; **44**(11)**:** 1137-1144.

71. Luby J, Mrakotsky C, Stalets M, Belden A, Heffelfinger A, Williams M *et al.* Risperidone in preschool children with autistic spectrum disorders: an investigation of safety and efficacy. *Journal of child and adolescent psychopharmacology*, vol. 162006, pp 575-587.

72. Nagaraj R, Singhi P, Malhi P. Risperidone in children with autism: Randomized, placebo-controlled, double-blind study. *Journal of Child Neurology* 2006; **21**(6)**:** 450-455.

73. Anderson GM, Scahill L, McCracken JT, McDougle CJ, Aman MG, Tierney E *et al.* Effects of Short- and Long-Term Risperidone Treatment on Prolactin Levels in Children with Autism. *Biological Psychiatry* 2007; **61**(4)**:** 545-550.

74. Pandina G, Bossie C, Youssef E, Zhu Y, Dunbar F. Risperidone improves behavioral symptoms in children with autism in a randomized, double-blind, placebo-controlled trial. *Journal of autism and developmental disorders*, vol. 372007, pp 367-373.

75. Troost PW, Lahuis BE, Hermans MH, Buitelaar JK, Van Engeland H, Scahill L *et al.* Prolactin release in children treated with risperidone: Impact and role of CYP2D6 metabolism. *Journal of Clinical Psychopharmacology* 2007; **27**(1)**:** 52-57.

76. Hellings JA, Cardona AM, Schroeder SR. Long-term safety and adverse events of risperidone in children, adolescents, and adults with pervasive developmental disorders. *Journal of Mental Health Research in Intellectual Disabilities* 2010; **3**(3)**:** 132-144.

77. Kent J, Hough D, Singh J, Karcher K, Pandina G. An open-label extension study of the safety and efficacy of risperidone in children and adolescents with autistic disorder. *Journal of child and adolescent psychopharmacology*, vol. 232013, pp 676-686.

78. Kent J, Kushner S, Ning X, Karcher K, Ness S, Aman M *et al.* Risperidone dosing in children and adolescents with autistic disorder: a double-blind, placebo-controlled study. *Journal of autism and developmental disorders*, vol. 432013, pp 1773-1783.

79. Scahill L, Jeon S, Boorin S, McDougle C, Aman M, Dziura J *et al.* Weight Gain and Metabolic Consequences of Risperidone in Young Children with Autism Spectrum Disorder. *Journal of the american academy of child and adolescent psychiatry*, vol. 552016, pp 415-423.

80. Findling RL, Mankoski R, Timko K, Lears K, McCartney T, McQuade RD *et al.* A randomized controlled trial investigating the safety and efficacy of aripiprazole in the long-term maintenance treatment of pediatric patients with irritability associated with autistic disorder. *Journal of Clinical Psychiatry* 2014; **75**(1)**:** 22-30.

81. Ghanizadeh A, Sahraeizadeh A, Berk M. A head-to-head comparison of aripiprazole and risperidone for safety and treating autistic disorders, a randomized double blind clinical trial. *Child Psychiatry & Human Development* 2014; **45**(2)**:** 185-192.

82. Ichikawa H, Mikami K, Okada T, Yamashita Y, Ishizaki Y, Tomoda A *et al.* Aripiprazole in the treatment of irritability in children and adolescents with autism spectrum disorder in Japan: A randomized, double-blind, placebo-controlled study. *Child Psychiatry and Human Development* 2017; **48**(5)**:** 796-806.

83. Park SY, Cervesi C, Galling B, Molteni S, Walyzada F, Ameis SH *et al.* Antipsychotic use trends in youth with autism spectrum disorder and/or intellectual disability: a meta-

analysis. *Journal of the American Academy of Child & Adolescent Psychiatry* 2016; **55**(6)**:** 456-468. e454.

84. Brophy S, Kennedy J, Fernandez-Gutierrez F, John A, Potter R, Linehan C *et al.* Characteristics of children prescribed antipsychotics: analysis of routinely collected data. *Journal of child and adolescent psychopharmacology* 2018; **28**(3)**:** 180-191.

85. Wink LK, Pedapati EV, Horn PS, McDougle CJ, Erickson CA. Multiple Antipsychotic Medication Use in Autism Spectrum Disorder. *Journal of Child and Adolescent Psychopharmacology* 2017; **27**(1)**:** 91-94.

86. Alfageh BH, Wang Z, Mongkhon P, Besag FM, Alhawassi TM, Brauer R *et al.* Safety and Tolerability of Antipsychotic Medication in Individuals with Autism Spectrum Disorder: A Systematic Review and Meta-Analysis. *Pediatric Drugs* 2019**:** 1-15.

87. Buescher AV, Cidav Z, Knapp M, Mandell DS. Costs of autism spectrum disorders in the United Kingdom and the United States. *JAMA pediatrics* 2014; **168**(8)**:** 721-728.

88. Posey DJ, McDougle CJ. Pharmacotherapeutic management of autism. *Expert opinion on pharmacotherapy* 2001; **2**(4)**:** 587-600.

89. National Collaborating Centre for Mental Health. AUTISM RECOGNITION, REFERRAL, DIAGNOSIS AND MANAGEMENT OF ADULTS ON THE AUTISM SPECTRUM. The British Psychological Society and The Royal College of Psychiatrists: Leicester, 2012.

90. Hsia Y, Wong AY, Murphy DG, Simonoff E, Buitelaar JK, Wong IC. Psychopharmacological prescriptions for people with autism spectrum disorder (ASD): a multinational study. *Psychopharmacology* 2014; **231**(6)**:** 999-1009.

91. Wong A, Hsia Y, Chan EW, Murphy DG, Simonoff E, Buitelaar JK *et al.* The variation of psychopharmacological prescription rates for people with autism spectrum disorder (ASD) in 30 countries. *Autism Research* 2014; **7**(5)**:** 543-554.

92. Loebel A, Brams M, Goldman R, Silva R, Hernandez D, Deng L *et al.* Lurasidone for the Treatment of Irritability Associated with Autistic Disorder. *Journal of autism and developmental disorders*, vol. 462016, pp 1153-1163.

93. Stigler K, Mullett J, Erickson C, Posey D, McDougle C. Paliperidone for irritability in adolescents and young adults with autistic disorder. *Psychopharmacology*, vol. 2232012, pp 237-245.

94. Hollander E, Wasserman S, Swanson E, Chaplin W, Schapiro M, Zagursky K *et al.* A double-blind placebo-controlled pilot study of olanzapine in childhood/adolescent pervasive developmental disorder. *Journal of child and adolescent psychopharmacology*, vol. 162006, pp 541-548.

95. Almandil NB, Liu Y, Murray ML, Besag FM, Aitchison KJ, Wong IC. Weight gain and other metabolic adverse effects associated with atypical antipsychotic treatment of children and adolescents: a systematic review and meta-analysis. *Paediatric drugs* 2013; **15**(2)**:** 139-150.

96. Almandil NB, Wong IC. Review on the current use of antipsychotic drugs in children and adolescents. *Archives of disease in childhood Education and practice edition* 2011; **96**(5)**:** 192-196.

97. Fleischhaker C, Heiser P, Hennighausen K, Herpertz-Dahlmann B, Holtkamp K, Mehler-Wex C *et al.* Clinical drug monitoring in child and adolescent psychiatry: side effects of atypical neuroleptics. *J Child Adolesc Psychopharmacol* 2006; **16**(3)**:** 308-316.

98. Rani FA, Byrne P, Cranswick N, Murray ML, Wong IC. Mortality in children and adolescents prescribed antipsychotic medication: a retrospective cohort study using the UK general practice research database. *Drug safety* 2011; **34**(9)**:** 773-781.

99. Sheehan R, Horsfall L, Strydom A, Osborn D, Walters K, Hassiotis A. Movement side effects of antipsychotic drugs in adults with and without intellectual disability: UK population-based cohort study. *BMJ open* 2017; **7**(8)**:** e017406.

100. Star K, Iessa N, Almandil NB, Wilton L, Curran S, Edwards IR *et al.* Rhabdomyolysis reported for children and adolescents treated with antipsychotic medicines: a case series analysis. *J Child Adolesc Psychopharmacol* 2012; **22**(6)**:** 440-451.

101. Higgins JP, Green S,. Cochrane handbook for systematic reviews of interventions version 5.1. 0. *The cochrane collaboration* 2011; **5**(0).

102. Tacconelli E. Systematic reviews: CRD's guidance for undertaking reviews in health care. *The Lancet Infectious Diseases* 2010; **10**(4)**:** 226.

103. Lam MT, De Longhi C, Turnbull J, Lam HR, Besa R. Has Embase replaced MEDLINE since coverage expansion? *Journal of the Medical Library Association: JMLA* 2018; **106**(2)**:** 227.

104. Dunikowski LG. EMBASE and MEDLINE searches. *Canadian Family Physician* 2005; **51**(9)**:** 1191.

105. Moher D, Liberati A, Tetzlaff J, Altman DG, Group P. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLoS medicine* 2009; **6**(7)**:** e1000097.

106. Orwin R, Cooper H, Hedges L. Evaluating coding decisions. In: The handbook of research synthesis. ∴ Russell Sage Foundation1994, pp 140-160.

107. Higgins JP, Altman DG, Gøtzsche PC, Jüni P, Moher D, Oxman AD *et al.* The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *Bmj* 2011; **343:** d5928.

108. Cochrane Database of Systematic Reviews. http://www.cochranelibrary.com/cochrane-database-of-systematic-reviews/index.html, 2017, Accessed Date Accessed 2017 Accessed.

109. Adapted version of a modified Newcastle-Ottawa Scale for a single use in a specific context. https://static-content.springer.com/esm/art%3A10.1186%2Fs13643-015-0038-y/MediaObjects/13643_2015_38_MOESM2_ESM.pdf, 2015, Accessed Date Accessed 2015 Accessed.

110. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ: British Medical Journal* 2003; **327**(7414)**:** 557.

111. Wink LK, Early M, Schaefer T, Pottenger A, Horn P, McDougle CJ *et al.* Body mass index change in autism spectrum disorders: Comparison of treatment with risperidone and aripiprazole. *Journal of Child and Adolescent Psychopharmacology* 2014; **24**(2)**:** 78-82.

112. Findling RL, Maxwell K, Wiznitzer M. An open clinical trial of risperidone monotherapy in young children with autistic disorder. *Psychopharmacology Bulletin* 1997; **33**(1)**:** 155-159.

113. McDougle CJ, Holmes JP, Bronson MR, Anderson GM, Volkmar FR, Price LH *et al.* Risperidone treatment of children and adolescents with pervasive developmental disorders: A prospective, open-label study. *Journal of the American Academy of Child & Adolescent Psychiatry* 1997; **36**(5)**:** 685-693.

114. McDougle CJ, Holmes JP, Carlson C, Pelton GH, Cohen DJ, Price LH. A double-blind, placebo-controlled study of risperidone in adults with autistic disorder and other pervasive developmental disorders. *Archives of General Psychiatry* 1998; **55**(7)**:** 633-641.

115. Nicolson R, Awad G, Sloman L. An open trial of risperidone in young autistic children. *Journal of the American Academy of Child & Adolescent Psychiatry* 1998; **37**(4)**:** 372-376.

116. Masi G, Cosenza A, Mucci M. Prolactin levels in young children with pervasive developmental disorders during risperidone treatment. *Journal of Child and Adolescent Psychopharmacology* 2001; **11**(4)**:** 389-394.

117. Masi G, Cosenza A, Mucci M, Brovedani P. Open trial of risperidone in 24 young children with pervasive developmental disorders. *Journal of the American Academy of Child & Adolescent Psychiatry* 2001; **40**(10)**:** 1206-1214.

118. Masi G, Cosenza A, Mucci M, De Vito G. Risperidone monotherapy in preschool children with pervasive developmental disorders. *Journal of Child Neurology* 2001; **16**(6)**:** 395-400.

119. Remington G, Sloman L, Konstantareas M, Parker K, Gow R. Clomipramine versus haloperidol in the treatment of autistic disorder: a double-blind, placebo-controlled, crossover study. *Journal of clinical psychopharmacology*, vol. 212001, pp 440-444.

120. Kemner C, Willemsen-Swinkels SH, de Jonge M, Tuynman-Qua H, van Engeland H. Open-label study of olanzapine in children with pervasive developmental disorder. *Journal of Clinical Psychopharmacology* 2002; **22**(5)**:** 455-460.

121. Malone RP, Maislin G, Choudhury MS, Gifford C, Delaney MA. Risperidone treatment in children and adolescents with autism: Short- and long-term safety and effectiveness. *Journal of the American Academy of Child & Adolescent Psychiatry* 2002; **41**(2)**:** 140-147.

122. Shea S, Turgay A, Carroll A, Schulz M, Orlik H, Smith I *et al.* Risperidone in the treatment of disruptive behavioral symptoms in children with autistic and other pervasive developmental disorders. *Pediatrics*, vol. 1142004, pp e634-641.

123. Malone RP, Delaney MA, Hyman SB, Cater JR. Ziprasidone in adolescents with autism: an open-label pilot study. *Journal of Child & Adolescent Psychopharmacology* 2007; **17**(6)**:** 779-790.

124. Capone GT, Goyal P, Grados M, Smith B, Kammann H. Risperidone use in children with Down syndrome, severe intellectual disability, and comorbid autistic spectrum disorders: A naturalistic study. *Journal of Developmental and Behavioral Pediatrics* 2008; **29**(2)**:** 106-116.

125. Gencer O, Emiroglu F, Miral S, Baykara B, Baykara A, Dirik E. Comparison of long-term efficacy and safety of risperidone and haloperidol in children and adolescents with autistic disorder: An open label maintenance study. *European Child & Adolescent Psychiatry* 2008; **17**(4)**:** 217-225.

126. Marcus R, Owen R, Kamen L, Manos G, McQuade R, Carson W *et al.* A placebo-controlled, fixed-dose study of aripiprazole in children and adolescents with irritability associated with autistic disorder. *Journal of the american academy of child and adolescent psychiatry*, vol. 482009, pp 1110-1119.

127. Owen R, Sikich L, Marcus R, Corey-Lisle P, Manos G, McQuade R *et al.* Aripiprazole in the treatment of irritability in children and adolescents with autistic disorder. *Pediatrics*, vol. 1242009, pp 1533-1540.

128. Stigler KA, Diener JT, Kohn AE, Li L, Erickson CA, Posey DJ *et al.* Aripiprazole in pervasive developmental disorder not otherwise specified and asperger's disorder: A 14-week, prospective, open-label study. *Journal of Child and Adolescent Psychopharmacology* 2009; **19**(3)**:** 265-274.

129. Marcus RN, Owen R, Manos G, Mankoski R, Kamen L, McQuade RD *et al.* Safety and tolerability of aripiprazole for irritability in pediatric patients with autistic disorder: A 52-

week, open-label, multicenter study. *Journal of Clinical Psychiatry* 2011; **72**(9)**:** 1270-1276.

130. Vo L, Snyder C, McCracken C, McDougle C, McCracken J, Aman M *et al.* No Apparent Cardiac Conduction Effects of Acute Treatment with Risperidone in Children with Autism Spectrum Disorder. *Journal of child and adolescent psychopharmacology*, vol. 262016, pp 900-908.

131. Nikvarz N, Alaghband-Rad J, Tehrani-Doost M, Alimadadi A, Ghaeli P. Comparing Efficacy and Side Effects of Memantine vs. Risperidone in the Treatment of Autistic Disorder. *Pharmacopsychiatry* 2017; **50**(1)**:** 19-25.

132. Ichikawa H, Hiratani M, Yasuhara A, Tsujii N, Oshimo T, Ono H *et al.* An open-label extension long-term study of the safety and efficacy of aripiprazole for irritability in children and adolescents with autistic disorder in Japan. *Psychiatry and clinical neurosciences* 2018; **72**(2)**:** 84-94.

133. Masi G, Cosenza A, Mucci M, Brovedani P. A 3-year naturalistic study of 53 preschool children with pervasive developmental disorders treated with risperidone. *Journal of Clinical Psychiatry* 2003; **64**(9)**:** 1039-1047.

134. Corson AH, Barkenbus JE, Posey DJ, Stigler KA, McDougle CJ. A retrospective analysis of quetiapine in the treatment of pervasive developmental disorders. *The Journal of clinical psychiatry* 2004; **65**(11)**:** 1531-1536.

135. Masi G, Cosenza A, Millepiedi S, Muratori F, Pari C, Salvadori F. Aripiprazole monotherapy in children and young adolescents with pervasive developmental disorders: A retrospective study. *CNS Drugs* 2009; **23**(6)**:** 511-521.

136. Beherec L, Lambrey S, Quilici G, Rosier A, Falissard B, Guillin O. Retrospective review of clozapine in the treatment of patients with autism spectrum disorder and severe disruptive behaviors. *Journal of Clinical Psychopharmacology* 2011; **31**(3)**:** 341-344.

137. Boon-Yasidhi V, Jearnarongrit P, Tulayapichitchock P, Tarugsa J. Adverse effects of risperidone in children with autism spectrum disorders in a naturalistic clinical setting at siriraj hospital, Thailand. *Psychiatry Journal Print* 2014; **2014:** 136158.

138. Aman M, Rettiganti M, Nagaraja HN, Hollway JA, McCracken J, McDougle CJ *et al.* Tolerability, safety, and benefits of risperidone in children and adolescents with autism: 21-month follow-up after 8-week placebo-controlled trial. *Journal of Child and Adolescent Psychopharmacology* 2015; **25**(6)**:** 482-493.

139. Hellings JA, Jadhav M, Jain S, Jadhav S, Genovese A. Low Dose Loxapine: Neuromotor Side Effects and Tolerability in Autism Spectrum Disorders. *Journal of Child and Adolescent Psychopharmacology* 2015; **25**(8)**:** 618-624.

140. Hongkaew Y, Ngamsamut N, Puangpetch A, Vanwong N, Srisawasdi P, Chamnanphon M *et al.* Hyperprolactinemia in Thai children and adolescents with autism spectrum disorder treated with risperidone. *Neuropsychiatric Disease and Treatment* 2015; **11:** 191-196.

141. Ngamsamut N, Hongkaew Y, Vanwong N, Srisawasdi P, Puangpetch A, Chamkrachangpada B *et al.* 9-Hydroxyrisperidone-Induced Hyperprolactinaemia in Thai Children and Adolescents with Autism Spectrum Disorder. *Basic and Clinical Pharmacology and Toxicology* 2016; **119**(3)**:** 267-272.

142. Nuntamool N, Ngamsamut N, Vanwong N, Puangpetch A, Chamnanphon M, Hongkaew Y *et al.* Pharmacogenomics and Efficacy of Risperidone Long-Term Treatment in Thai Autistic Children and Adolescents. *Basic & Clinical Pharmacology & Toxicology* 2017; **121**(4)**:** 316-324.

143. Srisawasdi P, Vanwong N, Hongkaew Y, Puangpetch A, Vanavanan S, Intachak B *et al.* Impact of risperidone on leptin and insulin in children and adolescents with autistic spectrum disorders. *Clinical Biochemistry* 2017; **50**(12)**:** 678-685.

144. Vanwong N, Srisawasdi P, Ngamsamut N, Nuntamool N, Puangpetch A, Chamkrachangpada B *et al.* Hyperuricemia in children and adolescents with autism spectrum disorder treated with risperidone: The risk factors for metabolic adverse effects. *Frontiers in Pharmacology* 2017; **7 (JAN) (no pagination)**(527).

145. Kim HW, Park EJ, Kim JH, Boon-Yasidhi V, Tarugsa J, Reyes A *et al.* Aripiprazole for Irritability in Asian Children and Adolescents with Autistic Disorder: A 12-Week, Multinational, Multicenter, Prospective Open-Label Study. *Journal of Child and Adolescent Psychopharmacology* 2018; **28**(6)**:** 402-408.

146. DeVane CL, Charles JM, Abramson RK, Williams JE, Carpenter LA, Raven S *et al.* Pharmacotherapy of Autism Spectrum Disorder: Results from the Randomized BAART Clinical Trial. *Pharmacotherapy* 2019; **39**(6)**:** 626-635.

147. Sukasem C, Vanwong N, Srisawasdi P, Ngamsamut N, Nuntamool N, Hongkaew Y *et al.* Pharmacogenetics of Risperidone-Induced Insulin Resistance in Children and Adolescents with Autism Spectrum Disorder. *Basic and Clinical Pharmacology and Toxicology* 2018; **123**(1)**:** 42-50.

148. Kloosterboer SM, de Winter BCM, Reichart CG, Kouijzer MEJ, de Kroon MMJ, van Daalen E *et al.* Risperidone plasma concentrations are associated with side effects and effectiveness in children and adolescents with autism spectrum disorder. *British Journal of Clinical Pharmacology* 2020.

149. Tural Hesapcioglu S, Ceylan MF, Kasak M, Sen CP. Olanzapine, risperidone, and aripiprazole use in children and adolescents with Autism Spectrum Disorders. *Research in Autism Spectrum Disorders* 2020; **72 (no pagination)**(101520).

150. Brylewski J, Duggan L. Antipsychotic medication for challenging behaviour in people with learning disability. *The Cochrane Library* 2004.

151. Kirino E. Serum prolactin levels and sexual dysfunction in patients with schizophrenia treated with antipsychotics: comparison between aripiprazole and other atypical antipsychotics. *Annals of general psychiatry* 2017; **16:** 43.

152. Yasui-Furukori N, Furukori H, Sugawara N, Fujii A, Kaneko S. Dose-dependent effects of adjunctive treatment with aripiprazole on hyperprolactinemia induced by risperidone in female patients with schizophrenia. *Journal of clinical psychopharmacology* 2010; **30**(5)**:** 596-599.

153. Chen J-X, Su Y-A, Bian Q-T, Wei L-H, Zhang R-Z, Liu Y-H *et al.* Adjunctive aripiprazole in the treatment of risperidone-induced hyperprolactinemia: A randomized, double-blind, placebo-controlled, dose–response study. *Psychoneuroendocrinology* 2015; **58:** 130-140.

154. Moher D, Pham B, Lawson M, Klassen T. The inclusion of reports of randomised trials published in languages other than English in systematic reviews. *Health Technol Assess* 2003; **7**(41)**:** 1-90.

155. Galandi D, Schwarzer G, Antes G. The demise of the randomised controlled trial: bibliometric study of the German-language health care literature, 1948 to 2004. *BMC medical research methodology* 2006; **6**(1)**:** 30.

156. Chang J, Peysakhovich F, Wang W, Zhu J. The UK health care system. *The United Kingdom* 2011; **30:** 2019.

157. Grosios K, Gahan PB, Burbidge J. Overview of healthcare in the UK. *EPMA Journal* 2010; **1**(4)**:** 529-534.

158. Vezyridis P, Timmons S. Evolution of primary care databases in UK: a scientometric analysis of research output. *BMJ open* 2016; **6**(10).

159. Chaudhry Z, Mannan F, Gibson-White A, Syed U, Ahmed S, Kousoulis A *et al.* Outputs and growth of primary care databases in the United Kingdom: bibliometric analysis. *Journal of innovation in health informatics* 2017; **24**(3)**:** 942-.

160. Carbonari DM, Saine ME, Newcomb CW, Blak B, Roy JA, Haynes K *et al.* Use of demographic and pharmacy data to identify patients included within both the Clinical Practice Research Datalink (CPRD) and The Health Improvement Network (THIN). *Pharmacoepidemiology and drug safety* 2015; **24**(9)**:** 999-1003.

161. Petherick ES, Pickett KE, Cullum NA. Can different primary care databases produce comparable estimates of burden of disease: results of a study exploring venous leg ulceration. *Family practice* 2015; **32**(4)**:** 374-380.

162. CPRD-Home. https://www.cprd.com/, Accessed Date Accessed.

163. THIN. https://www.iqvia.com/blogs/2020/04/harnessing-the-value-of-real-world-data-in-understanding-vaccines, Accessed Date Accessed.

164. Lewis JD, Schinnar R, Bilker WB, Wang X, Strom BL. Validation studies of the health improvement network (THIN) database for pharmacoepidemiology research. *Pharmacoepidemiology and drug safety* 2007; **16**(4)**:** 393-401.

165. QResearch-Home. https://www.qresearch.org/, Accessed Date Accessed.

166. IQVIA – about us. https://www.iqvia.com/about-us, Accessed Date Accessed.

167. de Lusignan S, Liaw S-T, Dedman D, Khunti K, Sadek K, Jones S. An algorithm to improve diagnostic accuracy in diabetes in computerised problem orientated medical records (POMR) compared with an established algorithm developed in episode orientated records (EOMR). *J Innov Health Inform* 2015; **22**(2)**:** 255-264.

168. Taggar JS, Coleman T, Lewis S, Szatkowski L. The impact of the Quality and Outcomes Framework (QOF) on the recording of smoking targets in primary care medical records: cross-sectional analyses from The Health Improvement Network (THIN) database. *BMC public health* 2012; **12:** 329.

169. Gillam SJ, Siriwardena AN, Steel N. Pay-for-performance in the United Kingdom: impact of the quality and outcomes framework—a systematic review. *The Annals of Family Medicine* 2012; **10**(5)**:** 461-468.

170. Blak B, Thompson M, Dattani H, Bourke A. Generalisability of The Health Improvement Network (THIN) database: demographics, chronic disease prevalence and mortality rates. *Journal of Innovation in Health Informatics* 2011; **19**(4)**:** 251-255.

171. Robinson D, Schulz E, Brown P, Price C. Updating the Read Codes: user-interactive maintenance of a dynamic clinical vocabulary. *J Am Med Inform Assoc* 1997; **4**(6)**:** 465-472.

172. Alfageh BH, Man KK, Besag FM, Alhawassi TM, Wong IC, Brauer R. Psychotropic medication prescribing for neuropsychiatric comorbidities in individuals diagnosed with autism spectrum disorder (ASD) in the UK. *Journal of autism and developmental disorders* 2020; **50**(2)**:** 625-633.

173. Fombonne E, Heavey L, Smeeth L, Rodrigues LC, Cook C, Smith PG *et al.* Validation of the diagnosis of autism in general practitioner records. *BMC public health* 2004; **4:** 5.

174. Smeeth L, Cook C, Fombonne E, Heavey L, Rodrigues LC, Smith PG *et al.* MMR vaccination and pervasive developmental disorders: a case-control study. *Lancet (London, England)* 2004; **364**(9438)**:** 963-969.

175. Smeeth L, Cook C, Fombonne PE, Heavey L, Rodrigues LC, Smith PG *et al.* Rate of first recorded diagnosis of autism and other pervasive developmental disorders in United Kingdom general practice, 1988 to 2001. *BMC medicine* 2004; **2:** 39.

176. CPRD @ Cambridge – Code Lists. http://www.phpc.cam.ac.uk/pcu/cprd_cam/codelists/, Accessed Date Accessed.

177. Barnett K, Mercer SW, Norbury M, Watt G, Wyke S, Guthrie B. Epidemiology of multimorbidity and implications for health care, research, and medical education: a cross-sectional study. *Lancet (London, England)* 2012; **380**(9836)**:** 37-43.

178. Carey IM, Hosking FJ, Harris T, DeWilde S, Beighton C, Cook DG. An evaluation of the effectiveness of annual health checks and quality of health care for adults with intellectual disability: an observational study using a primary care database. *Health Services and Delivery Research* 2017; **5**(25).

179. Hire AJ. ADHD incidence, treatment and associated comorbidity in children and adolescents: an epidemiological study using electronic healthcare records. *University of Manchester* 2016.

180. Bartholomeeusen S, Kim C-Y, Mertens R, Faes C, Buntinx F. The denominator in general practice, a new approach from the Intego database. *Family Practice* 2005; **22**(4)**:** 442-447.

181. Spronk I, Korevaar JC, Poos R, Davids R, Hilderink H, Schellevis FG *et al.* Calculating incidence rates and prevalence proportions: not as simple as it seems. *BMC public health* 2019; **19**(1)**:** 512.

182. Otite FO, Patel S, Sharma R, Khandwala P, Desai D, Latorre JG *et al.* Trends in incidence and epidemiologic characteristics of cerebral venous thrombosis in the United States. *Neurology* 2020; **95**(16)**:** e2200-e2213.

183. Baio J, Wiggins L, Christensen DL, Maenner MJ, Daniels J, Warren Z *et al.* Prevalence of autism spectrum disorder among children aged 8 years—autism and developmental disabilities monitoring network, 11 sites, United States, 2014. *MMWR Surveillance Summaries* 2018; **67**(6)**:** 1.

184. Hamad AF, Alessi-Severini S, Mahmud SM, Brownell M, fan Kuo I. Annual trends in prevalence and incidence of autism spectrum disorders in Manitoba preschoolers and toddlers: 2004–2015. *Canadian Journal of Public Health* 2019; **110**(4)**:** 476-484.

185. Baird G, Simonoff E, Pickles A, Chandler S, Loucas T, Meldrum D *et al.* Prevalence of disorders of the autism spectrum in a population cohort of children in South Thames: the Special Needs and Autism Project (SNAP). *The lancet* 2006; **368**(9531)**:** 210-215.

186. Baron-Cohen S, Scott FJ, Allison C, Williams J, Bolton P, Matthews FE *et al.* Prevalence of autism-spectrum conditions: UK school-based population study. *The British journal of psychiatry* 2009; **194**(6)**:** 500-509.

187. Devnani PA, Hegde AU. Autism and sleep disorders. *Journal of pediatric neurosciences* 2015; **10**(4)**:** 304.

188. Houghton R, Ong RC, Bolognani F. Psychiatric comorbidities and use of psychotropic medications in people with autism spectrum disorder in the United States. *Autism Research* 2017; **10**(12)**:** 2037-2047.

189. Spencer D, Marshall J, Post B, Kulakodlu M, Newschaffer C, Dennen T *et al.* Psychotropic medication use and polypharmacy in children with autism spectrum disorders. *Pediatrics* 2013; **132**(5)**:** 833-840.

190. Downs J, Hotopf M, Ford T, Simonoff E, Jackson RG, Shetty H *et al.* Clinical predictors of antipsychotic use in children and adolescents with autism spectrum disorders: a historical open cohort study using electronic health records. *European child & adolescent psychiatry* 2016; **25**(6)**:** 649-658.

191. Ji NY, Findling RL. An update on pharmacotherapy for autism spectrum disorder in children and adolescents. *Current Opinion in Psychiatry* 2015; **28**(2)**:** 91-101.

192. Nagaraj R, Singhi P, Malhi P. Risperidone in children with autism: randomized, placebo-controlled, double-blind study. *Journal of child neurology*, vol. 212006, pp 450-455.

193. Pandina GJ, Bossie CA, Youssef E, Zhu Y, Dunbar F. Risperidone improves behavioral symptoms in children with autism in a randomized, double-blind, placebo-controlled trial. *Journal of Autism and Developmental Disorders* 2007; **37**(2)**:** 367-373.

194. Ghanizadeh A, Sahraeizadeh A, Berk M. A head-to-head comparison of aripiprazole and risperidone for safety and treating autistic disorders, a randomized double blind clinical trial. *Child Psychiatry and Human Development* 2014; **45**(2)**:** 185-192.

195. McDougle CJ, Scahill L, McCracken JT, Aman MG, Tierney E, Arnold LE *et al.* Research Units on Pediatric Psychopharmacology (RUPP) Autism Network: background and rationale for an initial controlled study of risperidone. *Child and adolescent psychiatric clinics of North America* 2000; **9**(1)**:** 201-224.

196. Shea S, Turgay A, Carroll A, Schulz M, Orlik H, Smith I *et al.* Risperidone in the treatment of disruptive behavioral symptoms in children with autistic and other pervasive developmental disorders. *Pediatrics* 2004; **114**(5)**:** e634-e641.

197. Owen R, Sikich L, Marcus RN, Corey-Lisle P, Manos G, McQuade RD *et al.* Aripiprazole in the treatment of irritability in children and adolescents with autistic disorder. *Pediatrics* 2009; **124**(6)**:** 1533-1540.

198. Caroff SN, Mann SC, Campbell EC, Sullivan KA. Movement disorders associated with atypical antipsychotic drugs. *The Journal of clinical psychiatry* 2002; **63:** 12-19.

199. Hedges D, Jeppson K, Whitehead P. Antipsychotic medication and seizures: a review. *Drugs Today (Barc)* 2003; **39**(7)**:** 551-557.

200. Lertxundi U, Hernandez R, Medrano J, Domingo-Echaburu S, García M, Aguirre C. Antipsychotics and seizures: higher risk with atypicals? *Seizure* 2013; **22**(2)**:** 141-143.

201. Volkmar FR, Nelson DS. Seizure disorders in autism. *Journal of the American Academy of Child & Adolescent Psychiatry* 1990; **29**(1)**:** 127-129.

202. Canitano R. Epilepsy in autism spectrum disorders. *European child & adolescent psychiatry* 2007; **16**(1)**:** 61-66.

203. Hedges D, Jeppson K, Whitehead P. Antipsychotic medication and seizures: a review. *Drugs Today (Barc)* 2003; **39**(7)**:** 551-557.

204. Rosenbaum PR, Rubin DB. The central role of the propensity score in observational studies for causal effects. *Biometrika* 1983; **70**(1)**:** 41-55.

205. Rubin DB. Causal inference using potential outcomes: Design, modeling, decisions. *Journal of the American Statistical Association* 2005; **100**(469)**:** 322-331.

206. Austin PC. An introduction to propensity score methods for reducing the effects of confounding in observational studies. *Multivariate behavioral research* 2011; **46**(3)**:** 399-424.

207. Rubin DB, Schenker N. Multiple imputation in health-are databases: An overview and some applications. *Statistics in medicine* 1991; **10**(4)**:** 585-598.

208. Jakobsen JC, Gluud C, Wetterslev J, Winkel P. When and how should multiple imputation be used for handling missing data in randomised clinical trials–a practical guide with flowcharts. *BMC medical research methodology* 2017; **17**(1)**:** 162.

209. Chui CS, Chan EW, Wong AY, Root A, Douglas IJ, Wong IC. Association between oral fluoroquinolones and seizures: a self-controlled case series study. *Neurology* 2016; **86**(18)**:** 1708-1715.

210. Sammon CJ, Charlton RA, Snowball J, Weil JG. The incidence of childhood and adolescent seizures in the UK from 1999 to 2011: A retrospective cohort study using the Clinical Practice Research Datalink. *Vaccine* 2015; **33**(51)**:** 7364-7369.

211. Desai RJ, Franklin JM. Alternative approaches for confounding adjustment in observational studies using weighting based on the propensity score: a primer for practitioners. *bmj* 2019; **367:** l5657.

212. Zhang Z, Kim HJ, Lonjon G, Zhu Y. Balance diagnostics after propensity score matching. *Annals of translational medicine* 2019; **7**(1).

213. Man KK, Chan EW, Ip P, Coghill D, Simonoff E, Chan PK *et al.* Prenatal antidepressant use and risk of attention-deficit/hyperactivity disorder in offspring: population based cohort study. *bmj* 2017; **357**.

214. Webster-Clark M, Stürmer T, Wang T, Man K, Marinac-Dabic D, Rothman KJ *et al.* Using propensity scores to estimate effects of treatment initiation decisions: State of the science. *Statistics in Medicine* 2020.

215. Patrick AR, Schneeweiss S, Brookhart MA, Glynn RJ, Rothman KJ, Avorn J *et al.* The implications of propensity score variable selection strategies in pharmacoepidemiology: an empirical illustration. *Pharmacoepidemiology and drug safety* 2011; **20**(6)**:** 551-559.

216. Ochoa-Gomez L, Lopez-Pison J, Moros CL, Rodrigo CF, Martínez RF, Samper-Villagrasa P *et al.* A study of epilepsy according to the age at onset and monitored for 3 years in a regional reference paediatric neurology unit. *Anales de Pediatría (English Edition)* 2017; **86**(1)**:** 11-19.

217. Carlson C, Dugan P, Kirsch HE, Friedman D, Investigators E. Sex differences in seizure types and symptoms. *Epilepsy & Behavior* 2014; **41:** 103-108.

218. Dworetzky BA, Bromfield EB, Townsend MK, Kang JH. A prospective study of smoking, caffeine, and alcohol as risk factors for seizures or epilepsy in young adult women: data from the Nurses' Health Study II. *Epilepsia* 2010; **51**(2)**:** 198-205.

219. Yun C, Xuefeng W. Association between seizures and diabetes mellitus: a comprehensive review of literature. *Current Diabetes Reviews* 2013; **9**(4)**:** 350-354.

220. Couillard P, Almekhlafi M, Irvine A, Jette N, Pow J, Germaine-Smith CS *et al.* Subacute seizure incidence in thrombolysis-treated ischemic stroke patients. *Neurocritical care* 2012; **16**(2)**:** 241-245.

221. Hitchings AW. Drugs that lower the seizure threshold. *Adverse drug reaction bulletin* 2016; **298**(1)**:** 1151-1154.

222. Klein-Schwartz W, Stassinos GL, Isbister GK. Treatment of sulfonylurea and insulin overdose. *British journal of clinical pharmacology* 2016; **81**(3)**:** 496-504.

223. Shafaroodi H, Moezi L, Ghorbani H, Zaeri M, Hassanpour S, Hassanipour M *et al.* Sub-chronic treatment with pioglitazone exerts anti-convulsant effects in pentylenetetrazole-induced seizures of mice: The role of nitric oxide. *Brain Research Bulletin* 2012; **87**(6)**:** 544-550.

224. Thundiyil JG, Kearney TE, Olson KR. Evolving epidemiology of drug-induced seizures reported to a Poison Control Center System. *Journal of medical toxicology* 2007; **3**(1)**:** 15-19.

225. Boostani R, Derakhshan S. Tramadol induced seizure: A 3-year study. *Caspian journal of internal medicine* 2012; **3**(3)**:** 484.

226. Singh G, Rees JH, Sander JW. Seizures and epilepsy in oncological practice: causes, course, mechanisms and treatment. *Journal of Neurology, Neurosurgery & Psychiatry* 2007; **78**(4)**:** 342-349.

227. Dhar R. Chapter 30 - Neurologic complications of transplantation. In: Wijdicks EFM, Kramer AH (eds). *Handbook of Clinical Neurology*, vol. 141. Elsevier2017, pp 545-572.

228. Smoking, drinking and drug use among young people in England. https://files.digital.nhs.uk/47/829A59/sdd-2016-rep-cor-new.pdf, 2017, Accessed Date Accessed 2017 Accessed.

229. McCabe SE, Dickinson K, West BT, Wilens TE. Age of onset, duration, and type of medication therapy for attention-deficit/hyperactivity disorder and substance use during adolescence: a multi-cohort national study. *Journal of the American Academy of Child & Adolescent Psychiatry* 2016; **55**(6)**:** 479-486.

230. Bloechliger M, Rüegg S, Jick SS, Meier CR, Bodmer M. Antipsychotic drug use and the risk of seizures: follow-up study with a nested case-control analysis. *CNS Drugs* 2015; **29**(7)**:** 591-603.

231. Schuemie MJ, Ryan PB, Man KKC, Wong ICK, Suchard MA, Hripcsak G. A plea to stop using the case-control design in retrospective database studies. *Stat Med* 2019; **38**(22)**:** 4199-4208.

232. Wu CS, Wang SC, Yeh IJ, Liu SK. Comparative risk of seizure with use of first- and second-generation antipsychotics in patients with schizophrenia and mood disorders. *J Clin Psychiatry* 2016; **77**(5)**:** e573-579.

233. Górska N, Słupski J, Cubała WJ. Antipsychotic drugs in epilepsy. *Neurologia i neurochirurgia polska* 2019; **53**(6)**:** 408-412.

234. Grover S, Hazari N, Chakrabarti S, Avasthi A. Association of Clozapine with Seizures: A Brief Report Involving 222 Patients Prescribed Clozapine. *East Asian archives of psychiatry : official journal of the Hong Kong College of Psychiatrists = Dong Ya jing shen ke xue zhi : Xianggang jing shen ke yi xue yuan qi kan* 2015; **25**(2)**:** 73-78.

235. Varma S, Bishara D, Besag FM, Taylor D. Clozapine-related EEG changes and seizures: dose and plasma-level relationships. *Therapeutic advances in psychopharmacology* 2011; **1**(2)**:** 47-66.

236. Miller E, Goldacre M, Pugh S, Colville A, Farrington P, Flower A *et al.* Risk of aseptic meningitis after measles, mumps, and rubella vaccine in UK children. *Lancet (London, England)* 1993; **341**(8851)**:** 979-982.

237. Farrington C. Relative incidence estimation from case series for vaccine safety evaluation. *Biometrics* 1995**:** 228-235.

238. Farrington C, Nash J, Miller E. Case series analysis of adverse reactions to vaccines: a comparative evaluation. *American journal of epidemiology* 1996; **143**(11)**:** 1165-1173.

239. Douglas IJ, Langham J, Bhaskaran K, Brauer R, Smeeth L. Orlistat and the risk of acute liver injury: self controlled case series study in UK Clinical Practice Research Datalink. *Bmj* 2013; **346**.

240. Masclee GM, Valkhoff VE, Coloma PM, de Ridder M, Romio S, Schuemie MJ *et al.* Risk of upper gastrointestinal bleeding from different drug combinations. *Gastroenterology* 2014; **147**(4)**:** 784-792. e789.

241. Man KK, Chan EW, Coghill D, Douglas I, Ip P, Leung L-p *et al.* Methylphenidate and the risk of trauma. *Pediatrics* 2015; **135**(1)**:** 40-48.

242. Root AA, Wong AY, Ghebremichael-Weldeselassie Y, Smeeth L, Bhaskaran K, Evans SJ *et al.* Evaluation of the risk of cardiovascular events with clarithromycin using both propensity score and self-controlled study designs. *British journal of clinical pharmacology* 2016; **82**(2)**:** 512-521.

243. Shin J-Y, Roughead EE, Park B-J, Pratt NL. Cardiovascular safety of methylphenidate among children and young people with attention-deficit/hyperactivity disorder (ADHD): nationwide self controlled case series study. *bmj* 2016; **353:** i2550.

244. Man KK, Coghill D, Chan EW, Lau WC, Hollis C, Liddle E *et al.* Association of risk of suicide attempts with methylphenidate treatment. *JAMA psychiatry* 2017; **74**(10)**:** 1048-1055.

245. Brauer R, Herrero-Zazo M, Barlow DJ, Gaughran F, Taylor D, Howard LM. Minocycline and the risk of acute psychiatric events in adolescence: A self-controlled case series. *Journal of Psychopharmacology* 2019; **33**(4)**:** 466-471.

246. Lipsitch M, Tchetgen ET, Cohen T. Negative controls: a tool for detecting confounding and bias in observational studies. *Epidemiology (Cambridge, Mass)* 2010; **21**(3)**:** 383.

247. Arnold BF, Ercumen A, Benjamin-Chung J, Colford JMJ. Brief Report: Negative Controls to Detect Selection Bias and Measurement Bias in Epidemiologic Studies. *Epidemiology* 2016; **27**(5)**:** 637-641.

248. Whitaker HJ, Hocine MN, Farrington CP. The methodology of self-controlled case series studies. *Statistical methods in medical research* 2009; **18**(1)**:** 7-26.

249. Whitaker HJ, Farrington CP, Spiessens B, Musonda P. Tutorial in biostatistics: the self-controlled case series method. *Stat Med* 2006; **25**(10)**:** 1768-1797.

250. Farrington CP, Hocine MN. Within-individual dependence in self-controlled case series models for recurrent events. *Journal of the Royal Statistical Society: Series C (Applied Statistics)* 2010; **59**(3)**:** 457-475.

251. Petersen I, Douglas I, Whitaker H. Self controlled case series methods: an alternative to standard epidemiological study designs. *bmj* 2016; **354:** i4515.

252. Farrington CP, Anaya-Izquierdo K, Whitaker HJ, Hocine MN, Douglas I, Smeeth L. Self-controlled case series analysis with event-dependent observation periods. *Journal of the American Statistical Association* 2011; **106**(494)**:** 417-426.

253. Farrington C, Whitaker H. Semiparametric analysis of case series data. *Journal of the Royal Statistical Society: Series C (Applied Statistics)* 2006; **55**(5)**:** 553-594.

254. Colton CW, Manderscheid RW. PEER REVIEWED: Congruencies in Increased Mortality Rates, Years of Potential Life Lost, and Causes of Death Among Public Mental Health Clients in Eight States. *Preventing chronic disease* 2006; **3**(2).

255. Saha S, Chant D, McGrath J. A systematic review of mortality in schizophrenia: is the differential mortality gap worsening over time? *Archives of general psychiatry* 2007; **64**(10)**:** 1123-1131.

256. Baptista T, De Mendoza S, Beaulieu S, Bermúdez A, Martinez M. The metabolic syndrome during atypical antipsychotic drug treatment: mechanisms and management. *Metabolic Syndrome and Related Disorders* 2004; **2**(4)**:** 290-307.

257. Kroeze WK, Hufeisen SJ, Popadak BA, Renock SM, Steinberg S, Ernsberger P *et al.* H1-histamine receptor affinity predicts short-term weight gain for typical and atypical antipsychotic drugs. *Neuropsychopharmacology* 2003; **28**(3)**:** 519.

258. Regenold WT, Thapar RK, Marano C, Gavirneni S, Kondapavuluru PV. Increased prevalence of type 2 diabetes mellitus among psychiatric inpatients with bipolar I

affective and schizoaffective disorders independent of psychotropic drug use. *Journal of affective disorders* 2002; **70**(1)**:** 19-26.

259. De Hert M, Correll CU, Bobes J, Cetkovich-Bakmas M, Cohen D, Asai I *et al.* Physical illness in patients with severe mental disorders. I. Prevalence, impact of medications and disparities in health care. *World psychiatry* 2011; **10**(1)**:** 52.

260. Newcomer JW. Second-generation (atypical) antipsychotics and metabolic effects. *CNS drugs* 2005; **19**(1)**:** 1-93.

261. Newcomer JW. Metabolic syndrome and mental illness. *American Journal of managed care* 2007; **13**(7)**:** S170.

262. Osborn DP, Levy G, Nazareth I, Petersen I, Islam A, King MB. Relative risk of cardiovascular and cancer mortality in people with severe mental illness from the United Kingdom's General Practice Research Database. *Archives of general psychiatry* 2007; **64**(2)**:** 242-249.

263. Brauer R, Douglas I, Smeeth L. The association between antipsychotic agents and the risk of myocardial infarction: a systematic review. *British journal of clinical pharmacology* 2011; **72**(6)**:** 871-878.

264. Yu Zh, Jiang Hy, Shao L, Zhou Yy, Shi Hy, Ruan B. Use of antipsychotics and risk of myocardial infarction: a systematic review and meta-analysis. *British journal of clinical pharmacology* 2016; **82**(3)**:** 624-632.

265. Zivkovic S, Koh CH, Kaza N, Jackson CA. Antipsychotic drug use and risk of stroke and myocardial infarction: a systematic review and meta-analysis. *BMC psychiatry* 2019; **19**(1)**:** 189.

266. Wu CS, Tsai YT, Tsai HJ. Antipsychotic drugs and the risk of ventricular arrhythmia and/or sudden cardiac death: a nation-wide case-crossover study. *Journal of the American Heart Association* 2015; **4**(2)**:** e001568.

267. Correll CU, Joffe BI, Rosen LM, Sullivan TB, Joffe RT. Cardiovascular and cerebrovascular risk factors and events associated with second-generation antipsychotic compared to antidepressant use in a non-elderly adult sample: results from a claims-based inception cohort study. *World Psychiatry* 2015; **14**(1)**:** 56-63.

268. Lin S-T, Chen C-C, Tsang H-Y, Lee C-S, Yang P, Cheng K-D *et al.* Association between antipsychotic use and risk of acute myocardial infarction: a nationwide case-crossover study. *Circulation* 2014; **130**(3)**:** 235-243.

269. Murray-Thomas T, Jones ME, Patel D, Brunner E, Shatapathy CC, Motsko S *et al.* Risk of mortality (including sudden cardiac death) and major cardiovascular events in atypical and typical antipsychotic users: a study with the general practice research database. *Cardiovascular psychiatry and neurology* 2013; **2013**.

270. Brauer R, Smeeth L, Anaya-Izquierdo K, Timmis A, Denaxas SC, Farrington CP *et al.* Antipsychotic drugs and risks of myocardial infarction: a self-controlled case series study. *European heart journal* 2015; **36**(16)**:** 984-992.

271. Herrett E, Shah AD, Boggon R, Denaxas S, Smeeth L, van Staa T *et al.* Completeness and diagnostic validity of recording acute myocardial infarction events in primary care, hospital care, disease registry, and national mortality records: cohort study. *Bmj* 2013; **346:** f2350.

272. Brauer R, Lau WC, Hayes JF, Man KK, Osborn DP, Howard R *et al.* Trazodone use and risk of dementia: A population-based cohort study. *PLoS medicine* 2019; **16**(2)**:** e1002728.

273. Khurshid S, Choi SH, Weng L-C, Wang EY, Trinquart L, Benjamin EJ *et al.* Frequency of cardiac rhythm abnormalities in a half million adults. *Circulation: Arrhythmia and Electrophysiology* 2018; **11**(7)**:** e006273.

274. Levy D, Kenchaiah S, Larson MG, Benjamin EJ, Kupka MJ, Ho KK *et al.* Long-term trends in the incidence of and survival with heart failure. *New England Journal of Medicine* 2002; **347**(18)**:** 1397-1402.

275. Hardoon SL, Whincup PH, Lennon LT, Wannamethee SG, Capewell S, Morris RW. How much of the recent decline in the incidence of myocardial infarction in British men can be explained by changes in cardiovascular risk factors? Evidence from a prospective population-based study. *Circulation* 2008; **117**(5)**:** 598-604.

276. Yusuf S, Hawken S, Ôunpuu S, Dans T, Avezum A, Lanas F *et al.* Effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries (the INTERHEART study): case-control study. *The lancet* 2004; **364**(9438)**:** 937-952.

277. Motsko SP, Rascati KL, Busti AJ, Wilson JP, Barner JC, Lawson KA *et al.* Temporal relationship between use of NSAIDs, including selective COX-2 inhibitors, and cardiovascular risk. *Drug safety* 2006; **29**(7)**:** 621-632.

278. Azoulay L, Suissa S. Sulfonylureas and the risks of cardiovascular events and death: a methodological meta-regression analysis of the observational studies. *Diabetes Care* 2017; **40**(5)**:** 706-714.

279. Rottlaender D, Michels G, Erdmann E, Hoppe U. Therapy with glitazones--a risk for cardiovascular disease? *Deutsche medizinische Wochenschrift (1946)* 2007; **132**(49)**:** 2629.

280. Maxwell CB, Jenkins AT. Drug-induced heart failure. *American Journal of Health-System Pharmacy* 2011; **68**(19)**:** 1791-1804.

281. Feenstra J, Grobbee DE, Remme WJ, Stricker BHC. Drug-induced heart failure. *Journal of the American College of Cardiology* 1999; **33**(5)**:** 1152-1162.

282. Wang Y, Chen H-J. Use of percentiles and z-scores in anthropometry. *Handbook of anthropometry*. Springer2012, pp 29-48.

283. Pan H, Cole T. LMSgrowth, a Microsoft Excel add-in to access growth references based on the LMS method. *Version* 2012; **2:** 11017.

284. Conolly A, Davies B. Health survey for England 2017—adult and child overweight and obesity. *NHS Digital, NHS: Leeds, UK* 2018.

285. Ho JG, Caldwell RL, McDougle CJ, Orsagh-Yentis DK, Erickson CA, Posey DJ *et al.* The effects of aripiprazole on electrocardiography in children with pervasive developmental disorders. *Journal of child and adolescent psychopharmacology* 2012; **22**(4)**:** 277-283.

286. Dominick K, Wink LK, McDougle CJ, Erickson CA. A retrospective naturalistic study of ziprasidone for irritability in youth with autism spectrum disorder. *Journal of child and adolescent psychopharmacology* 2015; **25**(5)**:** 397-401.

287. Kloosterboer SM, de Winter BC, Reichart CG, Kouijzer ME, de Kroon MM, van Daalen E *et al.* Risperidone plasma concentrations are associated with side effects and effectiveness in children and adolescents with autism spectrum disorder. *British Journal of Clinical Pharmacology* 2020.

288. Blanz B, Schmidt MH. Clozapine for schizophrenia. *Journal of the American Academy of Child & Adolescent Psychiatry* 1993.

289. Toren P, Ratner S, Laor N, Weizman A. Benefit-risk assessment of atypical antipsychotics in the treatment of schizophrenia and comorbid disorders in children and adolescents. *Drug safety* 2004; **27**(14)**:** 1135-1156.

290. Blair J, Scahill L, State M, Martin A. Electrocardiographic changes in children and adolescents treated with ziprasidone: a prospective study. *Journal of the American Academy of Child & Adolescent Psychiatry* 2005; **44**(1)**:** 73-79.

291. Funk MJ, Landi SN. Misclassification in administrative claims data: quantifying the impact on treatment effect estimates. *Current epidemiology reports* 2014; **1**(4)**:** 175-185.

292. Hong J-L, Meier CR, Sandler RS, Jick SS, Stürmer T. Risk of colorectal cancer after initiation of orlistat: matched cohort study. *Bmj* 2013; **347**.

293. Anderson G, Scahill L, McCracken J, McDougle C, Aman M, Tierney E *et al.* Effects of short- and long-term risperidone treatment on prolactin levels in children with autism. *Biological psychiatry*, vol. 612007, pp 545-550.

294. Ichikawa H, Hiratani M, Yasuhara A, Tsujii N, Oshimo T, Ono H *et al.* An open-label extension long-term study of the safety and efficacy of aripiprazole for irritability in children and adolescents with autistic disorder in Japan. *Psychiatry & Clinical Neurosciences* 2017; **23:** 23.

Appendices

Appendix (1): Search strategy of the systematic review and meta-analyses

1- The Cochrane library

No.	Key word	Mesh	Free text
1	Safety	Safety	• Safet* • Side effect* • Undesirable effect* • Toxicit* • Adverse drug reaction* • Adverse drug effect* • Adverse drug outcome* • Adverse drug event*
	Tolerability	-	• Tolerab*
	Mortality	Mortality	• Mortalit* • Death • Fatal
2	Antipsychotic	Antipsychotic Agents	• Antipsychotic* • Antipsychotic Agent* • Antipsychotic Drug* • Antipsychotic Effect* • Typical antipsychotic* • Atypical antipsychotic* • First generation antipsychotic* • Second generation antipsychotic* • Chloropromazin* or levomepromazin* or methotrimeprazin* or promazin* or pericyazin* or thioridazin* or pipotiazin* or fluphenazin* or perphenazin* or prochlorperazin* or trifluoperazin* or benperidol*, droperidol* or haloperidol* or flupentixol* or thiothixen* or zuclopenthixol* or pimozid* or sulpirid* or loxapin* or oxypertin* or amisulprid* or clozapin* or olanzapin* or paliperidon* or quetiapin* or lurasidon* or asenapin* or iloperidon* or risperidon* or aripiprazol*
3	Autism spectrum disorder	Child Development Disorders, Pervasive	• Autis* • Autism spectrum disorder* • ASD* • Infantile autism • Early infantile autism • Kanner* • Rett* • Asperger* • Pervasive* development* disorder* • PDD*

The Cochrane library total (455)

1. MeSH descriptor: [Safety] explode all trees
2. safet* (Word variations have been searched)
3. antipsychotic* (Word variations have been searched)
4. Antipsychotic agent* (Word variations have been searched)
5. Antipsychotic Drug* (Word variations have been searched)
6. Antipsychotic Effect* (Word variations have been searched)
7. child (Word variations have been searched)
8. MeSH descriptor: [Child] explode all trees
9. children (Word variations have been searched)
10. MeSH descriptor: [Adolescent] explode all trees
11. Adolescent* (Word variations have been searched)
12. autism spectrum disorder* (Word variations have been searched)
13. MeSH descriptor: [Child Development Disorders, Pervasive] explode all trees
14. MeSH descriptor: [Antipsychotic Agents] explode all trees
15. aripiprazol* (Word variations have been searched)
16. clozapin* (Word variations have been searched)
17. haloperidol (Word variations have been searched)
18. olanzapin* (Word variations have been searched)
19. paliperidon* (Word variations have been searched)
20. quetiapin* (Word variations have been searched)
21. resperidon* (Word variations have been searched)
22. ziprasidon* (Word variations have been searched)
23. side effect* (Word variations have been searched)
24. undesirable effect* (Word variations have been searched)
25. tolerability (Word variations have been searched)
26. toxicity (Word variations have been searched)
27. adverse drug reaction* (Word variations have been searched)
28. adverse drug effect* (Word variations have been searched)
29. adverse drug outcome* (Word variations have been searched)
30. adverse drug event* (Word variations have been searched)
31. youth (Word variations have been searched)
32. "juvenile" (Word variations have been searched)
33. #1 or #2 or #23 or #24 or #25 or #26 or #27 or #28 or #29 or #30
34. #3 or #4 or #5 or #6 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22
35. #7 or #8 or #9 or #10 or #11 or #31 or #32
36. #12 or #13
37. #33 and #34 and #35 and 36

2- PsychINFO, Embase and Medline

No.	Key word	Mesh	Free text
1	Safety	• Safety • Patient safety	• Safet* • Side effect* • Undesirable effect* • Toxicit* • Adverse drug reaction* • Adverse drug outcome* • Adverse drug effect* • Adverse drug event* • Drug* toxicit* • Drug* safet* • Patient* safet* • Adverse effect* • Adverse reaction* • Adverse event* • Drug side effect* • Drug-related side effect* and adverse reaction* • Long term adverse effect*
	Tolerability	Side Effects (Drug)	• Drug tolerabil* • Tolerabil*
	Mortality	Death and Dying	• Mortalit* • Death • Fatal
2	Antipsychotic	Neuroleptic Drugs Haloperidol Risperidone Olanzapine Clozapine	• Antipsychotic* • Antipsychotic agent* • Antipsychotic drug* • Antipsychotic agent*, butyrophenone • Antipsychotic agent*, phenothiazine • Antipsychotic agent*, thioxanthene • Antipsychotic agent*, diphenylbutylpiperidine • Antipsychotic agent*, Substituted benzamide • Antipsychotic agent*, dibenzoxazepine • Neuroleptic* • Neuroleptic drug* • Major tranquilizer* • Tranquilizing agent*, major • Classical antipsychotic* • Typical neuroleptic* • Typical antipsychotic* drug* • Atypical antipsychotic* drug* • First generation antipsychotic* • Second generation antipsychotic* • Chloropromazin* or levomepromazin* or methotrimeprazin* or promazin* or pericyazin* or thioridazin* or pipotiazin* or fluphenazin* or perphenazin* or prochlorperazin* or trifluoperazin* or benperidol*, droperidol* or haloperidol* or flupentixol* or thiothixen* or zuclopenthixol* or pimozid* or sulpirid* or loxapin* or oxypertin* or amisulprid* or clozapin* or olanzapin* or paliperidon* or quetiapin* or

			lurasidon* or asenapin* or iloperidon* or risperidon* or aripiprazol*
3	Autism spectrum disorder	Autism spectrum disorders	• Autis* spectrum disorder • Autis* or ASD or ASDs • Autistic child* • Autistic disorder • Infantile autism • Early infantile autism • Childhood autism • Classical autism • Typical autism • Kanner syndrome • Kanner* • Asperger* • Rett* • Child development disorders, pervasive • Pervasive adj3 child* • Pervasive development* disorder* or PDD or PDDs

PsychINFO total (338)

1. exp PATIENT SAFETY / or safety.mp. or exp SAFETY/
2. safet*.mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures]
3. exp "Side Effects (Drug)"/ or exp "Side Effects (Treatment)"/ or side effect.mp.
4. side effect*.mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures]
5. adverse drug reaction.mp.
6. adverse drug reaction*.mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures]
7. undesirable effect.mp.
8. undesirable effect*.mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures]
9. tolerability.mp.
10. tolerabilit*.mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures]
11. Toxicity.mp. or exp TOXICITY/
12. toxicit*.mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures]
13. adverse drug event.mp.
14. adverse drug event*.mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures]
15. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14
16. exp Neuroleptic Drugs/ or Antipsychotic.mp.
17. antipsychotic*.mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures]
18. typical antipsychotic*.mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures]
19. exp Clozapine/ or exp Olanzapine/ or exp Haloperidol/ or typical antipsychotic.mp. or exp Risperidone/
20. exp Olanzapine/ or exp Haloperidol/ or atypical antipsychotic.mp. or exp Clozapine/ or exp Aripiprazole/
21. atypical antipsychotic*.mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures]
22. (paliperidon* or quetiapin* or ziprasidon*).mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures]
23. 16 or 17 or 18 or 19 or 20 or 21 or 22
24. Child.mp.
25. child*.mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures]
26. Adolescent.mp.
27. Adolescent*.mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures]
28. (juvenile or youth).mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures]
29. 24 or 25 or 26 or 27 or 28
30. Autism spectrum disorder.mp. or exp Autism Spectrum Disorders/
31. Autism spectrum disorder*.mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures]
32. 30 or 31
33. 15 and 23 and 29 and 32

Embase total (1647)

1. drug safety/ or patient safety/ or child safety/ or safety/
2. safet*.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word]
3. (safet* or drug* safet* or patient* safet* or child* safet*).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word]
4. adverse drug reaction/ or side effect/ or side effect.mp.
5. (side reaction* or adverse drug effect* or adverse drug event* or adverse effect* or adverse reaction* or drug adverse reaction* or drug side effect* or (drug-related side effects and adverse reaction*) or long term adverse effect* or (metabolic side effect* of drug* and substance*)).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word]
6. drug tolerability/ or tolerability.mp.
7. Toxicity.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word]
8. 1 or 2 or 3 or 4 or 5 or 6 or 7
9. Antipsychotic.mp. or neuroleptic agent/
10. (antipsychotic agent* or antipsychotic agent*, butyrophenone or antipsychotic agent*, phenothiazine or antipsychotic drug* or antipsychotic* or butyrophenone tranquilizer* or classical antipsychotic or classical antipsychotic agent or classical antipsychotic drug or long acting neuroleptic or major tranquilizer or neuroleptic or neuroleptic drug or neurolepticum or phenothiazine tranquilizer* or tranquilizing agents, major or typical antipsychotic or typical antipsychotic agent or typical antipsychotic drug or typical neuroleptic or typical neuroleptic agent or typical neuroleptic drug).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word]
11. (aripiprazol* or clozapin* or haloperidol or olanzapin* or paliperidon* or quetiapin* or resperidon* or ziprasidon).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word]
12. 9 or 10 or 11
13. (child* or adolescent).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word]
14. (juvenile or youth).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word]
15. 13 or 14
16. Autism spectrum disorder.mp. or autism/
17. (autis* spectrum disorder* or autism, early infantile or autism, infantile or autistic child or autistic children or autistic disorder* or child development disorder*, pervasive or childhood autism or classical autism or Kanner syndrome or PDD or pervasive developmental disorder* or typical autism).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word]
18. 16 or 17
19.8 and 12 and 15 and 18

Medline total (365)

1. exp Safety/ or safety.mp.
2. safet*.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
3. side effect.mp.
4. side effect*.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
5. Adverse drug reaction.mp. or exp "Drug-Related Side Effects and Adverse Reactions"/

6. (adverse drug event* or adverse drug reaction* or (drug related side effect* and adverse reaction*) or drug side effect* or drug toxicit* or side effects of drugs or toxicit*, drug).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
7. 1 or 2 or 3 or 4 or 5 or 6
8. Antipsychotic.mp. or exp Antipsychotic Agents/
9. (antipsychotic agent* or antipsychotic drugs or antipsychotic effect* or antipsychotic* or major tranquilizer* or major tranquilizing agent* or neuroleptic agent* or neuroleptic drug* or neuroleptics).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
10. exp Haloperidol/ or Typical antipsychotic.mp. or exp Clozapine/ or exp Risperidone/

11. typical antipsychotic*.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
12. exp Risperidone/ or atypical antipsychotic.mp. or exp Clozapine/ or exp Haloperidol/

13. atypical antipsychotic*.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
14. (aripiprazol* or olanzapine* or paliperidon* or quetiapin* or ziprasidon*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
15. 8 or 9 or 10 or 11 or 12 or 13 or 14
16. child*.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
17. exp Adolescent/ or Adolescent.mp.
18. Adolescent*.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
19. (juvenile or youth).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
20. 16 or 17 or 18 or 19
21. exp Asperger Syndrome/ or Autism spectrum disorder.mp. or exp Autistic Disorder/ or exp Autism Spectrum Disorder/
22. (autism spectrum disorder* or autism or autistic disorder* or early infantile autism or infantile autism or kanner* syndrome or Asperger* disease* or Asperger* disorder* or Asperger* syndrome).mp. [mp=title, abstract, original title, name of substance word,

subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
23. 21 or 22
24.7 and 15 and 20 and 23

Appendix (2): Quality assessment of the included studies in the systematic review and meta-analyses

1- Assessment of RCTs using Cochrane Collaboration tool.

Citation (year)		Selection bias		Performance bias	Detection bias	Attrition bias	Reporting bias
		Random sequence generation	Allocation concealment	Blinding of participants and personnel*	Blinding of outcome assessment*	Incomplete outcome data*	Selective reporting
McCracken et al. (2005)[69]	**Judgment**	Low risk	Unclear risk	High risk	Low risk	Low risk	Low risk
	Support	'Eligible subjects were randomly assigned to receive risperidone or placebo for 8 weeks; details are provided elsewhere (4)'	(description of allocation is not included)	(open label phase)	'assessed by a blinded clinician'	(the dropout and reasons were reported)	(reported AE as stated in method)
Anderson GM et al. (2007)[293]	**Judgment**	Unclear risk	Unclear risk	Low risk	Unclear risk	Unclear risk	Low risk
	Support	(No description of random sequence generation)	(description of allocation is not included)	(double blind)	(Assessment blinding were not specified)	(did not report the no. of lost F/U)	(reported AE as stated in method)
McCracken Jt et al. (2002)[66]	**Judgment**	Unclear risk	Unclear risk	Low risk	Low risk	Low risk	Low risk
	Support	(No description of random sequence generation)	(description of allocation is not included)	(double blind)	'it was assessed by two clinicians who were unaware of the treatment assignment'	(the withdrawal and reasons were reported)	(reported AE as stated in method)
Vo Lc et al. (2016)[130]	**Judgment**	Unclear risk	Unclear risk	Low risk	Low risk	Low risk	Low risk
	Support	(No description of random sequence generation)	(description of allocation is not included)	(double blind)	(the electrophysiologist was blinded)	(clarify the completeness of outcome data and analysis)	(reported AE as stated in method)

Citation (year)		Selection bias		Performance bias	Detection bias	Attrition bias	Reporting bias
		Random sequence generation	Allocation concealment	Blinding of participants and personnel*	Blinding of outcome assessment*	Incomplete outcome data*	Selective reporting
Findling RL et al. (2014)[80]	**Judgment**	Unclear risk	Unclear risk	Low risk	Unclear risk	Low risk	Low risk
	Support	(No description of random sequence generation)	(description of allocation is not included)	(double blind)	(Assessment blinding were not specified)	(reported the reason for discontinuation in each arm)	(reported AE as stated in method)
Gencer O et al. (2008)[125]	**Judgment**	Unclear risk	Unclear risk	High risk	Unclear risk	Low risk	Low risk
	Support	(No description of random sequence generation)	(description of allocation is not included)	(open label phase)	(Assessment blinding were not specified)	(clarified the completeness of outcome data and analysis)	(reported AE as stated in method)
Ghanizadeh A et al. (2014)[81]	**Judgment**	Unclear risk	Unclear risk	Low risk	Low risk	Low risk	Low risk
	Support	(No description of random sequence generation)	(description of allocation is not included)	(participants were blinded)	(the clinicians was blinded)	(clarified the completeness of outcome data and analysis)	(reported AE as stated in method)
Ichikawa H et al. (2017)[82]	**Judgment**	Unclear risk	Unclear risk	Low risk	Low risk	Low risk	Low risk
	Support	(No description of random sequence generation)	(description of allocation is not included)	(The investigators and subjects were blinded to the trial drug randomisation code)	(The investigators and subjects were blinded to the trial drug randomisation code)	(clarified the completeness of outcome data)	(reported AE as stated in method)

Citation (year)		Selection bias		Performance bias	Detection bias	Attrition bias	Reporting bias
		Random sequence generation	Allocation concealment	Blinding of participants and personnel*	Blinding of outcome assessment*	Incomplete outcome data*	Selective reporting
Ichikawa H et al. (2017)[294]	**Judgment**	High risk	High risk	High risk	Unclear risk	Low risk	Low risk
	Support	(no randomisation, it is one arm study)	(no allocation concealment)	(open label phase)	(Assessment blinding were not specified)	(reported the reason for discontinuation)	(reported AE as stated in method)
Nikvarz N et al. (2017)[131]	**Judgment**	Low risk	Unclear risk	High risk	Unclear risk	Low risk	Low risk
	Support	'Patients were randomly allocated to receive treatments based on simple, balanced, blocked randomization'	(description of allocation is not included)	(open label phase)	(Assessment blinding were not specified)	(clarified the completeness of outcome data)	(reported AE as stated in method)
Loebel, A et al. (2016)[92]	**Judgment**	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
	Support	'randomized, double-blind, in a 1:1:1 ratio (via an interactive voice/web response system)'	randomized, double-blind, in a 1:1:1 ratio (via an interactive voice/web response system)	(double blind)	(The investigators and subjects were blinded to the trial drug randomisation code)	(clarified the completeness of outcome data)	(reported AE as stated in method)
Kent, Jm et al. (2013)[78]	**Judgment**	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
	Support	'The randomization was conducted by using randomly permuted blocks'	used randomized blocks of subjects for allocation	(double blind)	(The investigators and subjects were blinded to the trial drug randomisation code)	(clarified the completeness of outcome data)	(reported AE as stated in method)
Kent, Jm et al. (2013)[77]	**Judgment**	Low risk	Unclear risk	High risk	High risk	Low risk	Low risk
	Support	(randomisation, continued from RCT phase)	(description of allocation is not included)	(open label phase)	(Single blind (both site and staff) not for participants and evaluator)	(clarify the completeness of outcome data)	(reported AE as stated in method)

Citation (year)		Selection bias		Performance bias	Detection bias	Attrition bias	Reporting bias
		Random sequence generation	Allocation concealment	Blinding of participants and personnel*	Blinding of outcome assessment*	Incomplete outcome data*	Selective reporting
Stigler, Ka et al. (2012)[93]	**Judgment**	High risk	High risk	High risk	Unclear risk	Low risk	Low risk
	Support	(non- randomised)	(no allocation concealment)	(open label phase)	(Assessment blinding were not specified)	(described dropout)	(reported AE as stated in method)
Marcus, RN et al. (2009)[126]	**Judgment**	Unclear risk	Unclear risk	Low risk	Unclear risk	Low risk	Low risk
	Support	(No description of random sequence generation)	(description of allocation is not included)	(double blind)	(Assessment blinding were not specified)	(clarify the completeness of outcome data)	(reported AE as stated in method)
Owen, R et al. (2009)[62]	**Judgment**	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
	Support	'a computer-generated randomization schedule using a permuted block design'	'Investigational sites accessed a call-in interactive voice response system when patients were ready to be randomly assigned. The system assigned a medication bottle number to each patient.'	(double blind, participants and investigator)	(double blind, participants and investigator)	(reported the reason for discontinuation)	(reported AE as stated in method)
Marcus, Rn et al. (2011)[129]	**Judgment**	High risk	High risk	High risk	High risk	Low risk	Low risk
	Support	(no randomization)	(no allocation concealment)	(open label phase)	(outcome assessment was un-blinded)	(reported the reason for discontinuation)	(reported AE as stated in method)

Citation (year)		Selection bias		Performance bias	Detection bias	Attrition bias	Reporting bias
		Random sequence generation	Allocation concealment	Blinding of participants and personnel*	Blinding of outcome assessment*	Incomplete outcome data*	Selective reporting
Hellings, JA et al. (2010)[76]	Judgment	High risk	High risk	High risk	High risk	Low risk	Low risk
	Support	(no randomization)	(no allocation concealment)	(open label phase)	(outcome assessment was un-blinded)	(described the reason of withdrawal)	(reported AE as stated in method)
Stigler, KA et al. (2009)[128]	Judgment	High risk	High risk	High risk	High risk	Low risk	Low risk
	Support	(no randomization)	(no allocation concealment)	(open label phase)	(outcome assessment was un-blinded)	(described the reason of withdrawal)	(reported AE as stated in method)
Capone, GT et al. (2008)[124]	Judgment	High risk	High risk	High risk	High risk	High risk	Low risk
	Support	(no randomization)	(no allocation concealment)	(open label phase)	(outcome assessment was un-blinded)	(did not report the no. of lost F/U or give any reasons)	(reported AE as stated in method)
Troost, PW et al. (2007)[75]	Judgment	High risk	High risk	High risk	High risk	Low risk	Low risk
	Support	(no randomization)	(no allocation concealment)	(open label phase)	(outcome assessment was un-blinded)	(described the reason of withdrawal)	(reported AE as stated in method)
Pandina, Gj et al. (2007)[74]	Judgment	Unclear risk	Unclear risk	Low risk	Unclear risk	Low risk	Low risk
	Support	(No description of random sequence generation)	(description of allocation is not included)	(double blind)	(Assessment blinding were not specified)	(described the reason of withdrawal or incompleteness of data)	(reported AE as stated in method)

Citation (year)		Selection bias		Performance bias	Detection bias	Attrition bias	Reporting bias
		Random sequence generation	Allocation concealment	Blinding of participants and personnel*	Blinding of outcome assessment*	Incomplete outcome data*	Selective reporting
Malone, RP et al. (2007)[123]	**Judgment**	High risk	High risk	High risk	High risk	Low risk	Low risk
	Support	(no randomization)	(no allocation concealment)	(open label phase)	(outcome assessment was un-blinded)	(clarify the response rate and method performed LOCF for analysis)	(reported AE as stated in)
Nagaraj, R et al. (2006)[72]	**Judgment**	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
	Support	(generated a randomization sequence)	(used randomized blocks of subjects for allocation)	(double blind)	(persons engaged in interviewing and administering the test instruments were blinded)	(described the reason of withdrawal or incompleteness of data)	(reported AE as stated in method)
Luby, J et al. (2006)[71]	**Judgment**	Low risk	Unclear risk	Low risk	High risk	Low risk	Low risk
	Support	'Randomization table obtained from the WUSM pharmacy and derived using a standard software package.'	(description of allocation is not included)	(double blind)	(psychiatrists were not blinded to the treatment condition)	(all participants completed the trial)	(reported AE as stated in method)
Hollander, E et al. (2006)[94]	**Judgment**	Unclear risk	Unclear risk	Low risk	Unclear risk	Low risk	Low risk
	Support	(No description of random sequence generation)	(description of allocation is not included)	(double blind)	(Assessment blinding were not specified)	(described the drop out and gave reasons)	(reported AE as stated in method)
Troost, Pieter W. (2005)[70]	**Judgment**	High risk	High risk	High risk	High risk	Low risk	Low risk
	Support	(no randomization)	(no allocation concealment)	(open label phase)	(outcome assessment was un-blinded)	(described and gave reasons for discontinuation)	(reported AE as stated in method)

Citation (year)		Selection bias		Performance bias	Detection bias	Attrition bias	Reporting bias
		Random sequence generation	Allocation concealment	Blinding of participants and personnel*	Blinding of outcome assessment*	Incomplete outcome data*	Selective reporting
Shea, S (2004)[61]	**Judgment**	Unclear risk	Unclear risk	Low risk	Unclear risk	Low risk	Low risk
	Support	(No description of random sequence generation)	(description of allocation is not included)	(double blind)	(Assessment blinding were not specified)	(described the drop out and gave reasons and use ITT as an analysis)	(reported AE as stated in method)
Gagliano, A. (2004)[68]	**Judgment**	High risk	High risk	High risk	High risk	Low risk	Low risk
	Support	(no randomization)	(no allocation concealment)	(open label)	(outcome assessment was un-blinded)	(all participants completed the trial)	(reported AE as stated in method)
Malone, Richard P. (2002)[121]	**Judgment**	High risk	High risk	High risk	High risk	Low risk	Low risk
	Support	(no randomization)	(no allocation concealment)	(open label)	(outcome assessment was un-blinded)	(all participants completed the trial)	(reported AE as stated in method)
Kemner, C. (2002)[120]	**Judgment**	High risk	High risk	High risk	High risk	Low risk	Low risk
	Support	(no randomization)	(no allocation concealment)	(open label)	(outcome assessment was un-blinded)	(described and gave reasons for discontinuation)	(reported AE as stated in method)
Masi, G. (2001)[118]	**Judgment**	High risk	High risk	High risk	High risk	Low risk	Low risk
	Support	(no randomization)	(no allocation concealment)	(open label)	(non-blinded)	(described and gave reasons for discontinuation)	(reported AE as stated in method)

Citation (year)		Selection bias		Performance bias	Detection bias	Attrition bias	Reporting bias
		Random sequence generation	Allocation concealment	Blinding of participants and personnel*	Blinding of outcome assessment*	Incomplete outcome data*	Selective reporting
Masi, Gabriele (2001)[117]	**Judgment**	High risk	High risk	High risk	High risk	Low risk	Low risk
	Support	(no randomization)	(no allocation concealment)	(open label)	(non-blinded)	(described and gave reasons for discontinuation)	(reported AE as stated in method)
Masi, Gabriele (2001)[116]	**Judgment**	High risk	High risk	High risk	High risk	Low risk	Low risk
	Support	(no randomization)	(no allocation concealment)	(open label)	(non-blinded)	(all participants completed the trial)	(reported AE as stated in method)
Nicolson, Rob (1998)[115]	**Judgment**	High risk	High risk	High risk	High risk	Low risk	Low risk
	Support	(no randomization)	(no allocation concealment)	(open label)	(non-blinded)	(all participants completed the trial)	(reported AE as stated in method)
McDougle, Christopher J. (1997)[113]	**Judgment**	High risk	High risk	High risk	High risk	Low risk	Low risk
	Support	(no randomization)	(no allocation concealment)	(open label)	(non-blinded)	(all participants completed the trial)	(reported AE as stated in method)
Findling, RL. (1997)[112]	**Judgment**	High risk	High risk	High risk	High risk	Low risk	Low risk
	Support	(no randomization)	(no allocation concealment)	(open label)	(non-blinded)	(all participants completed the trial)	(reported AE as stated in method)

Citation (year)		Selection bias		Performance bias	Detection bias	Attrition bias	Reporting bias
		Random sequence generation	Allocation concealment	Blinding of participants and personnel*	Blinding of outcome assessment*	Incomplete outcome data*	Selective reporting
Remington, G (2001)[119]	**Judgment**	Unclear risk	Unclear risk	Low risk	Unclear risk	Low risk	Low risk
	Support	(No description of random sequence generation)	(description of allocation is not included)	(double blind)	(Assessment blinding were not specified)	(reported the incompleteness of data)	(reported AE as stated in method)
Scahill, L (2016)[79]	**Judgment**	Unclear risk	Unclear risk	Low risk	Low risk	Low risk	Low risk
	Support	(No description of random sequence generation)	(description of allocation is not included)	(double blind)	(clinicians and evaluators were blinded)	(reported the incompleteness of data and showed the differences between included subjects and dropped out subjects)	(reported AE as stated in method)
McDougle, Christopher J. (1998)[65]	**Judgment**	Low risk	Unclear risk	Low risk	Low risk	Low risk	Low risk
	Support	'patients were randomly allocated according to a computer-generated list'	(description of allocation is not included)	(double blind)	(clinicians and evaluators were blinded)	(reported the incompleteness of data)	(reported AE as stated in method)
Kim, HW et al. (2018)[145]	**Judgment**	High risk	High risk	High risk	High risk	Low risk	Low risk
	Support	(no randomization)	(no allocation concealment)	(open label)	(non-blinded)	(the withdrawal and reasons were reported)	(reported AE as stated in method)
DeVane, CL et al. (2019)[146]	**Judgment**	Unclear risk	Unclear risk	Low risk	Low risk	Low risk	Low risk
	Support	(No description of random sequence generation)	(description of allocation is not included)	(double blind)	'All research personnel were blinded to study medication and dosage throughout the study'	(the withdrawal and reasons were reported)	(reported AE as stated in method)

1- Assessment of observational studies using an adapted version of modified Newcastle-Ottawa scale (NOS).

0-3 (0 definitely no, 3 definitely yes)

Domain of evaluation		Masi G, et al. (2003)[133]	Corson AH, et al. (2004)[134]	Masi G, et al. (2009)[135]	Beherec L, et al. (2011)[136]	Boon-Y V, et al. (2014)[137]	Wink LK, et al. (2014)[111]	Aman M, et al. (2015)[138]
Methods for selecting study participants (i.e. Selection bias)	Is the source population (cases, controls, cohorts) appropriate and representative of the population of interest?	2	2	2	1	2	2	3
Methods to control confounding (i.e. Performance bias)	Is the sample size adequate and is there sufficient power to detect a meaningful difference in the outcome of interest?	1	1	1	0	1	2	2
	Did the study identify and adjust for any variables or confounders that may influence the outcome?	2	1	2	1	2	1	2
Statistical methods (i.e. Detection bias)	Did the study use appropriate statistical analysis methods relative to the outcome of interest?	3	2	3	2	3	2	3
	Is there little missing data and did the study handle it accordingly?	2	2	2	2	2	2	2
Methods for measuring outcome variables (i.e. Information bias)	Is the methodology of the outcome measurement explicitly stated and is it appropriate?	2	2	3	2	1	2	3

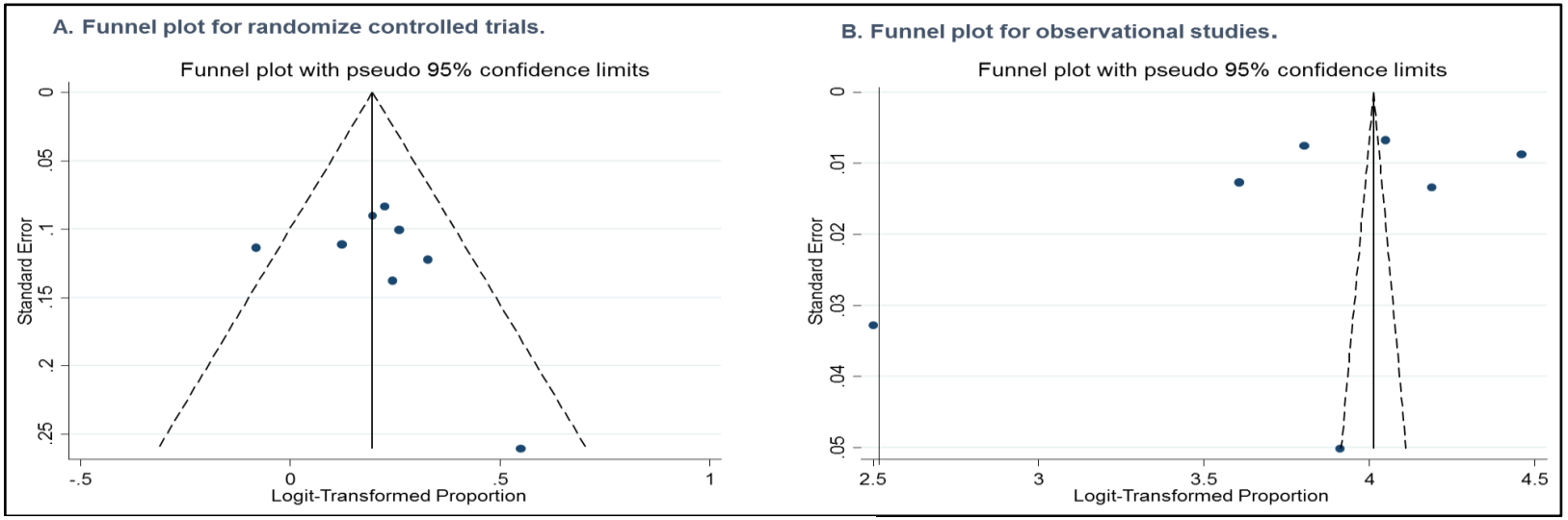
	Is there an objective assessment of the outcome of interest?	2	2	3	1	2	2	2
Domain of evaluation		**Hellings J A, et al. (2015)[139]**	**Hongkaew Y, et al. (2015)[140]**	**Ngamsamut N, et al. (2016)[141]**	**Nuntamool N, et al. (2017)[142]**	**Srisawasdi P, et al. (2017)[143]**	**Vanwong N, et al (2017)[144]**	**Wink L K, et al. (2017)[85]**
Methods for selecting study participants (i.e. Selection bias)	Is the source population (cases, controls, cohorts) appropriate and representative of the population of interest?	2	2	2	2	2	2	3
Methods to control confounding (i.e. Performance bias)	Is the sample size adequate and is there sufficient power to detect a meaningful difference in the outcome of interest?	2	2	2	2	2	2	2
	Did the study identify and adjust for any variables or confounders that may influence the outcome?	2	2	1	2	3	1	2
Statistical methods (i.e. Detection bias)	Did the study use appropriate statistical analysis methods relative to the outcome of interest?	3	3	3	3	3	2	3
	Is there little missing data and did the study handle it accordingly?	2	2	2	2	2	2	2
Methods for measuring outcome variables (i.e. Information bias)	Is the methodology of the outcome measurement explicitly stated and is it appropriate?	3	3	3	3	3	2	3

	Is there an objective assessment of the outcome of interest?	2	2	2	3	2	2	2

Domain of evaluation		Sukasem C, et al. (2018)[147]	Kloosterboer SM, et al. (2020)[148]	Tural Hesapcioglu S, et al. (2020)[149]
Methods for selecting study participants (i.e. Selection bias)	Is the source population (cases, controls, cohorts) appropriate and representative of the population of interest?	2	2	3
Methods to control confounding (i.e. Performance bias)	Is the sample size adequate and is there sufficient power to detect a meaningful difference in the outcome of interest?	2	2	2
	Did the study identify and adjust for any variables or confounders that may influence the outcome?	3	3	2
Statistical methods (i.e. Detection bias)	Did the study use appropriate statistical analysis methods relative to the outcome of interest?	3	3	3
	Is there little missing data and did the study handle it accordingly?	2	2	2
Methods for measuring outcome variables (i.e. Information bias)	Is the methodology of the outcome measurement explicitly stated and is it appropriate?	3	3	3

	Is there an objective assessment of the outcome of interest?	3	3	2

Appendix (3): Publication bias funnel plots of the systematic review and meta-analyses included studies



Tests for RCTs' Publication Bias
Begg's Test

adj. Kendall's Score (P-Q) = 6
Std. Dev. of Score = 8.08
Number of Studies = 8
z = 0.74
Pr > |z| = 0.458
z = 0.62 (continuity corrected)
Pr > |z| = 0.536 (continuity corrected)

Egger's test

Std_Eff	Coef.	Std. Err.	t	P>|t|	[95% Conf.	Interval]
slope	.0557482	.1869998	0.30	0.776	-.4018237	.5133201
bias	1.316251	1.690496	0.78	0.466	-2.820243	5.452745

Tests for Observational Studies' Publication Bias
Begg's Test

adj. Kendall's Score (P-Q) = -5
Std. Dev. of Score = 6.66
Number of Studies = 7
z = -0.75
Pr > |z| = 0.453
z = 0.60 (continuity corrected)
Pr > |z| = 0.548 (continuity corrected)

Egger's test

Std_Eff	Coef.	Std. Err.	t	P>|t|	[95% Conf.	Interval]
slope	4.240709	.2841422	14.92	0.000	3.510299	4.97112
bias	-24.74086	27.41186	-0.90	0.408	-95.20528	45.72356

Appendix (4): IMRD-UK ethical approval letter for drug utilisation study

SRC Feedback

Researcher Name: Basmah Alfageh
Organisation: UCL School of Pharmacy
SRC Reference Number: 18THIN010
Date: 23rd March 2018
Study title: Psychotropic medications prescribing in UK patients diagnosed with autism spectrum disorder (ASD)

Committee opinion: Approved

The following feedback has been supplied by the SRC.

Notes from the Chair:

Approved

Approved documents:

Approved document	Version	Date
SRC_Protocol_18THIN010_v2_23-03-2018	2	23/03/2018
SRC_ response_18THIN010		

We are pleased to inform that you can proceed with the study as this is now approved. IQVIA will let the relevant Ethics committee know this study has been approved by the SRC.

Once the study has been completed and published, it is important for you to inform IQVIA in order for us to advise the SRC and your reference number to be closed.

References to all published studies are added to our website enabling other researchers to become aware of your work. In order to identify your study as using the THIN database, we recommend that you include the words "The Health Improvement Network (THIN)" within your title. Copies of publication(s), where available, will be appreciated.

I wish you and your team all the best with the study progression.

Mustafa Dungarwalla
Consultant

Appendix (5): ASD Read code list

Read code	Description
Eu84z11	Autistic spectrum disorder
E140.12	Autism
Eu84500	Asperger's syndrome
Eu84011	autistic disorder
E140.00	infantile autism
Eu84000	childhood autism
Eu84.00	pervasive developmental disorders
Eu84100	atypical autism
E140.13	childhood autism
E140000	active infantile autism
Eu84111	atypical childhood psychosis
Eu84z00	pervasive developmental disorder, unspecified
E140.11	kanner's syndrome
E140100	residual infantile autism
E140z00	infantile autism nos
E141.00	disintegrative psychosis
E141.11	heller's syndrome
E141000	active disintegrative psychoses
E141100	residual disintegrative psychoses
E141z00	disintegrative psychosis nos
Eu84012	infantile autism
Eu84013	infantile psychosis
Eu84014	kanner's syndrome
Eu84112	mental retardation with autistic features
Eu84300	other childhood disintegrative disorder
Eu84311	dementia infantalis
Eu84312	disintegrative psychosis
Eu84313	heller's syndrome
Eu84314	symbiotic psychosis
Eu84400	overactive disorder assoc mental retard/stereotype movts
Eu84511	autistic psychopathy
Eu84y00	other pervasive developmental disorders

Appendix (6): Neuropsychiatric comorbidities Read codes lists

A. Anxiety

Read code	Description
E201.00	Hysteria
E201000	Hysteria unspecified
E201100	Hysterical blindness
E201200	Hysterical deafness
E201300	Hysterical tremor
E201400	Hysterical paralysis
E201500	Hysterical seizures
E201511	Fit - hysterical
E201600	Other conversion disorder
E201611	Astasia - abasia, hysterical
E201612	Globus hystericus
E201A00	Dissociative reaction unspecified
E201z00	Hysteria NOS
E201z11	Aphonia - hysterical
E201z12	Ataxia - hysterical
E201z13	Ganser's syndrome - hysterical
E202.00	Phobic disorders
E202.11	Social phobic disorders
E202.12	Phobic anxiety
E202000	Phobia unspecified
E202300	Social phobia, fear of eating in public
E202400	Social phobia, fear of public speaking
E202500	Social phobia, fear of public washing
E202600	Acrophobia
E202700	Animal phobia
E202800	Claustrophobia
E202900	Fear of crowds
E202A00	Fear of flying
E202B00	Cancer phobia
E202C00	Dental phobia
E202D00	Fear of death
E202E00	Fear of pregnancy
E202z00	Phobic disorder NOS
E205.00	Neurasthenia - nervous debility
E206.00	Depersonalisation syndrome
E20y.00	Other neurotic disorders
E20y000	Somatization disorder
E20y011	Briquet's disorder
E20y200	Other occupational neurosis
E20yz00	Other neurotic disorder NOS
E20z.00	Neurotic disorder NOS
Eu40100	[X]Social phobias
Eu40111	[X]Anthropophobia
Eu40112	[X]Social neurosis

Eu40200	[X]Specific (isolated) phobias
Eu40211	[X]Acrophobia
Eu40212	[X]Animal phobias
Eu40213	[X]Claustrophobia
Eu40214	[X]Simple phobia
Eu40300	[X]Needle phobia
Eu40z11	[X]Phobia NOS
Eu40z12	[X]Phobic state NOS
Eu41011	[X]Panic attack
Eu41012	[X]Panic state
Eu43.00	[X]Reaction to severe stress, and adjustment disorders
Eu43000	[X]Acute stress reaction
Eu43011	[X]Acute crisis reaction
Eu43012	[X]Acute reaction to stress
Eu43013	[X]Combat fatigue
Eu43014	[X]Crisis state
Eu43015	[X]Psychic shock
Eu43100	[X]Post - traumatic stress disorder
Eu43111	[X]Traumatic neurosis
Eu43200	[X]Adjustment disorders
Eu43211	[X]Culture shock
Eu43212	[X]Grief reaction
Eu43213	[X]Hospitalism in children
Eu43y00	[X]Other reactions to severe stress
Eu43z00	[X]Reaction to severe stress, unspecified
Eu44.00	[X]Dissociative [conversion] disorders
Eu44.11	[X]Conversion hysteria
Eu44.12	[X]Conversion reaction
Eu44.13	[X]Hysteria
Eu44.14	[X]Hysterical psychosis
Eu44000	[X]Dissociative amnesia
Eu44100	[X]Dissociative fugue
Eu44200	[X]Dissociative stupor
Eu44300	[X]Trance and possession disorders
Eu44400	[X]Dissociative motor disorders
Eu44411	[X]Psychogenic aphonia
Eu44412	[X]Psychogenic dysphonia
Eu44700	[X]Mixed dissociative [conversion] disorders
Eu44y00	[X]Other dissociative [conversion] disorders
Eu44y13	[X]Psychogenic confusion
Eu44z00	[X]Dissociative [conversion] disorder, unspecified
Eu45.00	[X]Somatoform disorders
Eu45000	[X]Somatization disorder
Eu45011	[X]Multiple psychosomatic disorder
Eu45012	[X]Briquet's syndrome
Eu45013	[X]Briquet's disorder
Eu45100	[X]Undifferentiated somatoform disorder
Eu45111	[X]Undifferentiated psychosomatic disorder
Eu45215	[X]Nosophobia
Eu45300	[X]Somatoform autonomic dysfunction

Eu45414	[X]Somatoform pain disorder
Eu45500	[X]Globus pharyngeus
Eu45511	[X]Globus hystericus
Eu45y00	[X]Other somatoform disorders
Eu45y12	[X]Globus hystericus
Eu45z00	[X]Somatoform disorder, unspecified
Eu45z11	[X]Psychosomatic disorder NOS
Eu46.00	[X]Other neurotic disorders
Eu46000	[X]Neurasthenia
Eu46y00	[X]Other specified neurotic disorders
Eu46y11	[X]Briquet's disorder
Eu46y12	[X]Dhat syndrome
Eu46z00	[X]Neurotic disorder, unspecified
Eu46z11	[X]Neurosis NOS
Eu51511	[X]Dream anxiety disorder
Eu93000	[X]Separation anxiety disorder of childhood
Eu93100	[X]Phobic anxiety disorder of childhood
Eu93200	[X]Social anxiety disorder of childhood
1B13.12	Anxious
2253	O/E - distressed
1B1..00	General nervous symptoms
1B13.00	Anxiousness
1B13.11	Anxiousness - symptom
R2y2.00	[D]Nervousness
1B13.12	Anxious
1B1T.00	Feeling stressed
1466.00	H/O: anxiety state
173f.00	Anxiety about breathlessness
E200.00	Anxiety states
E200000	Anxiety state unspecified
E200100	Panic disorder
E200111	Panic attack
E200200	Generalised anxiety disorder
E200300	Anxiety with depression
E200400	Chronic anxiety
E200500	Recurrent anxiety
E200z00	Anxiety state NOS
E201B00	Compensation neurosis
E202100	Agoraphobia with panic attacks
E202200	Agoraphobia without mention of panic attacks
E205.11	Nervous exhaustion
E207.00	Hypochondriasis
E20y300	Psychasthenic neurosis
E20z.11	Nervous breakdown
E292000	Separation anxiety disorder
E2D0.00	Disturbance of anxiety and fearfulness childhood/adolescent
E2D0z00	Disturbance anxiety and fearfulness childhood/adolescent NOS
Eu05400	[X]Organic anxiety disorder
Eu34114	[X]Persistant anxiety depression
Eu40.00	[X]Phobic anxiety disorders

Eu40000	[X]Agoraphobia
Eu40011	[X]Agoraphobia without history of panic disorder
Eu40012	[X]Panic disorder with agoraphobia
Eu40y00	[X]Other phobic anxiety disorders
Eu40z00	[X]Phobic anxiety disorder, unspecified
Eu41.00	[X]Other anxiety disorders
Eu41000	[X]Panic disorder [episodic paroxysmal anxiety]
Eu41100	[X]Generalized anxiety disorder
Eu41111	[X]Anxiety neurosis
Eu41112	[X]Anxiety reaction
Eu41113	[X]Anxiety state
Eu41211	[X]Mild anxiety depression
Eu41300	[X]Other mixed anxiety disorders
Eu41y00	[X]Other specified anxiety disorders
Eu41y11	[X]Anxiety hysteria
Eu41z00	[X]Anxiety disorder, unspecified
Eu41z11	[X]Anxiety NOS
Eu45200	[X]Hypochondriacal disorder
Eu45211	[X]Body dysmorphic disorder
Eu45212	[X]Dysmorphophobia nondelusional
Eu45213	[X]Hypochondriacal neurosis
Eu45214	[X]Hypochondriasis
Eu45312	[X]Da Costa's syndrome
Eu45400	[X]Persistent somatoform pain disorder
Eu45411	[X]Psychalgia
Eu46y14	[X]Psychasthenia
Eu46y15	[X]Psychasthenia neurosis

B. Attention deficit hyperactivity disorder (ADHD)

Read code	Description
1P00.00	Hyperactive behaviour
6A61.00	Attention deficit hyperactivity disorder annual review
8BPT.00	Drug therapy ADHD (attention deficit hyperactivity disorder)
8BPT000	Stimulant drug therapy for ADHD
8BPT100	Non-stimulant drug therapy for ADHD
9Ngp.00	On drug ther ADHD (attention deficit hyperactivity disorder)
9Ngp000	On stim drug ther ADHD (attention def hyperactivity disordr)
9Ngp100	On non-stimulant drug therapy for ADHD
9OI8.00	ADHD monitoring invitation first letter
9OI9.00	ADHD monitoring invitation second letter
9OIA.00	ADHD monitoring invitation third letter
E2E0000	Attention deficit without hyperactivity
E2E0100	Attention deficit with hyperactivity
E2E0z00	Child attention deficit disorder NOS
Eu90011	[X]Attention deficit hyperactivity disorder
ZS9..00	Disorders of attention and motor control
ZS91.00	Attention deficit disorder
ZS91.11	ADD - Attention deficit disorder
ZS91.12	[X]Attention deficit disorder

ZS93.00	Deficits in attention motor control and perception
ZS93.11	DAMP - Deficits in attention motor control and perception
Eu90000	[X]Disturbance of activity and attention
E2E..11	Overactive child syndrome
Ry13.00	[D]Overactivity
Eu90.00	[X]Hyperkinetic disorders
E2E..00	Childhood hyperkinetic syndrome
E2E0.00	Child attention deficit disorder

C. Behavioural conduct disorders

Read code	Description
Eu91211	[X]Conduct disorder, group type
Eu90100	[X]Hyperkinetic conduct disorder
Eu91200	[X]Socialized conduct disorder
Eu91111	[X]Conduct disorder, solitary aggressive type
E2C2z00	Socialised conduct disorder NOS
E2C1.00	Nonaggressive unsocial conduct disorder
Eu91100	[X]Unsocialized conduct disorder
E2C2.00	Socialised conduct disorder
E2C0.00	Aggressive unsocial conduct disorder
E2C1z00	Nonaggressive unsocial conduct disorder NOS
E2C0z00	Aggressive unsocial conduct disorder NOS
Eu92000	[X]Depressive conduct disorder
E2E2.00	Hyperkinetic conduct disorder
Eu91z12	[X]Childhood conduct disorder NOS
Eu91.00	[X]Conduct disorders
Eu92y11	[X]Conduct disorder associated with emotional disorder
Eu92y12	[X]Conduct disorder associated with neurotic disorder
Eu91z00	[X]Conduct disorder, unspecified
Eu91y00	[X]Other conduct disorders
Eu90111	[X]Hyperkinetic disorder associated with conduct disorder
ZVu6K00	[X]Personal history/other mental and behavioural disorders
Eu...00	[X]Mental and behavioural disorders
Eu91z11	[X]Childhood behavioural disorder NOS
Eu1..00	[X]Mental and behavioural disorders due to psychoactive subs
E2C..11	Behaviour disorder
Eu06z00	[X]Unspec organ personality behav disorder brain dam dysfunc
Eu06.00	[X]Personality and behav disorder brain dis dam and dysfunct
1B16.11	Agitated - symptom
1469	H/O: behaviour problem
13Z8000	Social adjustment problem
E214100	Obsessional personality
E2Cy.00	Other conduct disturbances
Eu92.00	[X]Mixed disorders of conduct and emotions
Eu9yz00	[X]Unspec behav emotion disorder onst usual childhood adoles
R00zA00	[D]Physical violence
R00zD00	[D]Restlessness and agitation
E213.11	Aggressive personality
E2Dy000	Childhood and adolescent oppositional disorder

ZV40300	[V]Other behavioural problems
E21y500	Immature personality disorder
Eu60311	[X]Aggressive personality disorder
Eu9..00	[X]Behavioural/emotional disords onset childhood/adolescence
ZV40.11	[V]Behavioural problems
E211100	Hypomanic personality disorder
E213.00	Explosive personality disorder
E217.00	Antisocial or sociopathic personality disorder
Eu42100	[X]Predominantly compulsive acts [obsessional rituals]
Eu91112	[X]Unsocialised aggressive disorder
R00z800	[D]Irritability and anger
13Z4C00	Behavioural problems at school
225A.00	O/E - irritable
E21z.00	Personality disorder NOS
Eu60014	[X]Sensitive paranoid personality disorder
2256	O/E - agitated
1B15.11	Irritable - symptom
E21..00	Personality disorders
1B16.00	Agitated
E2C..00	Disturbance of conduct NEC
Eu62100	[X]Enduring personality change after psychiatric illness
E21y200	Borderline personality disorder
E2C1200	Tantrums
28C..00	O/E - embarrassing behaviour
Eu60214	[X]Psychopathic personality disorder
Eu60300	[X]Emotionally unstable personality disorder
Eu94.00	[X]Disorder social funct onset specific childhood/adolesc
3AB3.00	Change in behaviour
1P5..00	Aggressive behaviour
1B1X.00	Behavioural problem
1P50.00	Violent acts towards others

D. Depression

Read code	Description
E112z00	Single major depressive episode NOS
Eu32.11	[X]Single episode of depressive reaction
E112200	Single major depressive episode, moderate
E112300	Single major depressive episode, severe, without psychosis
E2B..00	Depressive disorder NEC
Eu32z11	[X]Depression NOS
E112.14	Endogenous depression
E200300	Anxiety with depression
E135.00	Agitated depression
E204.00	Neurotic depression reactive type
E290.00	Brief depressive reaction
2257	O/E - depressed
1B17.00	Depressed
1465	H/O: depression
Eu32z00	[X]Depressive episode, unspecified

Eu32z12	[X]Depressive disorder NOS
Eu33.00	[X]Recurrent depressive disorder
E2B1.00	Chronic depression
Eu32.00	[X]Depressive episode
1B17.11	C/O - feeling depressed
E112.11	Agitated depression
Eu32z14	[X] Reactive depression NOS
E113700	Recurrent depression
E112.12	Endogenous depression first episode
Eu32y00	[X]Other depressive episodes
E113.11	Endogenous depression - recurrent
E112.13	Endogenous depression first episode
Eu32.13	[X]Single episode of reactive depression
Eu34113	[X]Neurotic depression
Eu41211	[X]Mild anxiety depression
Eu34100	[X]Dysthymia
Eu34111	[X]Depressive neurosis
Eu33.15	[X]SAD - Seasonal affective disorder
Eu33.11	[X]Recurrent episodes of depressive reaction
Eu33.13	[X]Recurrent episodes of reactive depression
E11z200	Masked depression
Eu32100	[X]Moderate depressive episode
Eu32200	[X]Severe depressive episode without psychotic symptoms
1B1U.00	Symptoms of depression
1BT..00	Depressed mood
1B1U.11	Depressive symptoms
E211200	Depressive personality disorder
E112.00	Single major depressive episode
Eu32400	[X]Mild depression
Eu32y11	[X]Atypical depression
E118.00	Seasonal affective disorder
Eu33212	[X]Major depression, recurrent without psychotic symptoms
Eu33211	[X]Endogenous depression without psychotic symptoms
Eu32000	[X]Mild depressive episode
Eu41200	[X]Mixed anxiety and depressive disorder
9H91.00	Depression medication review
9H90.00	Depression annual review
E113200	Recurrent major depressive episodes, moderate
E113.00	Recurrent major depressive episode
Eu34114	[X]Persistant anxiety depression
E112100	Single major depressive episode, mild
E291.00	Prolonged depressive reaction
Eu32.12	[X]Single episode of psychogenic depression
Eu3y111	[X]Recurrent brief depressive episodes
Eu33.12	[X]Recurrent episodes of psychogenic depression
Eu33400	[X]Recurrent depressive disorder, currently in remission
Eu32212	[X]Single episode major depression w'out psychotic symptoms
E113z00	Recurrent major depressive episode NOS
E113300	Recurrent major depressive episodes, severe, no psychosis
E11y200	Atypical depressive disorder

Eu32z13	[X]Prolonged single episode of reactive depression
Eu33.14	[X]Seasonal depressive disorder
E113100	Recurrent major depressive episodes, mild
Eu33100	[X]Recurrent depressive disorder, current episode moderate
Eu33000	[X]Recurrent depressive disorder, current episode mild
9H92.00	Depression interim review
8CAa.00	Patient given advice about management of depression
8HHq.00	Referral for guided self-help for depression
Eu92000	[X]Depressive conduct disorder
Eu33200	[X]Recurr depress disorder cur epi severe without psyc sympt
E112000	Single major depressive episode, unspecified
E113000	Recurrent major depressive episodes, unspecified
E290z00	Brief depressive reaction NOS
Eu33z11	[X]Monopolar depression NOS
Eu32211	[X]Single episode agitated depressn w'out psychotic symptoms
9HA0.00	On depression register
E112500	Single major depressive episode, partial or unspec remission
Eu33z00	[X]Recurrent depressive disorder, unspecified
Eu33y00	[X]Other recurrent depressive disorders
E113600	Recurrent major depressive episodes, in full remission
E113500	Recurrent major depressive episodes,partial/unspec remission
Eu32y12	[X]Single episode of masked depression NOS
E112600	Single major depressive episode, in full remission
Eu32213	[X]Single episode vital depression w'out psychotic symptoms
Eu33214	[X]Vital depression, recurrent without psychotic symptoms
E113400	Recurrent major depressive episodes, severe, with psychosis
Eu32300	[X]Severe depressive episode with psychotic symptoms
Eu33311	[X]Endogenous depression with psychotic symptoms
Eu33313	[X]Recurr severe episodes/major depression+psychotic symptom
Eu33314	[X]Recurr severe episodes/psychogenic depressive psychosis
Eu33315	[X]Recurrent severe episodes of psychotic depression
Eu32500	[X]Major depression, mild
Eu32600	[X]Major depression, moderately severe
Eu32700	[X]Major depression, severe without psychotic symptoms
Eu32800	[X]Major depression, severe with psychotic symptoms
Eu32A00	[X]Recurr major depr ep, severe with psych, psych in remiss
Eu33213	[X]Manic-depress psychosis,depressd,no psychotic symptoms
Eu33312	[X]Manic-depress psychosis,depressed type+psychotic symptoms
Eu33316	[X]Recurrent severe episodes/reactive depressive psychosis
Eu31.13	[X]Manic-depressive reaction
Eu31.11	[X]Manic-depressive illness
E11..12	Depressive psychoses
E130.11	Psychotic reactive depression
E115.11	Manic-depressive - now depressed

E. Epilepsy

Read code	Description
F25..00	Epilepsy
F251000	Grand mal (major) epilepsy

F250011	Epileptic absences
F250000	Petit mal (minor) epilepsy
F254000	Temporal lobe epilepsy
F25z.11	Fit (in known epileptic) NOS
F253.11	Status epilepticus
667B.00	Nocturnal epilepsy
F251300	Epileptic seizures - myoclonic
F253.00	Grand mal status
F251400	Epileptic seizures - tonic
F255011	Focal epilepsy
F25X.00	Status epilepticus, unspecified
Eu05y11	[X]Epileptic psychosis NOS
F251500	Tonic-clonic epilepsy
2126000	Epilepsy resolved
F255000	Jacksonian, focal or motor epilepsy
F25z.00	Epilepsy NOS
F252.00	Petit mal status
F25y200	Locl-rlt(foc)(part)idiop epilep&epilptic syn seiz locl onset
F25yz00	Other forms of epilepsy NOS
F250.00	Generalised nonconvulsive epilepsy
F254500	Complex partial epileptic seizure
212J.00	Epilepsy resolved
F25y400	Benign Rolandic epilepsy
F251011	Tonic-clonic epilepsy
F254100	Psychomotor epilepsy
F250200	Epileptic seizures - atonic
F25y300	Complex partial status epilepticus
F255.00	Partial epilepsy without impairment of consciousness
F251.00	Generalised convulsive epilepsy
F255y00	Partial epilepsy without impairment of consciousness OS
F25F.00	Photosensitive epilepsy
F250300	Epileptic seizures - akinetic
Eu05212	[X]Schizophrenia-like psychosis in epilepsy
F254z00	Partial epilepsy with impairment of consciousness NOS
F254.00	Partial epilepsy with impairment of consciousness
F254400	Epileptic automatism
F250500	Lennox-Gastaut syndrome
F254200	Psychosensory epilepsy
F255200	Somatosensory epilepsy
F132100	Progressive myoclonic epilepsy
F25y.00	Other forms of epilepsy
1B1W.00	Transient epileptic amnesia
F255600	Simple partial epileptic seizure
F251z00	Generalised convulsive epilepsy NOS
Eu80300	[X]Acquired aphasia with epilepsy [Landau - Kleffner]
F250z00	Generalised nonconvulsive epilepsy NOS
F251y00	Other specified generalised convulsive epilepsy
F255100	Sensory induced epilepsy
Eu06013	[X]Limbic epilepsy personality
F25y100	Gelastic epilepsy

F25y000	Cursive (running) epilepsy
F254300	Limbic system epilepsy
F255400	Visual reflex epilepsy
F25D.00	Menstrual epilepsy
F250y00	Other specified generalised nonconvulsive epilepsy
F25E.00	Stress-induced epilepsy
F255012	Motor epilepsy
F255500	Unilateral epilepsy
F257.00	Kojevnikov's epilepsy
F255300	Visceral reflex epilepsy
F25A.00	Juvenile myoclonic epilepsy
F250400	Juvenile absence epilepsy
F255311	Partial epilepsy with autonomic symptoms
1473	H/O: epilepsy

F. Intellectual disabilities

Read code	Description
Eu84311	[X]Dementia infantalis
C03..11	Cretinism
C031.00	Goitrous cretin
C03z.12	Cretinism
C372z00	Other disorder of purine or pyrimidine metabolism NOS
E141.00	Disintegrative psychosis
E141.11	Heller’s syndrome
E141000	Active disintegrative psychoses
E141100	Residual disintegrative psychoses
E141z00	Disintegrative psychosis NOS
E3..00	Mental retardation
E30..00	Mild mental retardation, IQ in range 50–70
E30..11	Educationally subnormal
E30..12	Feeble-minded
E30..13	Moron
E31..00	Other specified mental retardation
E310.00	Moderate mental retardation, IQ in range 35–49
E310.11	Imbecile
E311.00	Severe mental retardation, IQ in range 20–34
E312.00	Profound mental retardation with IQ less than 20
E312.11	Idiocy
E31z.00	Other specified mental retardation NOS
E3y..00	Other specified mental retardation
E3z..00	Mental retardation NOS
Eu7..00	[X]Mental retardation
Eu70.00	[X]Mild mental retardation
Eu70.11	[X]Feeble-mindedness
Eu70.12	[X]Mild mental subnormality
Eu70000	[X]Mld mental retard with statement no or min impairm behav
Eu70100	[X]Mld mental retard sig impairment behav req attent/treatmt
Eu70y00	[X]Mild mental retardation, other impairments of behaviour
Eu70z00	[X]Mild mental retardation without mention impairment behav

Eu71.00	[X]Moderate mental retardation
Eu71.11	[X]Moderate mental subnormality
Eu71000	[X]Mod mental retard with statement no or min impairm behav
Eu71100	[X]Mod mental retard sig impairment behav req attent/treatmt
Eu71y00	[X]Mod retard oth behav impair
Eu71z00	[X]Mod mental retardation without mention impairment behav
Eu72.00	[X]Severe mental retardation
Eu72.11	[X]Severe mental subnormality
Eu72000	[X]Sev mental retard with statement no or min impairm behav
Eu72100	[X]Sev mental retard sig impairment behav req attent/treatmt
Eu72y00	[X]Severe mental retardation, other impairments of behaviour
Eu72z00	[X]Sev mental retardation without mention impairment behav
Eu73.00	[X]Profound mental retardation
Eu73.11	[X]Profound mental subnormality
Eu73000	[X]Profound ment retrd wth statement no or min impairm behav
Eu73100	[X]Profound ment retard sig impairmnt behav req attent/treat
Eu73y00	[X]Profound mental retardation, other impairments of behavr
Eu73z00	[X]Prfnd mental retardation without mention impairment behav
Eu7y.00	[X]Other mental retardation
Eu7y000	[X]Oth mental retard with statement no or min impairm behav
Eu7y100	[X]Oth mental retard sig impairment behav req attent/treatmt
Eu7yy00	[X]Other mental retardation, other impairments of behaviour
Eu7yz00	[X]Other mental retardation without mention impairment behav
Eu7z.00	[X]Unspecified mental retardation
Eu7z.11	[X]Mental deficiency NOS
Eu7z.12	[X]Mental subnormality NOS
Eu7z000	[X]Unsp mental retard with statement no or min impairm behav
Eu7z100	[X]Unsp mentl retard sig impairment behav req attent/treatmt
Eu7zy00	[X]Unspecified mental retardatn, other impairments of behav
Eu7zz00	[X]Unsp mental retardation without mention impairment behav
Eu81400	[X]Moderate learning disability
Eu81500	[X]Severe learning disability
Eu81600	[X]Mild learning disability
Eu81700	[X]Profound learning disability
Eu81z00	[X]Developmental disorder of scholastic skills, unspecified
Eu81z11	[X]Learning disability NOS
Eu81z12	[X]Learning disorder NOS
Eu81z13	[X]Learn acquisition disab NOS
Eu84112	[X]Mental retardation with autistic features
Eu84200	[X]Rett's syndrome
Eu84300	[X]Other childhood disintegrative disorder
Eu84312	[X]Disintegrative psychosis
Eu84313	[X]Heller's syndrome
Eu84400	[X]Overactive disorder assoc mental retard/stereotype movts
PJ0..00	Down's syndrome – trisomy 21
PJ0..11	Mongolism
PJ0..12	Trisomy 21
PJ0..13	Trisomy 22
PJ00.00	Trisomy 21, meiotic nondisjunction
PJ01.11	Trisomy 21, mitotic nondisjunction

PJ02.00	Trisomy 21, translocation
PJ02.11	Partial trisomy 21 in Down's syndrome
PJ0z.00	Down's syndrome NOS
PJ0z.11	Trisomy 21 NOS
PJ1..00	Patau's syndrome – trisomy 13
PJ10.00	Trisomy 13, meiotic nondisjunction
PJ11.00	Trisomy 13, mosaicism
PJ11.11	Trisomy 13, mitotic nondisjunction
PJ12.00	Trisomy 13, translocation
PJ12.11	Partial trisomy 13 in Patau's syndrome
PJ1z.00	Patau's syndrome NOS
PJ1z.11	Trisomy 13 NOS
PJ2..00	Edward's syndrome – trisomy 18
PJ20.00	Trisomy 18, meiotic nondisjunction
PJ21.00	Trisomy 18, mosaicism
PJ21.11	Trisomy 18, mitotic nondisjunction
PJ22.00	Trisomy 18, translocation
PJ22.11	Partial trisomy 18 in Edward's syndrome
PJ2z.00	Edward's syndrome NOS
PJ2z.11	TRISOMY 18 NOS
PJ30.00	Antimongolism syndrome
PJ30.11	Deletion of long arm of chromosome 21
PJ31.00	Cri-du-chat syndrome
PJ31.11	Deletion of short arm of chromosome 5
PJ32.00	Deletion of short arm of chromosome 4
PJ32.11	Wolff – Hirschorn syndrome
PJ33100	Deletion of long arm of chromosome 18
PJ33111	18p- syndrome
PJ33200	Deletion of short arm of chromosome 18
PJ33211	18q- syndrome
PJ33300	Smith-Magenis syndrome
PJ33400	Jacobsen syndrome
PJ33500	Greig cephalopolysyndactyly syndrome
PJ33700	3p deletion syndrome
PJ33800	Chromosome 4q deletion syndrome
PJ33900	Langer-Giedion syndrome
PJ33A00	Kleefstra syndrome
PJ3z.00	Monosomies and deletions from the autosomes NOS
PJ50.00	Whole chromosome trisomy syndromes
PJ50000	Trisomy 6
PJ50100	Trisomy 7
PJ50200	Trisomy 8
PJ50300	Trisomy 9
PJ50400	Trisomy 10
PJ50500	Trisomy 11
PJ50600	Trisomy 12
PJ50700	Other trisomy C syndromes
PJ50800	Trisomy 22
PJ50w00	Whole chromosome trisomy, meitotic nondisjunction
PJ50x00	Whole chromosome trisomy, mosaicism

PJ50x11	Whole chromosome trisomy, mitotic nondisjunction
PJ50y00	Other specified whole chromosome trisomy syndrome
PJ50z00	Whole chromosome trisomy syndrome NOS
PJ51.00	Partial trisomy syndromes
PJ51000	Major partial trisomy
PJ51100	Minor partial trisomy
PJ51200	10q partial trisomy syndrome
PJ51300	Trisomy 4p syndrome
PJ51400	Trisomy 9p syndrome
PJ51500	15q partial trisomy syndrome
PJ51z00	Partial trisomy syndrome NOS
PJ52.00	Trisomies of autosomes NEC
PJ52z00	Trisomy of autosomes NEC NOS
PJ9..00	Mowat-Wilson syndrome
PJyy200	Fragile X chromosome
PJyy400	Fragile X syndrome
PKy0.11	Prader-Willi Syndrome
PKy0.12	Prader-Willi syndrome
PKy4.00	William syndrome
PKy9300	Prader – Willi syndrome
Pyu0200	[X]Other reduction deformities of brain
PyuA000	[X]Oth specif trisomies & partial trisomies of autosomes
R034y11	[D]Global retardation
ZS34.00	Developmental disorder of scholastic skill
ZS34.11	Learning disability
Z7CBE00	Intellectual functioning disability
13VC900	Intellectual development disorder of unknown aetiology
13Z3.00	Low I.Q.
6664.00	Mental handicap problem
69DB.00	Learning disability health exam
918e.00	On learning disability register
9HB..00	Learning disabilities administration status
9HB0.00	Learning disabilities health action plan declined
9HB1.00	Learning disabilities health action plan offered
9HB2.00	Learning disabilities health action plan reviewed
9HB3.00	Learning disabilities health assessment
9HB4.00	Learning disabilities health action plan completed
9HB5.00	Learning disabilities annual health assessment
9HB6.00	Learning disabilities annual health assessment declined
9HB6.11	Learning disabilities annual health check declined
9HB7.00	Did not attend learning disabilities annual health assessment
9HB7.11	Did not attend learning disabilities annual health check
9hL..00	Exception reporting: learning disability quality indicators
9hL0.00	Exc learn disability quality indicators: informed dissent
9hL1.00	Exc learn disability quality indicators: patient unsuitable
9mA..00	Learning disability annual health check invitation
9mA0.00	Learning disability annual health check verbal invitation
9mA1.00	Learning disability annual health check telephone invitation
9mA2.00	Learning disability annual health check letter invitation
9mA2000	Learning disability annual health check invitation 1st letter

9mA2100	Learning disability annual health check invitation 2nd letter
9mA2200	Learning disability annual health check invitation 3rd letter
C372.11	Lesch – Nyhan syndrome
C372000	Hypoxanthine-guanine-phosphoribosyltransferase deficiency
C372011	Lesch – Nyhan syndrome
C372300	Lesch-Nyhan syndrome

G. Schizophrenia

Read code	Description
E10y.11	Cenesthopathic schizophrenia
Eu20z00	[X]Schizophrenia, unspecified
E103100	Subchronic paranoid schizophrenia
Eu25011	[X]Schizoaffective psychosis, manic type
Eu25100	[X]Schizoaffective disorder, depressive type
E107200	Chronic schizo-affective schizophrenia
Eu25211	[X]Cyclic schizophrenia
E103400	Acute exacerbation of chronic paranoid schizophrenia
Eu20500	[X]Residual schizophrenia
E107.11	Cyclic schizophrenia
Eu20311	[X]Atypical schizophrenia
Eu21.16	[X]Pseudoneurotic schizophrenia
E10z.00	Schizophrenia NOS
Eu25z00	[X]Schizoaffective disorder, unspecified
E105200	Chronic latent schizophrenia
E103300	Acute exacerbation of subchronic paranoid schizophrenia
Eu23214	[X]Schizophrenic reaction
Eu20y00	[X]Other schizophrenia
Eu21.00	[X]Schizotypal disorder
E100000	Unspecified schizophrenia
1464	H/O: schizophrenia
Eu20600	[X]Simple schizophrenia
E107000	Unspecified schizo-affective schizophrenia
E102000	Unspecified catatonic schizophrenia
Eu20011	[X]Paraphrenic schizophrenia
E101000	Unspecified hebephrenic schizophrenia
Eu25y00	[X]Other schizoaffective disorders
ZV11000	[V]Personal history of schizophrenia
Eu25.00	[X]Schizoaffective disorders
E10yz00	Other schizophrenia NOS
Eu25000	[X]Schizoaffective disorder, manic type
Eu25z11	[X]Schizoaffective psychosis NOS
E105500	Latent schizophrenia in remission
Eu25012	[X]Schizophreniform psychosis, manic type
E103200	Chronic paranoid schizophrenia
E100z00	Simple schizophrenia NOS
E101.00	Hebephrenic schizophrenia
E103.00	Paranoid schizophrenia
E106.00	Residual schizophrenia
E102100	Subchronic catatonic schizophrenia

E105z00	Latent schizophrenia NOS
Eu23112	[X]Cycloid psychosis with symptoms of schizophrenia
E10y000	Atypical schizophrenia
Eu84512	[X]Schizoid disorder of childhood
Eu20000	[X]Paranoid schizophrenia
E107100	Subchronic schizo-affective schizophrenia
Eu21.13	[X]Latent schizophrenia
Eu21.14	[X]Prepsychotic schizophrenia
Eu21.17	[X]Pseudopsychopathic schizophrenia
E102z00	Catatonic schizophrenia NOS
E100400	Acute exacerbation of chronic schizophrenia
13L3.12	Schizophrenic child
Eu20.00	[X]Schizophrenia
Eu2..00	[X]Schizophrenia, schizotypal and delusional disorders
E14z.11	Childhood schizophrenia NOS
Eu20y13	[X]Schizophrenifrm psychos NOS
Eu20y12	[X]Schizophreniform disord NOS
E103000	Unspecified paranoid schizophrenia
Eu20213	[X]Schizophrenic catatonia
E10..00	Schizophrenic disorders
E100.00	Simple schizophrenia
E102.00	Catatonic schizophrenia
E101z00	Hebephrenic schizophrenia NOS
E101500	Hebephrenic schizophrenia in remission
E103z00	Paranoid schizophrenia NOS
Eu20100	[X]Hebephrenic schizophrenia
E105.00	Latent schizophrenia
E102400	Acute exacerbation of chronic catatonic schizophrenia
E100200	Chronic schizophrenic
E100500	Schizophrenia in remission
E107z00	Schizo-affective schizophrenia NOS
E107500	Schizo-affective schizophrenia in remission
E107.00	Schizo-affective schizophrenia
Eu25212	[X]Mixed schizophrenic and affective psychosis
E101400	Acute exacerbation of chronic hebephrenic schizophrenia
E10y.00	Other schizophrenia
Eu60100	[X]Schizoid personality disorder
E100100	Subchronic schizophrenia
Eu20200	[X]Catatonic schizophrenia
E100.11	Schizophrenia simplex
Eu20111	[X]Disorganised schizophrenia
E102500	Catatonic schizophrenia in remission
E100300	Acute exacerbation of subchronic schizophrenia
Eu25112	[X]Schizophreniform psychosis, depressive type
Eu25200	[X]Schizoaffective disorder, mixed type
E105000	Unspecified latent schizophrenia
Eu20212	[X]Schizophrenic catalepsy
E107400	Acute exacerbation of chronic schizo-affective schizophrenia
E103500	Paranoid schizophrenia in remission
E104.00	Acute schizophrenic episode

Eu20214	[X]Schizophrenic flexibilatis cerea
Eu20511	[X]Chronic undifferentiated schizophrenia
Eu20400	[X]Post-schizophrenic depression
Eu20300	[X]Undifferentiated schizophrenia
Eu23211	[X]Brief schizophreniform disorder
Eu60100	Schizoid personality disorder
Eu23200	[X]Acute schizophrenia-like psychotic disorder

H. Sleep disorders

Read code	Description
9Ngt.00	On melatonin for sleep disorder
E274100	Transient insomnia
E274111	Insomnia NOS
E274200	Persistent insomnia
E274300	Transient hypersomnia
E274311	Hypersomnia NOS
E274400	Persistent hypersomnia
E274700	Somnambulism - sleep walking
E274800	Night terrors
E274900	Nightmares
E274A00	Sleep drunkenness
E274B00	Repeated rapid eye movement sleep interruptions
E274C00	Other sleep stage or arousal dysfunction
E274D00	Repetitive intrusions of sleep
E274D11	Restless sleep
E274E00	"Short-sleeper"
E274F00	Inversion of sleep rhythm
Eu51300	[X]Sleepwalking
Eu51400	[X]Sleep terrors
Eu51500	[X]Nightmares
Eu51511	[X]Dream anxiety disorder
Eu51z11	[X]Emotional sleep disorder NOS
Fy0..00	Sleep disorders
Fy00.00	Disorders of initiating and maintaining sleep
Fy01.00	Disorders of excessive somnolence
Fy02.00	Disorders of the sleep-wake schedule
Fy03.00	Sleep apnoea
Fy03.11	Obstructive sleep apnoea
Fy04.00	Sleep-related respiratory failure
Fy04.11	Ondine's curse
Fy05.00	Nocturnal sleep-related eating disorder
Fy06.00	Kleine-Levin syndrome
Fyu5800	[X]Other sleep disorders

I. Tic disorders

Read code	Description
E272200	Chronic motor tic disorder
Eu95000	[X]Transient tic disorder

Eu95100	[X]Chronic motor or vocal tic disorder
Eu95200	[X]Comb vocal multiple motor tic disorder - de la Tourette
E272300	Gilles de la Tourette's disorder
Eu95z00	[X]Tic disorder, unspecified
Eu95.00	[X]Tic disorders
Eu95y00	[X]Other tic disorders
E272000	Tic disorder unspecified
1B24.00	Has a tic
1B24.11	Tic - symptom
E272.00	Tics

Appendix (7): Psychotropic medication lists

Antidepressants	Antiepileptics	Antipsychotics	Antipsychotic depots	Anxiolytics	Hypnotics	Stimulants
Agomelatine	Acetazolamide	Amisulpride	Aripiprazole	Alprazolam	Chloral hydrate	Amphetamine
Amitriptyline	Beclamide	Aripiprazole	Flupentixol	Bromazepam	Clomethiazole	Ascorbic ac./cyanocob/ fencamfamin hyd/
Amoxapine	Brivaracetam	Asenapine	Fluphenazine	Buspirone	Cloral betaine	Atomoxetine
Bolvidon	Carbamazepine	Benperidol	Fluspirilene	Chlordiazepoxide	Clorazepate	Caffeine
Butriptyline	Clobazam	Chlorpromazine	Haloperidol	Chlordiazepozide	Dichloralphenazone	Dexamfetamine
Citalopram	Clonazepam	Chlorprothixene	Olanzapine	Chlormezanone	Flunitrazepam	Dexamphetamine
Clomipramine	Diazepam	Clozapine	Paliperidone	Clobazam	Flurazepam	Dexbrompheniramine/ pseudoephedrine
Desipramine	Epanutin	Dartalan	Pipotiazine	Clorazepate	Lormetazepam	Dexedrine
Dosulepin	Eslicarbazepine	Droperidol	Zuclopenthixol	Diazepam	Mandrax tab	Guanfacine
Dothiepin	Ethosuximide	Flupentixol		Generic Kalms	Melatonin	Lisdexamfetamine
Doxepin	Fosphenytoin	Fluphenazine		Ketazolam	Methyprylone	Methylperidate
Duloxetine	Gabapentin	Haldol		Lorazepam	Nitrados	Methylphenidate
Escitalopram	Gardenal	Haloperidol		Medazepam	Nitrazepam	Modafinil
Fluoxetine	Lacosamide	Levomepromazine		Meprobamate	Promethazine	Nicotin./prolintane hyd/pyridox.hyd/ribo
Fluvoxamine	Lamotrigine	Loxapine		Oxazepam	Sodium oxybate	Pemoline
Imipramine	Levetiracetam	Lurasidone		Prazepam	Temazepam	Prolintane
Iprindole	Mesuximide	Olanzapine		Serenid	Triazolam	Reactivan
Iproniazid	Methsuximide	Oxypertine		Valerian	Triclofos	Ronyl
Isocarboxazid	Methylphenobarbital	Paliperidone			Zaleplon	Sodium oxybate
Lofepramine	Midazolam	Pericyazine			Zolpidem	Tafamidis
L-tryptophan	Ospolot	Perphenazine			Zopiclone	
Maprotiline	Oxcarbazepine	Pimozide				
Merital	Paraldehyde	Promazine				
Mianserin	Paramethadione	Quetiapine				
Mirtazapine	Pentamidine	Remoxipride				
Moclobemide	Perampanel	Risperidone				
Nefazodone	Phenobarbital	Sertindole				
Nomifensine	Phenobarbitone	Sulpiride				

Antidepressant cont.	**Antiepileptic cont.**	
Nortriptyline	Phenytoin	Thioproperazine
Paroxetine	Pregabalin	Thioridazine
Phenelzine	Primidone	Trifluoperazine
Protriptyline	Retigabine	Trifluperidol
Reboxetine	Rufinamide	Zotepine
Sertraline	Sodium valproate	Zuclopenthixol
Sinequan	Stiripentol	
Tofranil	Sulthiame	
Tranylcypromine	Tiagabine	
Trazodone	Topiramate	
Tranylcypromine	Valproic acid	
Trimipramine	Vigabatrin	
Tryptophan	Zarontin	
Venlafaxine	Zonisamide	
Viloxazine		
Zimelidine		

Appendix (8): Psychotropic medication Drug codes list

A. Antidepressants

Drug code	Generic name
82861998	Agomelatine 25mg tablets
82862998	Agomelatine 25mg tablets
99472998	Amitriptyline & chlordiazepoxide 12.5mg+5mg capsules
99824992	Amitriptyline 100 mg tab
94703998	Amitriptyline 10mg / perphenazine 2mg tablets
94077990	Amitriptyline 10mg tablets
96328979	Amitriptyline 10mg tablets
97223998	Amitriptyline 10mg tablets
99861990	Amitriptyline 10mg tablets
99863990	Amitriptyline 10mg tablets
99864990	Amitriptyline 10mg tablets
99866990	Amitriptyline 10mg tablets
99868990	Amitriptyline 10mg tablets
99869990	Amitriptyline 10mg tablets
99870990	Amitriptyline 10mg tablets
99871990	Amitriptyline 10mg tablets
81085998	Amitriptyline 10mg/5ml oral solution
47944978	Amitriptyline 10mg/5ml oral solution sugar free
81084998	Amitriptyline 10mg/5ml oral suspension
92808996	Amitriptyline 10mg/5ml sugar free oral solution
98067988	Amitriptyline 10mg/5ml sugar free oral solution
98128998	Amitriptyline 10mg/5ml sugar free oral solution
96924998	Amitriptyline 10mg/ml injection
94704998	Amitriptyline 12.5mg / chlordiazepoxide 5mg capsules
70290979	Amitriptyline 2.5mg/5ml oral solution
99826992	Amitriptyline 200 mg tab
94704997	Amitriptyline 25mg / chlordiazepoxide 10mg capsules
98343998	Amitriptyline 25mg / chlordiazepoxide 10mg capsules
94703997	Amitriptyline 25mg / Perphenazine 2mg tablets
95574997	Amitriptyline 25mg / Perphenazine 2mg tablets
99017998	Amitriptyline 25mg / Perphenazine 2mg tablets
96925998	Amitriptyline 25mg modified-release capsules
94076990	Amitriptyline 25mg tablets
94771990	Amitriptyline 25mg tablets
96323979	Amitriptyline 25mg tablets
97223997	Amitriptyline 25mg tablets
99861989	Amitriptyline 25mg tablets
99862990	Amitriptyline 25mg tablets
99863989	Amitriptyline 25mg tablets
99864989	Amitriptyline 25mg tablets
99865990	Amitriptyline 25mg tablets
99866989	Amitriptyline 25mg tablets
99867989	Amitriptyline 25mg tablets
99868989	Amitriptyline 25mg tablets
99869988	Amitriptyline 25mg tablets

99870989	Amitriptyline 25mg tablets
99871989	Amitriptyline 25mg tablets
92808997	Amitriptyline 25mg/5ml oral solution sugar free
96891992	Amitriptyline 25mg/5ml oral solution sugar free
98067990	Amitriptyline 25mg/5ml oral solution sugar free
99825992	Amitriptyline 300 mg tab
96925997	Amitriptyline 50mg modified-release capsules
94075990	Amitriptyline 50mg tablets
97223996	Amitriptyline 50mg tablets
99863988	Amitriptyline 50mg tablets
99864988	Amitriptyline 50mg tablets
99866988	Amitriptyline 50mg tablets
99868988	Amitriptyline 50mg tablets
99869989	Amitriptyline 50mg tablets
99870988	Amitriptyline 50mg tablets
99871988	Amitriptyline 50mg tablets
92808998	Amitriptyline 50mg/5ml oral solution sugar free
98067989	Amitriptyline 50mg/5ml oral solution sugar free
81024979	Amitriptyline 5mg/5ml oral suspension
94067992	Amitriptyline 75 mg tab
96925996	Amitriptyline 75mg modified-release capsules
83620998	Amitriptyline hydrochloride & perphenazine 10mg+2mg tablets
99017997	Amitriptyline hydrochloride & perphenazine 10mg+2mg tablets
98129998	Amitriptyline hydrochloride 100mg/10ml injection
98130998	Amitriptyline hydrochloride 10mg tablets
98150998	Amitriptyline hydrochloride 10mg tablets
98138998	Amitriptyline hydrochloride 25mg modified release capsules
98130997	Amitriptyline hydrochloride 25mg tablets
98150997	Amitriptyline hydrochloride 25mg tablets
98138997	Amitriptyline hydrochloride 50mg modified release capsules
98130996	Amitriptyline hydrochloride 50mg tablets
98150996	Amitriptyline hydrochloride 50mg tablets
98129997	Amitriptyline hydrochloride 75mg modified release capsules
94005996	Amoxapine 100mg tablets
94009996	Amoxapine 100mg tablets
94004998	Amoxapine 150mg tablets
94008998	Amoxapine 150mg tablets
99791992	Amoxapine 25 mg tab
94005998	Amoxapine 25mg tablets
94009998	Amoxapine 25mg tablets
92478998	Amoxapine 50mg tablets
94005997	Amoxapine 50mg tablets
94009997	Amoxapine 50mg tablets
94663992	Ascorbic acid/pyridoxine hcl/l-tryptopha 20 mg pow
96987992	Bolvidon 60 mg tab
94688998	Butriptyline 25mg tablets
98134998	Butriptyline 25mg tablets
94688997	Butriptyline 50mg tablets
87251998	Citalopram 10mg tablets
91380997	Citalopram 10mg tablets

91395997	Citalopram 10mg tablets
93948990	Citalopram 10mg tablets
93994990	Citalopram 10mg tablets
94895990	Citalopram 10mg tablets
95271990	Citalopram 10mg tablets
95335990	Citalopram 10mg tablets
95421990	Citalopram 10mg tablets
95633990	Citalopram 10mg tablets
95668990	Citalopram 10mg tablets
95705990	Citalopram 10mg tablets
95995979	Citalopram 10mg tablets
69605979	Citalopram 10mg/5ml oral suspension
69606979	Citalopram 10mg/5ml oral suspension
91380998	Citalopram 20mg tablets
91395998	Citalopram 20mg tablets
93947990	Citalopram 20mg tablets
93996990	Citalopram 20mg tablets
94603990	Citalopram 20mg tablets
94894990	Citalopram 20mg tablets
94937990	Citalopram 20mg tablets
95270990	Citalopram 20mg tablets
95334990	Citalopram 20mg tablets
95420990	Citalopram 20mg tablets
95632990	Citalopram 20mg tablets
95667990	Citalopram 20mg tablets
95704990	Citalopram 20mg tablets
69604979	Citalopram 20mg/5ml oral suspension
91380996	Citalopram 40mg tablets
91395996	Citalopram 40mg tablets
93946990	Citalopram 40mg tablets
94880990	Citalopram 40mg tablets
94893990	Citalopram 40mg tablets
94936990	Citalopram 40mg tablets
95269990	Citalopram 40mg tablets
95333990	Citalopram 40mg tablets
95418990	Citalopram 40mg tablets
95631990	Citalopram 40mg tablets
95666990	Citalopram 40mg tablets
95703990	Citalopram 40mg tablets
95979979	Citalopram 40mg tablets
95984979	Citalopram 40mg tablets
92172998	Citalopram 40mg/ml oral drops sugar free
92174998	Citalopram 40mg/ml oral drops sugar free
96640998	Clomipramine 10mg capsules
97548990	Clomipramine 10mg capsules
98144998	Clomipramine 10mg capsules
98340990	Clomipramine 10mg capsules
99297990	Clomipramine 10mg capsules
97167992	Clomipramine 25 mg tab
96640997	Clomipramine 25mg capsules

96901989	Clomipramine 25mg capsules
97548989	Clomipramine 25mg capsules
97773989	Clomipramine 25mg capsules
98144997	Clomipramine 25mg capsules
98340989	Clomipramine 25mg capsules
99297989	Clomipramine 25mg capsules
96639998	Clomipramine 25mg/5ml oral solution
98143998	Clomipramine 25mg/5ml oral solution
80550979	Clomipramine 25mg/5ml oral suspension
93358992	Clomipramine 50mg capsules
96640996	Clomipramine 50mg capsules
96901988	Clomipramine 50mg capsules
97548988	Clomipramine 50mg capsules
98144996	Clomipramine 50mg capsules
98340988	Clomipramine 50mg capsules
99297988	Clomipramine 50mg capsules
80548979	Clomipramine 50mg/5ml oral solution
83878998	Clomipramine 50mg/5ml oral suspension
96638998	Clomipramine 75mg modified-release tablets
93360992	Clomipramine hydrochloride 10mg capsules
96637998	Clomipramine hydrochloride 25mg/2ml injection
99794992	Clomipramine hydrochloride 25mg/2ml injection
98142998	Clomipramine hydrochloride 75mg modified release tablets
96442998	Desipramine 25mg tablets
98146998	Desipramine hydrochloride 25mg tablets
82640998	Dosulepin 100mg/5ml oral solution
98783990	Dosulepin 25mg Capsule
88906998	Dosulepin 25mg capsules
94801990	Dosulepin 25mg capsules
96158990	Dosulepin 25mg capsules
96282979	Dosulepin 25mg capsules
96311998	Dosulepin 25mg capsules
96467990	Dosulepin 25mg capsules
96868990	Dosulepin 25mg capsules
96964990	Dosulepin 25mg capsules
97722998	Dosulepin 25mg capsules
97762990	Dosulepin 25mg capsules
97818998	Dosulepin 25mg capsules
98126998	Dosulepin 25mg capsules
98351989	Dosulepin 25mg capsules
98563989	Dosulepin 25mg capsules
99614990	Dosulepin 25mg capsules
98327997	Dosulepin 25mg/5ml mixture
80274979	Dosulepin 25mg/5ml oral solution
96311996	Dosulepin 25mg/5ml oral solution sugar free
98078990	Dosulepin 25mg/5ml oral solution sugar free
88906997	Dosulepin 75mg tablets
94800990	Dosulepin 75mg tablets
95247990	Dosulepin 75mg tablets
95248990	Dosulepin 75mg tablets

96311997	Dosulepin 75mg tablets
96868989	Dosulepin 75mg tablets
97722997	Dosulepin 75mg tablets
97762989	Dosulepin 75mg tablets
97818997	Dosulepin 75mg tablets
98126997	Dosulepin 75mg tablets
98351990	Dosulepin 75mg tablets
98563990	Dosulepin 75mg tablets
99614989	Dosulepin 75mg tablets
80278979	Dosulepin 75mg/5ml oral solution
98078989	Dosulepin 75mg/5ml oral solution sugar free
98327998	Dosulepin 75mg/5ml oral solution sugar free
94940992	Dothiepin 100 mg syr
94941992	Dothiepin 25 mg syr
94146992	Dothiepin hcl 100 mg syr
94944992	Dothiepin hcl 25 mg mix
94943992	Dothiepin hcl 25 mg syr
94942992	Dothiepin hcl 50 mg eli
94452992	Dothiepin hcl 75 mg mix
94145992	Dothiepin hcl 75 mg syr
96308998	Doxepin 10mg capsules
98124998	Doxepin 10mg capsules
85172998	Doxepin 25mg capsules
96308997	Doxepin 25mg capsules
98124997	Doxepin 25mg capsules
85171998	Doxepin 50mg capsules
96308996	Doxepin 50mg capsules
98124996	Doxepin 50mg capsules
80210979	Doxepin 50mg/5ml oral solution
96307998	Doxepin 75mg capsules
98123998	Doxepin 75mg capsules
39667978	Duloxetine 30mg gastro-resistant capsules
86997998	Duloxetine 30mg gastro-resistant capsules
86999998	Duloxetine 30mg gastro-resistant capsules
89023979	Duloxetine 30mg gastro-resistant capsules
37600978	Duloxetine 60mg gastro-resistant capsules
51109978	Duloxetine 60mg gastro-resistant capsules
86996998	Duloxetine 60mg gastro-resistant capsules
86998998	Duloxetine 60mg gastro-resistant capsules
88285998	Escitalopram 10mg tablets
89381979	Escitalopram 10mg tablets
89383979	Escitalopram 10mg tablets
91671998	Escitalopram 10mg tablets
85970998	Escitalopram 10mg/ml drops
85971998	Escitalopram 10mg/ml oral drops sugar free
98088998	Escitalopram 20mg tablets
98561998	Escitalopram 20mg tablets
82790998	Escitalopram 20mg/ml oral drops sugar free
82791998	Escitalopram 20mg/ml oral drops sugar free
87662998	Escitalopram 5mg tablets

87663998	Escitalopram 5mg tablets
30932978	Fluoxetine 10mg capsules
82367998	Fluoxetine 10mg tablets
80064979	Fluoxetine 2.5mg/5ml oral solution
80062979	Fluoxetine 2.5mg/5ml oral suspension
90159998	Fluoxetine 20mg capsules
90814998	Fluoxetine 20mg capsules
93066990	Fluoxetine 20mg capsules
93905990	Fluoxetine 20mg capsules
94447998	Fluoxetine 20mg capsules
94490998	Fluoxetine 20mg capsules
95388990	Fluoxetine 20mg capsules
96161979	Fluoxetine 20mg capsules
96162979	Fluoxetine 20mg capsules
96168979	Fluoxetine 20mg capsules
96272990	Fluoxetine 20mg capsules
96281990	Fluoxetine 20mg capsules
96606990	Fluoxetine 20mg capsules
96643990	Fluoxetine 20mg capsules
96644990	Fluoxetine 20mg capsules
96647990	Fluoxetine 20mg capsules
96651990	Fluoxetine 20mg capsules
96654990	Fluoxetine 20mg capsules
96659990	Fluoxetine 20mg capsules
96674990	Fluoxetine 20mg capsules
96709990	Fluoxetine 20mg capsules
96729990	Fluoxetine 20mg capsules
99592998	Fluoxetine 20mg capsules
75904978	Fluoxetine 20mg dispersible tablets sugar free
75905978	Fluoxetine 20mg dispersible tablets sugar free
76398978	Fluoxetine 20mg dispersible tablets sugar free
84403998	Fluoxetine 20mg/5ml oral solution
90766998	Fluoxetine 20mg/5ml oral solution
91923990	Fluoxetine 20mg/5ml oral solution
91928990	Fluoxetine 20mg/5ml oral solution
94447997	Fluoxetine 20mg/5ml oral solution
94490997	Fluoxetine 20mg/5ml oral solution
95426990	Fluoxetine 20mg/5ml oral solution
95813990	Fluoxetine 20mg/5ml oral solution
95820990	Fluoxetine 20mg/5ml oral solution
96155979	Fluoxetine 20mg/5ml oral solution
84436998	Fluoxetine 20mg/5ml oral solution sugar free
30041978	Fluoxetine 30mg capsules
29604978	Fluoxetine 40mg capsules
30444978	Fluoxetine 40mg capsules
94447996	Fluoxetine 60mg capsules
94490996	Fluoxetine 60mg capsules
95610990	Fluoxetine 60mg capsules
96143979	Fluoxetine 60mg capsules
96504997	Flupentixol 1mg tablets

99634997	Flupentixol 1mg tablets
96504998	Flupentixol 500microgram tablets
99634998	Flupentixol 500microgram tablets
97632998	Fluphenazine hydrochloride & nortriptyline 1.5mg+30mg tablets
96499998	Fluphenazine hydrochloride & nortriptyline 500mcg+10mg tablets
97634998	Fluphenazine hydrochloride & nortriptyline 500mcg+10mg tablets
96345989	Fluvoxamine 100mg tablets
96492997	Fluvoxamine 100mg tablets
96493997	Fluvoxamine 100mg tablets
96810989	Fluvoxamine 100mg tablets
96093990	Fluvoxamine 50mg tablets
96492998	Fluvoxamine 50mg tablets
96493998	Fluvoxamine 50mg tablets
96687992	Imipramine 100 mg tab
97112998	Imipramine 10mg tablets
99554990	Imipramine 10mg tablets
99555990	Imipramine 10mg tablets
95155992	Imipramine 25mg tablets
96265979	Imipramine 25mg tablets
97112997	Imipramine 25mg tablets
98140997	Imipramine 25mg tablets
98149990	Imipramine 25mg tablets
99554989	Imipramine 25mg tablets
99555989	Imipramine 25mg tablets
99556989	Imipramine 25mg tablets
96130998	Imipramine 25mg/5ml oral solution
62948979	Imipramine 25mg/5ml oral solution sugar free
82432998	Imipramine 25mg/5ml oral solution sugar free
95156992	Imipramine 50 mg tab
95154992	Imipramine 75 mg tab
97593992	Imipramine hcl 12.5 mg inj
97091998	Imipramine hydrochloride 10mg tablets
98140998	Imipramine hydrochloride 10mg tablets
98140996	Imipramine hydrochloride 25mg/5ml syrup
96108998	Iprindole 15mg tablets
96109998	Iprindole hc 15mg
96109997	Iprindole hc 30mg
96107998	Iproniazid 25mg
99448998	Iproniazid 25mg tablets
96105998	Isocarboxazid 10mg tablets
97169990	Isocarboxazid 10mg tablets
99450998	Isocarboxazid 10mg tablets
95999998	Lofepramine 70mg tablets
96793990	Lofepramine 70mg tablets
96855990	Lofepramine 70mg tablets
96963990	Lofepramine 70mg tablets
97142990	Lofepramine 70mg tablets
97192990	Lofepramine 70mg tablets
97743990	Lofepramine 70mg tablets
97861990	Lofepramine 70mg tablets

98132998	Lofepramine 70mg tablets
67063979	Lofepramine 70mg/5ml oral solution
89205998	Lofepramine 70mg/5ml oral suspension sugar free
95999997	Lofepramine 70mg/5ml oral suspension sugar free
98077990	Lofepramine 70mg/5ml oral suspension sugar free
99937992	L-tryptophan 500 mg cap
95928998	Maprotiline 10mg tablets
95928997	Maprotiline 25mg tablets
95928996	Maprotiline 50mg tablets
95927998	Maprotiline 75mg tablets
97704992	Maprotiline hcl 75 mg tab
98148998	Maprotiline hydrochloride 10mg tablets
98148997	Maprotiline hydrochloride 25mg tablets
98148996	Maprotiline hydrochloride 50mg tablets
98147998	Maprotiline hydrochloride 75mg tablets
94498992	Merital 25 25 mg cap
94234992	Merital 50 50 mg cap
95262992	Merital am 100 mg tab
95809998	Mianserin 10mg tablets
95809997	Mianserin 20mg tablets
99494989	Mianserin 20mg tablets
95809996	Mianserin 30mg tablets
99338998	Mianserin hydrochloride 10mg tablets
99882998	Mianserin hydrochloride 10mg tablets
99338997	Mianserin hydrochloride 20mg tablets
99882997	Mianserin hydrochloride 20mg tablets
99338996	Mianserin hydrochloride 30mg tablets
99882996	Mianserin hydrochloride 30mg tablets
58747979	Mirtazapine 15mg orodispersible tablets
87685998	Mirtazapine 15mg orodispersible tablets
87687998	Mirtazapine 15mg orodispersible tablets
90119979	Mirtazapine 15mg orodispersible tablets
90125979	Mirtazapine 15mg orodispersible tablets
92454990	Mirtazapine 15mg orodispersible tablets
92906990	Mirtazapine 15mg orodispersible tablets
92981990	Mirtazapine 15mg orodispersible tablets
92988990	Mirtazapine 15mg orodispersible tablets
92994990	Mirtazapine 15mg orodispersible tablets
93180990	Mirtazapine 15mg orodispersible tablets
86982998	Mirtazapine 15mg tablets
92814990	Mirtazapine 15mg tablets
94037990	Mirtazapine 15mg tablets
94250990	Mirtazapine 15mg tablets
94401990	Mirtazapine 15mg tablets
87430998	Mirtazapine 15mg/ml oral solution sugar free
94870990	Mirtazapine 15mg/ml oral solution sugar free
87945998	Mirtazapine 30mg orodispersible tablets
87946998	Mirtazapine 30mg orodispersible tablets
90094979	Mirtazapine 30mg orodispersible tablets
90097979	Mirtazapine 30mg orodispersible tablets

90105979	Mirtazapine 30mg orodispersible tablets
92980990	Mirtazapine 30mg orodispersible tablets
88715998	Mirtazapine 30mg tablets
88717998	Mirtazapine 30mg tablets
94126990	Mirtazapine 30mg tablets
94611990	Mirtazapine 30mg tablets
94773990	Mirtazapine 30mg tablets
94797990	Mirtazapine 30mg tablets
94847990	Mirtazapine 30mg tablets
95949979	Mirtazapine 30mg tablets
87684998	Mirtazapine 45mg orodispersible tablets
58745979	Mirtazapine 45mg tablets
86981998	Mirtazapine 45mg tablets
87686998	Mirtazapine 45mg tablets
92813990	Mirtazapine 45mg tablets
92903990	Mirtazapine 45mg tablets
92979990	Mirtazapine 45mg tablets
92986990	Mirtazapine 45mg tablets
92992990	Mirtazapine 45mg tablets
93178990	Mirtazapine 45mg tablets
94035990	Mirtazapine 45mg tablets
94400990	Mirtazapine 45mg tablets
93749998	Moclobemide 150mg tablets
93759998	Moclobemide 150mg tablets
96061990	Moclobemide 150mg tablets
96199979	Moclobemide 150mg tablets
93749997	Moclobemide 300mg tablets
93759997	Moclobemide 300mg tablets
91361998	Nefazodone 100mg tablets
91362998	Nefazodone 100mg tablets
91361997	Nefazodone 200mg tablets
91362997	Nefazodone 200mg tablets
91362996	Nefazodone hydrochloride 50mg+100mg+200mg tablet pack
91361996	Nefazodone starter pack
97807992	Nomifensine hydrogen maleate 25 mg cap
96365992	Nomifensine hydrogen maleate 50 mg cap
94249992	Nortriptyline 10 mg eli
94630998	Nortriptyline 10mg / fluphenazine 500microgram tablets
95695998	Nortriptyline 10mg capsule
92015990	Nortriptyline 10mg tablets
95696998	Nortriptyline 10mg tablets
96248979	Nortriptyline 10mg tablets
98152998	Nortriptyline 10mg tablets
95695996	Nortriptyline 10mg/5ml liquid
64091979	Nortriptyline 10mg/5ml oral suspension
95695997	Nortriptyline 25mg capsule
92014990	Nortriptyline 25mg tablets
95696997	Nortriptyline 25mg tablets
96244979	Nortriptyline 25mg tablets
98152997	Nortriptyline 25mg tablets

94630997	Nortriptyline 30mg / fluphenazine 1.5mg tablets
98154998	Nortriptyline hydrochloride 10mg capsules
98154996	Nortriptyline hydrochloride 10mg/5ml liquid
98154997	Nortriptyline hydrochloride 25mg capsules
54494979	Paroxetine 10mg tablets
54495979	Paroxetine 10mg tablets
84807998	Paroxetine 10mg tablets
85382998	Paroxetine 10mg tablets
66539979	Paroxetine 10mg/5ml oral suspension
66541979	Paroxetine 10mg/5ml oral suspension sugar free
93489996	Paroxetine 10mg/5ml oral suspension sugar free
93490996	Paroxetine 10mg/5ml oral suspension sugar free
96068979	Paroxetine 10mg/5ml oral suspension sugar free
96070979	Paroxetine 10mg/5ml oral suspension sugar free
93489998	Paroxetine 20mg tablets
93490998	Paroxetine 20mg tablets
95051990	Paroxetine 20mg tablets
95332990	Paroxetine 20mg tablets
95350990	Paroxetine 20mg tablets
95578990	Paroxetine 20mg tablets
96087990	Paroxetine 20mg tablets
96098979	Paroxetine 20mg tablets
93487990	Paroxetine 30mg tablets
93489997	Paroxetine 30mg tablets
93490997	Paroxetine 30mg tablets
94852990	Paroxetine 30mg tablets
95007990	Paroxetine 30mg tablets
95028990	Paroxetine 30mg tablets
96082979	Paroxetine 30mg tablets
29586978	Paroxetine 40mg tablets
95574998	Perphenazine 2mg with amitriptyline 10mg tablet
95560998	Phenelzine 15mg tablets
99377998	Phenelzine 15mg tablets
95372997	Protriptyline 10mg tablet
95372998	Protriptyline 5mg tablet
90000979	Protriptyline 5mg tablets
96416992	Protriptyline hcl 10 mg tab
97505998	Protriptyline hydrochloride 10mg tablets
97507998	Protriptyline hydrochloride 5mg tablets
88836998	Reboxetine 4mg tablets
88838998	Reboxetine 4mg tablets
52706979	Sertraline 100mg tablets
60187979	Sertraline 100mg tablets
92729990	Sertraline 100mg tablets
93173997	Sertraline 100mg tablets
93174997	Sertraline 100mg tablets
93732990	Sertraline 100mg tablets
93752990	Sertraline 100mg tablets
93842990	Sertraline 100mg tablets
96114979	Sertraline 100mg tablets

96118979	Sertraline 100mg tablets
79261979	Sertraline 100mg/5ml oral suspension
66189979	Sertraline 12.5mg/5ml oral suspension
66187979	Sertraline 150mg/5ml oral suspension
66185979	Sertraline 20mg/5ml oral suspension
66183979	Sertraline 25mg/5ml oral suspension
60188979	Sertraline 50mg tablets
92728990	Sertraline 50mg tablets
93173998	Sertraline 50mg tablets
93174998	Sertraline 50mg tablets
93694990	Sertraline 50mg tablets
93733990	Sertraline 50mg tablets
93749990	Sertraline 50mg tablets
93753990	Sertraline 50mg tablets
93843990	Sertraline 50mg tablets
96136979	Sertraline 50mg tablets
86159998	Sertraline 50mg/5ml oral suspension
98027992	Sinequan 15 mg tab
98183992	Tofranil 50 mg tab
99280998	Tranylcypromine & trifluoperazine 10mg+1mg tablets
95144998	Tranylcypromine 10mg tablets
95665990	Tranylcypromine 10mg tablets
99281998	Tranylcypromine 10mg tablets
95143998	Tranylcypromine with trifluoperazine tablet
95142997	Trazodone 100mg capsules
96295989	Trazodone 100mg capsules
96422989	Trazodone 100mg capsules
96443989	Trazodone 100mg capsules
96726989	Trazodone 100mg capsules
98486997	Trazodone 100mg capsules
65273979	Trazodone 100mg/5ml oral solution
65269979	Trazodone 10mg/5ml oral solution
95141997	Trazodone 150mg modified-release tablets
95142996	Trazodone 150mg tablets
95527990	Trazodone 150mg tablets
96295988	Trazodone 150mg tablets
96422988	Trazodone 150mg tablets
96443988	Trazodone 150mg tablets
98486996	Trazodone 150mg tablets
65265979	Trazodone 150mg/5ml oral solution
65263979	Trazodone 150mg/5ml oral suspension
65261979	Trazodone 250mg/5ml oral solution
65255979	Trazodone 25mg/5ml oral suspension
95142998	Trazodone 50mg capsules
96295990	Trazodone 50mg capsules
96422990	Trazodone 50mg capsules
96443990	Trazodone 50mg capsules
96726990	Trazodone 50mg capsules
98486998	Trazodone 50mg capsules
65251979	Trazodone 50mg/5ml oral solution sugar free

65253979 Trazodone 50mg/5ml oral solution sugar free
83781998 Trazodone 50mg/5ml oral solution sugar free
91934990 Trazodone 50mg/5ml oral solution sugar free
95141998 Trazodone 50mg/5ml oral solution sugar free
98312998 Trazodone 50mg/5ml oral solution sugar free
65249979 Trazodone 75mg/5ml oral solution
98312997 Trazodone hydrochloride 150mg modified release tablets
94626998 Trifluoperazine with tranylcypromine 1mg + 10mg tablet
93841990 Trimipramine 10mg tablets
95107998 Trimipramine 10mg tablets
98136998 Trimipramine 10mg tablets
93840990 Trimipramine 25mg tablets
95107997 Trimipramine 25mg tablets
98136997 Trimipramine 25mg tablets
65015979 Trimipramine 25mg/5ml oral suspension
93839990 Trimipramine 50mg capsules
95107996 Trimipramine 50mg capsules
98136996 Trimipramine 50mg capsules
98212992 Trimipramine 50mg capsules
65013979 Trimipramine 50mg/5ml oral solution
94512992 Tryptophan 1g/6g powder
52984979 Tryptophan 500mg capsules
52985979 Tryptophan 500mg capsules
95099998 Tryptophan 500mg tablets
95352992 Tryptophan 500mg tablets
98257998 Tryptophan 500mg tablets
99294998 Tryptophan 500mg tablets
99316998 Tryptophan 500mg tablets
95098997 Tryptophan with ascorbic acid and pyridoxine powder
52700979 Venlafaxine 150mg modified-release capsules
81749998 Venlafaxine 150mg modified-release capsules
81929998 Venlafaxine 150mg modified-release capsules
82190998 Venlafaxine 150mg modified-release capsules
82874998 Venlafaxine 150mg modified-release capsules
83074998 Venlafaxine 150mg modified-release capsules
83114998 Venlafaxine 150mg modified-release capsules
83145998 Venlafaxine 150mg modified-release capsules
83149998 Venlafaxine 150mg modified-release capsules
83204998 Venlafaxine 150mg modified-release capsules
83209998 Venlafaxine 150mg modified-release capsules
83217998 Venlafaxine 150mg modified-release capsules
83264998 Venlafaxine 150mg modified-release capsules
88755997 Venlafaxine 150mg modified-release capsules
88776997 Venlafaxine 150mg modified-release capsules
96022979 Venlafaxine 150mg modified-release capsules
96023979 Venlafaxine 150mg modified-release capsules
96024979 Venlafaxine 150mg modified-release capsules
96029979 Venlafaxine 150mg modified-release capsules
52165979 Venlafaxine 150mg modified-release tablets
80024978 Venlafaxine 150mg modified-release tablets

82962998	Venlafaxine 150mg modified-release tablets
83157998	Venlafaxine 150mg modified-release tablets
83159998	Venlafaxine 150mg modified-release tablets
64976979	Venlafaxine 150mg/5ml oral suspension
39137978	Venlafaxine 225mg modified-release capsules
39138978	Venlafaxine 225mg modified-release capsules
30261978	Venlafaxine 225mg modified-release capsules
82959998	Venlafaxine 225mg modified-release tablets
82961998	Venlafaxine 225mg modified-release tablets
79303978	Venlafaxine 37.5mg modified-release capsules
79304978	Venlafaxine 37.5mg modified-release capsules
81505998	Venlafaxine 37.5mg modified-release tablets
81506998	Venlafaxine 37.5mg modified-release tablets
83163998	Venlafaxine 37.5mg tablets
92597990	Venlafaxine 37.5mg tablets
96059979	Venlafaxine 37.5mg tablets
96065979	Venlafaxine 37.5mg tablets
98336998	Venlafaxine 37.5mg tablets
99896998	Venlafaxine 37.5mg tablets
64642979	Venlafaxine 37.5mg/5ml oral solution
86431998	Venlafaxine 37.5mg/5ml oral suspension
98336996	Venlafaxine 50mg tablets
99896996	Venlafaxine 50mg tablets
81750998	Venlafaxine 75mg modified-release capsules
81930998	Venlafaxine 75mg modified-release capsules
82191998	Venlafaxine 75mg modified-release capsules
82540998	Venlafaxine 75mg modified-release capsules
82875998	Venlafaxine 75mg modified-release capsules
83075998	Venlafaxine 75mg modified-release capsules
83115998	Venlafaxine 75mg modified-release capsules
83146998	Venlafaxine 75mg modified-release capsules
83150998	Venlafaxine 75mg modified-release capsules
83205998	Venlafaxine 75mg modified-release capsules
83210998	Venlafaxine 75mg modified-release capsules
83218998	Venlafaxine 75mg modified-release capsules
83265998	Venlafaxine 75mg modified-release capsules
88755998	Venlafaxine 75mg modified-release capsules
88776998	Venlafaxine 75mg modified-release capsules
96033979	Venlafaxine 75mg modified-release capsules
96034979	Venlafaxine 75mg modified-release capsules
96036979	Venlafaxine 75mg modified-release capsules
96041979	Venlafaxine 75mg modified-release capsules
52164979	Venlafaxine 75mg modified-release tablets
80023978	Venlafaxine 75mg modified-release tablets
82963998	Venlafaxine 75mg modified-release tablets
83158998	Venlafaxine 75mg modified-release tablets
83160998	Venlafaxine 75mg tablets
83162998	Venlafaxine 75mg tablets
92596990	Venlafaxine 75mg tablets
96052979	Venlafaxine 75mg tablets

96054979	Venlafaxine 75mg tablets
98336997	Venlafaxine 75mg tablets
99896997	Venlafaxine 75mg tablets
64640979	Venlafaxine 75mg/5ml oral solution
64638979	Venlafaxine 75mg/5ml oral suspension
98959998	Viloxazine 50mg tablets
95624998	Viloxazine hcl 50mg tablets
45795978	Vortioxetine 10mg tablets
45796978	Vortioxetine 10mg tablets
45793978	Vortioxetine 20mg tablets
45794978	Vortioxetine 20mg tablets
45791978	Vortioxetine 5mg tablets
45792978	Vortioxetine 5mg tablets
98327992	Zimelidine hcl 100 mg tab

B. Antiepileptics

Drug code	Generic name
96987998	Acetazolamide 500mg modified-release capsules
96914998	Beclamide 500mg tablets
37885978	Brivaracetam 100mg tablets
37886978	Brivaracetam 100mg tablets
37881978	Brivaracetam 25mg tablets
37882978	Brivaracetam 25mg tablets
37879978	Brivaracetam 50mg tablets
37880978	Brivaracetam 50mg tablets
37878978	Brivaracetam 50mg/5ml solution for injection vials
37874978	Brivaracetam 75mg tablets
93531998	Carbamazepine 100mg chewable tablets
93530998	Carbamazepine 100mg chewable tablets sugar free
52641979	Carbamazepine 100mg tablets
61092979	Carbamazepine 100mg tablets
76918978	Carbamazepine 100mg tablets
92837998	Carbamazepine 100mg tablets
95307979	Carbamazepine 100mg tablets
96697989	Carbamazepine 100mg tablets
96916990	Carbamazepine 100mg tablets
97033998	Carbamazepine 100mg tablets
97779990	Carbamazepine 100mg tablets
98338990	Carbamazepine 100mg tablets
98361998	Carbamazepine 100mg tablets
99751990	Carbamazepine 100mg tablets
99752990	Carbamazepine 100mg tablets
68169979	Carbamazepine 100mg/5ml oral suspension
91860990	Carbamazepine 100mg/5ml oral suspension sugar free
95258979	Carbamazepine 100mg/5ml oral suspension sugar free
95265979	Carbamazepine 100mg/5ml oral suspension sugar free
96479992	Carbamazepine 100mg/5ml oral suspension sugar free
96885998	Carbamazepine 100mg/5ml oral suspension sugar free
98360998	Carbamazepine 100mg/5ml oral suspension sugar free

68165979	Carbamazepine 10mg/5ml oral suspension
92734998	Carbamazepine 125mg suppositories
92735998	Carbamazepine 125mg suppositories
93531997	Carbamazepine 200mg chewable tablets
93530997	Carbamazepine 200mg chewable tablets sugar free
76917978	Carbamazepine 200mg modified-release tablets
81480998	Carbamazepine 200mg modified-release tablets
89384998	Carbamazepine 200mg modified-release tablets
92131998	Carbamazepine 200mg modified-release tablets
92837997	Carbamazepine 200mg modified-release tablets
93532998	Carbamazepine 200mg modified-release tablets
93579998	Carbamazepine 200mg modified-release tablets
95279979	Carbamazepine 200mg modified-release tablets
95283979	Carbamazepine 200mg modified-release tablets
95284979	Carbamazepine 200mg modified-release tablets
95285979	Carbamazepine 200mg modified-release tablets
95288979	Carbamazepine 200mg modified-release tablets
96128990	Carbamazepine 200mg modified-release tablets
96446990	Carbamazepine 200mg modified-release tablets
96536990	Carbamazepine 200mg modified-release tablets
97086998	Carbamazepine 200mg modified-release tablets
97128990	Carbamazepine 200mg modified-release tablets
61091979	Carbamazepine 200mg tablets
83281978	Carbamazepine 200mg tablets
95301979	Carbamazepine 200mg tablets
95303979	Carbamazepine 200mg tablets
96697988	Carbamazepine 200mg tablets
96916989	Carbamazepine 200mg tablets
97033997	Carbamazepine 200mg tablets
97779989	Carbamazepine 200mg tablets
98338989	Carbamazepine 200mg tablets
98361997	Carbamazepine 200mg tablets
99751989	Carbamazepine 200mg tablets
99752989	Carbamazepine 200mg tablets
92734997	Carbamazepine 250mg suppositories
92735997	Carbamazepine 250mg suppositories
88217997	Carbamazepine 400mg modified release tablets
76916978	Carbamazepine 400mg modified-release tablets
81479998	Carbamazepine 400mg modified-release tablets
89384997	Carbamazepine 400mg modified-release tablets
92131997	Carbamazepine 400mg modified-release tablets
92282998	Carbamazepine 400mg modified-release tablets
92837996	Carbamazepine 400mg modified-release tablets
93532997	Carbamazepine 400mg modified-release tablets
93579997	Carbamazepine 400mg modified-release tablets
95266979	Carbamazepine 400mg modified-release tablets
95269979	Carbamazepine 400mg modified-release tablets
95270979	Carbamazepine 400mg modified-release tablets
95273979	Carbamazepine 400mg modified-release tablets
95275979	Carbamazepine 400mg modified-release tablets

95276979	Carbamazepine 400mg modified-release tablets
96127990	Carbamazepine 400mg modified-release tablets
96446989	Carbamazepine 400mg modified-release tablets
96536989	Carbamazepine 400mg modified-release tablets
97128989	Carbamazepine 400mg modified-release tablets
61090979	Carbamazepine 400mg tablets
95297979	Carbamazepine 400mg tablets
95298979	Carbamazepine 400mg tablets
96916988	Carbamazepine 400mg tablets
97033996	Carbamazepine 400mg tablets
97779988	Carbamazepine 400mg tablets
98338988	Carbamazepine 400mg tablets
98361996	Carbamazepine 400mg tablets
99751988	Carbamazepine 400mg tablets
97158992	Clobazam 1 mg sus
69586979	Clobazam 100mg/5ml oral suspension
96648998	Clobazam 10mg capsules
99622998	Clobazam 10mg capsules
96648997	Clobazam 10mg tablets
96753979	Clobazam 10mg tablets
99622997	Clobazam 10mg tablets
47484978	Clobazam 10mg/5ml oral suspension sugar free
52980979	Clobazam 10mg/5ml oral suspension sugar free
52981979	Clobazam 10mg/5ml oral suspension sugar free
97159992	Clobazam 2.5 mg cap
85423998	Clobazam 2.5mg capsules
80592979	Clobazam 2.5mg/5ml oral solution
80590979	Clobazam 2.5mg/5ml oral suspension
80586979	Clobazam 20mg/5ml oral suspension
82713998	Clobazam 25mg/5ml oral solution
82714998	Clobazam 25mg/5ml oral suspension
69574979	Clobazam 3.75mg/5ml oral suspension
80572979	Clobazam 4mg/5ml oral suspension
97161992	Clobazam 5 mg cap
96160992	Clobazam 5 mg tab
81126998	Clobazam 5mg/5ml oral solution
46957978	Clobazam 5mg/5ml oral suspension sugar free
47483978	Clobazam 5mg/5ml oral suspension sugar free
52978979	Clobazam 5mg/5ml oral suspension sugar free
52979979	Clobazam 5mg/5ml oral suspension sugar free
80557979	Clobazam 5mg/5ml oral suspension sugar free
97160992	Clobazam 7.5 mg cap
69558979	Clobazam 7.5mg/5ml oral suspension
96634996	Clonazepam 1mg/1ml solution for injection ampoules and diluent
98517998	Clonazepam 1mg/1ml solution for injection ampoules and diluent
88423998	Clonazepam 2.5mg/ml drops sugar free
95244979	Clonazepam 2mg tablets
96634997	Clonazepam 2mg tablets
99176997	Clonazepam 2mg tablets
59819979	Clonazepam 2mg/5ml oral solution sugar free

88423996	Clonazepam 2mg/5ml oral solution sugar free
96571990	Clonazepam 2mg/5ml oral solution sugar free
80513979	Clonazepam 2mg/5ml oral suspension
69776979	Clonazepam 312.5micrograms/5ml oral suspension
62337979	Clonazepam 500microgram tablets
92796990	Clonazepam 500microgram tablets
95246979	Clonazepam 500microgram tablets
95247979	Clonazepam 500microgram tablets
96634998	Clonazepam 500microgram tablets
99176998	Clonazepam 500microgram tablets
58780979	Clonazepam 500micrograms/5ml oral solution sugar free
59576979	Clonazepam 500micrograms/5ml oral solution sugar free
59577979	Clonazepam 500micrograms/5ml oral solution sugar free
81083998	Clonazepam 500micrograms/5ml oral solution sugar free
86604998	Clonazepam 500micrograms/5ml oral solution sugar free
88423997	Clonazepam 500micrograms/5ml oral solution sugar free
93913990	Clonazepam 500micrograms/5ml oral solution sugar free
94664990	Diazepam 10mg/2.5ml rectal solution tube
96407997	Diazepam 10mg/2.5ml rectal solution tube
97291992	Diazepam 10mg/2.5ml rectal solution tube
97533997	Diazepam 10mg/2.5ml rectal solution tube
98649988	Diazepam 10mg/2.5ml rectal solution tube
99705997	Diazepam 10mg/2.5ml rectal solution tube
92858998	Diazepam 10mg/2ml emulsion for injection ampoules
97282992	Diazepam 10mg/2ml emulsion for injection ampoules
99761998	Diazepam 10mg/2ml emulsion for injection ampoules
92858997	Diazepam 10mg/2ml solution for injection ampoules
96195992	Diazepam 10mg/2ml solution for injection ampoules
97259990	Diazepam 10mg/2ml solution for injection ampoules
98570989	Diazepam 10mg/2ml solution for injection ampoules
96407996	Diazepam 2.5mg/1.25ml rectal solution tube
99705996	Diazepam 2.5mg/1.25ml rectal solution tube
91354998	Diazepam 20mg rectal tubes
92573998	Diazepam 20mg rectal tubes
94837979	Diazepam 5mg/2.5ml rectal solution tube
96407998	Diazepam 5mg/2.5ml rectal solution tube
97292992	Diazepam 5mg/2.5ml rectal solution tube
97533998	Diazepam 5mg/2.5ml rectal solution tube
98135990	Diazepam 5mg/2.5ml rectal solution tube
99705998	Diazepam 5mg/2.5ml rectal solution tube
94455992	Epanutin + phenobarb cap
82574998	Eslicarbazepine 800mg tablets
82576998	Eslicarbazepine 800mg tablets
86109998	Ethosuximide 250mg capsules
96767998	Ethosuximide 250mg capsules
98949998	Ethosuximide 250mg capsules
99697998	Ethosuximide 250mg capsules
29629978	Ethosuximide 250mg/5ml oral solution
85954998	Ethosuximide 250mg/5ml oral solution
96767997	Ethosuximide 250mg/5ml oral solution

98949997	Ethosuximide 250mg/5ml oral solution
99697997	Ethosuximide 250mg/5ml syrup
97402992	Ethosuximide pow
89991998	Fosphenytoin 750mg/10ml solution for injection vials
92064998	Fosphenytoin 750mg/10ml solution for injection vials
93051990	Gabapentin 100mg capsules
93812990	Gabapentin 100mg capsules
94834998	Gabapentin 100mg capsules
94835998	Gabapentin 100mg capsules
95045979	Gabapentin 100mg capsules
95049979	Gabapentin 100mg capsules
95161990	Gabapentin 100mg capsules
95190990	Gabapentin 100mg capsules
80032979	Gabapentin 100mg/5ml oral solution
69149979	Gabapentin 200mg/5ml oral solution
93743990	Gabapentin 250mg/5ml oral solution
81991998	Gabapentin 250mg/5ml oral suspension
92871990	Gabapentin 300mg capsules
94834997	Gabapentin 300mg capsules
94835997	Gabapentin 300mg capsules
95032979	Gabapentin 300mg capsules
95159990	Gabapentin 300mg capsules
95189990	Gabapentin 300mg capsules
80027979	Gabapentin 300mg/5ml oral solution
80023979	Gabapentin 300mg/5ml oral suspension
90424998	Gabapentin 300mg+600mg pack
94834996	Gabapentin 400mg capsules
94835996	Gabapentin 400mg capsules
95158990	Gabapentin 400mg capsules
95188990	Gabapentin 400mg capsules
64705979	Gabapentin 400mg/5ml oral solution
86362998	Gabapentin 400mg/5ml oral suspension
80017979	Gabapentin 50mg/5ml oral solution
53063979	Gabapentin 50mg/ml oral solution sugar free
53267979	Gabapentin 50mg/ml oral solution sugar free
86485998	Gabapentin 50mg/ml oral solution sugar free
90426998	Gabapentin 600mg tablets
92463990	Gabapentin 600mg tablets
95157990	Gabapentin 600mg tablets
95187990	Gabapentin 600mg tablets
98989998	Gabapentin 600mg tablets
90425998	Gabapentin 600mg tablets and gabapentin 300mg capsules
64951979	Gabapentin 600mg/5ml oral solution
64949979	Gabapentin 600mg/5ml oral suspension
90426997	Gabapentin 800mg tablets
95186990	Gabapentin 800mg tablets
98989997	Gabapentin 800mg tablets
97511992	Gardenal 15 mg tab
83513998	Lacosamide 100mg tablets
83514998	Lacosamide 100mg tablets

58783979	Lacosamide 10mg/ml oral solution sugar free
61056979	Lacosamide 10mg/ml oral solution sugar free
83511998	Lacosamide 150mg tablets
83512998	Lacosamide 150mg tablets
83516998	Lacosamide 15mg/ml oral solution sugar free
83515998	Lacosamide 15mg/ml sugar free oral solution
83509998	Lacosamide 200mg tablets
83510998	Lacosamide 200mg tablets
83517998	Lacosamide 200mg/20ml solution for infusion vials
83518998	Lacosamide 200mg/20ml solution for infusion vials
83507998	Lacosamide 50mg tablets
83508998	Lacosamide 50mg tablets
92700996	Lamotrigine 100mg dispersible tablets sugar free
92709996	Lamotrigine 100mg dispersible tablets sugar free
94008990	Lamotrigine 100mg dispersible tablets sugar free
94043990	Lamotrigine 100mg dispersible tablets sugar free
94011990	Lamotrigine 100mg tablets
94118990	Lamotrigine 100mg tablets
95126979	Lamotrigine 100mg tablets
95133979	Lamotrigine 100mg tablets
95404997	Lamotrigine 100mg tablets
95444997	Lamotrigine 100mg tablets
67426979	Lamotrigine 15mg/5ml oral suspension
91465998	Lamotrigine 200mg tablets
91596998	Lamotrigine 200mg tablets
94010990	Lamotrigine 200mg tablets
94046990	Lamotrigine 200mg tablets
95067979	Lamotrigine 200mg tablets
92700997	Lamotrigine 25mg dispersible tablets sugar free
92709997	Lamotrigine 25mg dispersible tablets sugar free
94009990	Lamotrigine 25mg dispersible tablets sugar free
94044990	Lamotrigine 25mg dispersible tablets sugar free
94088990	Lamotrigine 25mg dispersible tablets sugar free
95081979	Lamotrigine 25mg dispersible tablets sugar free
95091979	Lamotrigine 25mg dispersible tablets sugar free
60178979	Lamotrigine 25mg tablets
94013990	Lamotrigine 25mg tablets
94049990	Lamotrigine 25mg tablets
94086990	Lamotrigine 25mg tablets
94120990	Lamotrigine 25mg tablets
95109979	Lamotrigine 25mg tablets
95112979	Lamotrigine 25mg tablets
95117979	Lamotrigine 25mg tablets
95404996	Lamotrigine 25mg tablets
95444996	Lamotrigine 25mg tablets
91465997	Lamotrigine 2mg dispersible tablets sugar free
91596997	Lamotrigine 2mg dispersible tablets sugar free
81677998	Lamotrigine 50mg suppository
60180979	Lamotrigine 50mg tablets
86019998	Lamotrigine 50mg tablets

93460992	Lamotrigine 50mg tablets
94012990	Lamotrigine 50mg tablets
94048990	Lamotrigine 50mg tablets
94119990	Lamotrigine 50mg tablets
95143979	Lamotrigine 50mg tablets
95150979	Lamotrigine 50mg tablets
95404998	Lamotrigine 50mg tablets
95444998	Lamotrigine 50mg tablets
79740979	Lamotrigine 50mg/5ml oral suspension
92700998	Lamotrigine 5mg dispersible tablets sugar free
92709998	Lamotrigine 5mg dispersible tablets sugar free
93527990	Lamotrigine 5mg dispersible tablets sugar free
95097979	Lamotrigine 5mg dispersible tablets sugar free
95100979	Lamotrigine 5mg dispersible tablets sugar free
60617979	Levetiracetam 100mg/ml oral solution sugar free
60938979	Levetiracetam 100mg/ml oral solution sugar free
79658978	Levetiracetam 100mg/ml oral solution sugar free
80914979	Levetiracetam 100mg/ml oral solution sugar free
80919979	Levetiracetam 100mg/ml oral solution sugar free
80920979	Levetiracetam 100mg/ml oral solution sugar free
87193998	Levetiracetam 100mg/ml oral solution sugar free
87195998	Levetiracetam 100mg/ml oral solution sugar free
91881990	Levetiracetam 100mg/ml oral solution sugar free
52992979	Levetiracetam 1g granules sachets sugar free
52993979	Levetiracetam 1g granules sachets sugar free
89210996	Levetiracetam 1g tablets
91850990	Levetiracetam 1g tablets
92375996	Levetiracetam 1g tablets
52990979	Levetiracetam 250mg granules sachets sugar free
52991979	Levetiracetam 250mg granules sachets sugar free
47245978	Levetiracetam 250mg tablets
57800979	Levetiracetam 250mg tablets
60174979	Levetiracetam 250mg tablets
80964998	Levetiracetam 250mg tablets
89210998	Levetiracetam 250mg tablets
91853990	Levetiracetam 250mg tablets
91885990	Levetiracetam 250mg tablets
92375998	Levetiracetam 250mg tablets
94842979	Levetiracetam 250mg tablets
94848979	Levetiracetam 250mg tablets
94851979	Levetiracetam 250mg tablets
52988979	Levetiracetam 500mg granules sachets sugar free
52989979	Levetiracetam 500mg granules sachets sugar free
55743978	Levetiracetam 500mg tablets
60175979	Levetiracetam 500mg tablets
80963998	Levetiracetam 500mg tablets
89210997	Levetiracetam 500mg tablets
91852990	Levetiracetam 500mg tablets
91884990	Levetiracetam 500mg tablets
92375997	Levetiracetam 500mg tablets

94854979	Levetiracetam 500mg tablets
94858979	Levetiracetam 500mg tablets
94861979	Levetiracetam 500mg tablets
85968998	Levetiracetam 500mg/5ml solution for infusion vials
85969998	Levetiracetam 500mg/5ml solution for infusion vials
57760979	Levetiracetam 750mg tablets
80962998	Levetiracetam 750mg tablets
87194998	Levetiracetam 750mg tablets
87196998	Levetiracetam 750mg tablets
84001998	Mesuximide 300mg capsule
96817992	Methsuximide 300 mg cap
97736992	Methsuximide 3000 mg cap
95852996	Methylphenobarbital 200mg tablet
98461996	Methylphenobarbital 200mg tablets
95852998	Methylphenobarbital 30mg tablet
98461998	Methylphenobarbital 30mg tablets
95852997	Methylphenobarbital 60mg tablet
98461997	Methylphenobarbital 60mg tablets
31077978	Midazolam 10mg/2ml oromucosal solution pre-filled oral syringes sugar free
31078978	Midazolam 10mg/2ml oromucosal solution pre-filled oral syringes sugar free
62805979	Midazolam 10mg/2ml oromucosal solution pre-filled oral syringes sugar free
81185998	Midazolam 10mg/2ml oromucosal solution pre-filled oral syringes sugar free
81188998	Midazolam 10mg/2ml oromucosal solution pre-filled oral syringes sugar free
87797998	Midazolam 10mg/ml buccal solution
87798998	Midazolam 10mg/ml buccal solution
31075978	Midazolam 2.5mg/0.5ml oromucosal solution pre-filled oral syringes sugar free
31076978	Midazolam 2.5mg/0.5ml oromucosal solution pre-filled oral syringes sugar free
62804979	Midazolam 2.5mg/0.5ml oromucosal solution pre-filled oral syringes sugar free
81187998	Midazolam 2.5mg/0.5ml oromucosal solution pre-filled oral syringes sugar free
81190998	Midazolam 2.5mg/0.5ml oromucosal solution pre-filled oral syringes sugar free
31073978	Midazolam 5mg/1ml oromucosal solution pre-filled oral syringes sugar free
31074978	Midazolam 5mg/1ml oromucosal solution pre-filled oral syringes sugar free
62803979	Midazolam 5mg/1ml oromucosal solution pre-filled oral syringes sugar free
81560998	Midazolam 5mg/1ml oromucosal solution pre-filled oral syringes sugar free
81561998	Midazolam 5mg/1ml oromucosal solution pre-filled oral syringes sugar free
31071978	Midazolam 7.5mg/1.5ml oromucosal solution pre-filled oral syringes sugar free
31072978	Midazolam 7.5mg/1.5ml oromucosal solution pre-filled oral syringes sugar free
62800979	Midazolam 7.5mg/1.5ml oromucosal solution pre-filled oral syringes sugar free
81186998	Midazolam 7.5mg/1.5ml oromucosal solution pre-filled oral syringes sugar free
81189998	Midazolam 7.5mg/1.5ml oromucosal solution pre-filled oral syringes sugar free
94256992	Ospolot 200 mg tab
95361992	Ospolot 50 mg tab
91625998	Oxcarbazepine 150mg tablets
92389990	Oxcarbazepine 150mg tablets
98730998	Oxcarbazepine 150mg tablets
91625997	Oxcarbazepine 300mg tablets
91626998	Oxcarbazepine 300mg tablets
89231998	Oxcarbazepine 600mg tablets
91625996	Oxcarbazepine 600mg tablets
91218998	Oxcarbazepine 60mg/ml oral suspension sugar free

91839998	Oxcarbazepine 60mg/ml oral suspension sugar free
96733992	PARALDEHYDE 10 ML INJ
97081997	Paraldehyde 100% solution for injection 5ml ampoules
97081998	Paraldehyde intramuscular injection
98091998	Paraldehyde intravenous injection
98091997	Paraldehyde rectal solution
97867992	Paramethadione 300 mg cap
93827998	Pentamidine 300mg powder for solution for injection vials
93828998	Pentamidine 300mg powder for solution for injection vials
98757998	Pentamidine 300mg/5ml nebuliser liquid
97872992	Pentamidine isethionate 200 mg inj
99412998	Pentamidine isethionate 300mg/5ml nebuliser solution
54932979	Perampanel 10mg tablets
54933979	Perampanel 10mg tablets
54931979	Perampanel 12mg tablets
54928979	Perampanel 2mg tablets
54929979	Perampanel 2mg tablets
54930979	Perampanel 2mg tablets
54926979	Perampanel 4mg tablets
54927979	Perampanel 4mg tablets
54924979	Perampanel 6mg tablets
54925979	Perampanel 6mg tablets
54922979	Perampanel 8mg tablets
54923979	Perampanel 8mg tablets
97202998	Phenobarbital 100mg tablet
84193998	Phenobarbital 100mg tablets
68311979	Phenobarbital 100mg/5ml oral suspension
68034979	Phenobarbital 10mg capsules
68909979	Phenobarbital 10mg/5ml oral suspension
33977978	Phenobarbital 15mg tablets
56157979	Phenobarbital 15mg tablets
94282992	Phenobarbital 15mg tablets
95234979	Phenobarbital 15mg tablets
95236979	Phenobarbital 15mg tablets
95415992	Phenobarbital 15mg tablets
97203998	Phenobarbital 15mg tablets
98049990	Phenobarbital 15mg tablets
98112988	Phenobarbital 15mg tablets
99458990	Phenobarbital 15mg tablets
93454998	Phenobarbital 15mg/1ml solution for injection ampoules
68677979	Phenobarbital 15mg/5ml elixir
68745979	Phenobarbital 15mg/5ml elixir
68746979	Phenobarbital 15mg/5ml elixir
95220979	Phenobarbital 15mg/5ml elixir
95221979	Phenobarbital 15mg/5ml elixir
98087998	Phenobarbital 15mg/5ml elixir
98688990	Phenobarbital 15mg/5ml elixir
99457990	Phenobarbital 15mg/5ml elixir
68675979	Phenobarbital 15mg/5ml oral suspension
95223979	Phenobarbital 200mg/1ml solution for injection ampoules

95553998	Phenobarbital 200mg/1ml solution for injection ampoules
95554998	Phenobarbital 200mg/1ml solution for injection ampoules
56156979	Phenobarbital 30mg tablets
94521992	Phenobarbital 30mg tablets
95228979	Phenobarbital 30mg tablets
95231979	Phenobarbital 30mg tablets
95232979	Phenobarbital 30mg tablets
97203997	Phenobarbital 30mg tablets
98049989	Phenobarbital 30mg tablets
98112989	Phenobarbital 30mg tablets
99458989	Phenobarbital 30mg tablets
99459989	Phenobarbital 30mg tablets
93454997	Phenobarbital 30mg/1ml solution for injection ampoules
68850979	Phenobarbital 34mg/5ml oral suspension
79019979	Phenobarbital 50mg/5ml oral solution
79020979	Phenobarbital 50mg/5ml oral solution
98087997	Phenobarbital 50mg/5ml oral solution
79021979	Phenobarbital 50mg/5ml oral suspension
87030998	Phenobarbital 50mg/5ml oral suspension
68665979	Phenobarbital 5mg/5ml oral solution
68026979	Phenobarbital 60mg capsules
56155979	Phenobarbital 60mg tablets
95226979	Phenobarbital 60mg tablets
95227979	Phenobarbital 60mg tablets
97203996	Phenobarbital 60mg tablets
98049988	Phenobarbital 60mg tablets
98112990	Phenobarbital 60mg tablets
98476997	Phenobarbital 60mg tablets
99459990	Phenobarbital 60mg tablets
93454996	Phenobarbital 60mg/1ml solution for injection ampoules
97080998	Phenobarbital sodium 30mg tablet
98476998	Phenobarbital sodium 30mg tablets
68713979	Phenobarbital sodium 50mg/5ml oral solution
68714979	Phenobarbital sodium 50mg/5ml oral solution
68712979	Phenobarbital sodium 50mg/5ml oral suspension
97080997	Phenobarbital sodium 60mg tablet
97884992	Phenobarbitone & phenytoin 60 mg cap
95409992	Phenobarbitone 10 mg pul
93404992	Phenobarbitone 10 mg tab
93768992	Phenobarbitone 100 mg spa
95418992	Phenobarbitone 20 mg tab
94279992	Phenobarbitone 22.5 mg tab
95411992	Phenobarbitone 30 mg eli
95417992	Phenobarbitone 5 mg eli
95420992	Phenobarbitone 5 mg tab
94285992	Phenobarbitone 50 mg cap
95421992	Phenobarbitone 50 mg tab
97883992	Phenobarbitone 50mg & phenytoin 100mg mg cap
95419992	Phenobarbitone 60 mg spa
96386992	Phenobarbitone 60mg & phenytoin 100mg mg tab

94284992	Phenobarbitone 7.5 mg tab
94278992	Phenobarbitone s/r 100 mg cap
93720992	Phenobarbitone sodium 100 mg tab
94281992	Phenobarbitone sodium 50 mg tab
93037992	Phenobarbitone sodium alcohol free 50 mg/5ml mix
94288992	Phenytoin 150 mg sus
94525992	Phenytoin 25 mg syr
97897992	Phenytoin 30 mg tab
63501979	Phenytoin 300mg/5ml oral solution
63498979	Phenytoin 300mg/5ml oral suspension
63499979	Phenytoin 300mg/5ml oral suspension
95532997	Phenytoin 30mg/5ml oral suspension
98658998	Phenytoin 30mg/5ml oral suspension
95533998	Phenytoin 50mg chewable tablets
97514997	Phenytoin 50mg chewable tablets
64759979	Phenytoin 90mg/5ml oral solution
92812998	Phenytoin 90mg/5ml oral solution sugar free
98075990	Phenytoin 90mg/5ml oral solution sugar free
78967979	Phenytoin 90mg/5ml oral suspension
81079998	Phenytoin 90mg/5ml oral suspension
47250978	Phenytoin sodium 100mg capsules
54822979	Phenytoin sodium 100mg capsules
54823979	Phenytoin sodium 100mg capsules
55600979	Phenytoin sodium 100mg capsules
79261978	Phenytoin sodium 100mg capsules
90780996	Phenytoin sodium 100mg capsules
95532998	Phenytoin sodium 100mg capsules
98315996	Phenytoin sodium 100mg capsules
99454989	Phenytoin sodium 100mg capsules
42677978	Phenytoin sodium 100mg tablets
52635979	Phenytoin sodium 100mg tablets
56154979	Phenytoin sodium 100mg tablets
92614990	Phenytoin sodium 100mg tablets
95213979	Phenytoin sodium 100mg tablets
96978990	Phenytoin sodium 100mg tablets
97140989	Phenytoin sodium 100mg tablets
97736997	Phenytoin sodium 100mg tablets
98090997	Phenytoin sodium 100mg tablets
98430990	Phenytoin sodium 100mg tablets
99121989	Phenytoin sodium 100mg tablets
99453990	Phenytoin sodium 100mg tablets
99455989	Phenytoin sodium 100mg tablets
95531998	Phenytoin sodium 250mg/5ml solution for injection ampoules
99692998	Phenytoin sodium 250mg/5ml solution for injection ampoules
54826979	Phenytoin sodium 25mg capsules
54827979	Phenytoin sodium 25mg capsules
55602979	Phenytoin sodium 25mg capsules
90780998	Phenytoin sodium 25mg capsules
95533997	Phenytoin sodium 25mg capsules
98315998	Phenytoin sodium 25mg capsules

54828979	Phenytoin sodium 300mg capsules
54829979	Phenytoin sodium 300mg capsules
55603979	Phenytoin sodium 300mg capsules
90776998	Phenytoin sodium 300mg capsules
95532996	Phenytoin sodium 300mg capsules
97514998	Phenytoin sodium 300mg capsules
46532978	Phenytoin sodium 50mg capsules
54824979	Phenytoin sodium 50mg capsules
54825979	Phenytoin sodium 50mg capsules
55601979	Phenytoin sodium 50mg capsules
90780997	Phenytoin sodium 50mg capsules
95533996	Phenytoin sodium 50mg capsules
98315997	Phenytoin sodium 50mg capsules
97736998	Phenytoin sodium 50mg tablets
98090998	Phenytoin sodium 50mg tablets
99122990	Phenytoin sodium 50mg tablets
66257979	Phenytoin sodium 50mg/5ml oral solution
66255979	Phenytoin sodium 50mg/5ml oral suspension
97896992	Phenytoin sodium/ phenobarbitone cap
95838992	Phenytoin sodium/ phenobarbitone sodium tab
51898978	Pregabalin 100mg capsules
51899978	Pregabalin 100mg capsules
55715978	Pregabalin 100mg capsules
87398998	Pregabalin 100mg capsules
87405998	Pregabalin 100mg capsules
51895978	Pregabalin 150mg capsules
55714978	Pregabalin 150mg capsules
87397998	Pregabalin 150mg capsules
87404998	Pregabalin 150mg capsules
89087979	Pregabalin 150mg capsules
89089979	Pregabalin 150mg capsules
64019979	Pregabalin 150mg/5ml oral solution
64017979	Pregabalin 150mg/5ml oral suspension
51892978	Pregabalin 200mg capsules
55713978	Pregabalin 200mg capsules
87396998	Pregabalin 200mg capsules
87403998	Pregabalin 200mg capsules
89079979	Pregabalin 200mg capsules
63818979	Pregabalin 200mg/5ml oral solution
58118979	Pregabalin 20mg/ml oral solution sugar free
58119979	Pregabalin 20mg/ml oral solution sugar free
51877978	Pregabalin 225mg capsules
55708978	Pregabalin 225mg capsules
84233998	Pregabalin 225mg capsules
84234998	Pregabalin 225mg capsules
51889978	Pregabalin 25mg capsules
55712978	Pregabalin 25mg capsules
87401998	Pregabalin 25mg capsules
87408998	Pregabalin 25mg capsules
89078979	Pregabalin 25mg capsules

51886978	Pregabalin 300mg capsules
51887978	Pregabalin 300mg capsules
51888978	Pregabalin 300mg capsules
55711978	Pregabalin 300mg capsules
87395998	Pregabalin 300mg capsules
87402998	Pregabalin 300mg capsules
89070979	Pregabalin 300mg capsules
51883978	Pregabalin 50mg capsules
51885978	Pregabalin 50mg capsules
55710978	Pregabalin 50mg capsules
87400998	Pregabalin 50mg capsules
87407998	Pregabalin 50mg capsules
89063979	Pregabalin 50mg capsules
51880978	Pregabalin 75mg capsules
51882978	Pregabalin 75mg capsules
55709978	Pregabalin 75mg capsules
87399998	Pregabalin 75mg capsules
87406998	Pregabalin 75mg capsules
89056979	Pregabalin 75mg capsules
64663979	Pregabalin 75mg/5ml oral suspension
84127998	Primidone 100mg/5ml oral solution
63675979	Primidone 100mg/5ml oral suspension
97949992	Primidone 200 mg tab
42674978	Primidone 250mg tablets
79789978	Primidone 250mg tablets
79790978	Primidone 250mg tablets
82205978	Primidone 250mg tablets
82569978	Primidone 250mg tablets
87106998	Primidone 250mg tablets
95196979	Primidone 250mg tablets
95202979	Primidone 250mg tablets
95203979	Primidone 250mg tablets
95403998	Primidone 250mg tablets
99383998	Primidone 250mg tablets
90211979	Primidone 250mg/5ml oral suspension
95403997	Primidone 250mg/5ml oral suspension
99383997	Primidone 250mg/5ml oral suspension
78964979	Primidone 25mg/5ml oral suspension
86349998	Primidone 25mg/5ml oral suspension
42566978	Primidone 50mg tablets
78555978	Primidone 50mg tablets
81830998	Primidone 50mg tablets
81842998	Primidone 50mg tablets
82181978	Primidone 50mg tablets
82534978	Primidone 50mg tablets
78963979	Primidone 50mg/5ml oral suspension
85180998	Primidone 50mg/5ml oral suspension
78962979	Primidone 62.5mg/5ml oral suspension
85466998	Primidone 62.5mg/5ml oral suspension
81402998	Retigabine 100mg tablets

81407998	Retigabine 100mg tablets
81401998	Retigabine 200mg tablets
81406998	Retigabine 200mg tablets
81400998	Retigabine 300mg tablets
81405998	Retigabine 300mg tablets
81399998	Retigabine 400mg tablets
81404998	Retigabine 400mg tablets
81403998	Retigabine 50mg tablets
81408998	Retigabine 50mg tablets
81396998	Retigabine 50mg tablets and Retigabine 100mg tablets
84417998	Rufinamide 100mg tablets
84420998	Rufinamide 100mg tablets
84416998	Rufinamide 200mg tablets
84419998	Rufinamide 200mg tablets
84415998	Rufinamide 400mg tablets
84418998	Rufinamide 400mg tablets
58718979	Rufinamide 40mg/ml oral suspension sugar free
58719979	Rufinamide 40mg/ml oral suspension sugar free
96463992	Sod valproate c/r 200 mg tab
81956998	Sodium valproate 100mg modified-release granules sachets sugar free
82857998	Sodium valproate 100mg modified-release granules sachets sugar free
83707998	Sodium valproate 100mg modified-release granules sachets sugar free
83794998	Sodium valproate 100mg modified-release granules sachets sugar free
94409996	Sodium valproate 100mg tablets
94568998	Sodium valproate 100mg tablets
97910990	Sodium valproate 100mg tablets
84667998	Sodium valproate 150mg modified-release capsules
84671998	Sodium valproate 150mg modified-release capsules
83790998	Sodium valproate 1g modified-release granules sachets sugar free
84664998	Sodium valproate 1g modified-release granules sachets sugar free
84668998	Sodium valproate 1g modified-release granules sachets sugar free
84089998	Sodium valproate 1g/10ml solution for injection ampoules
52634979	Sodium valproate 200mg gastro-resistant tablets
83480998	Sodium valproate 200mg gastro-resistant tablets
91690990	Sodium valproate 200mg gastro-resistant tablets
92802998	Sodium valproate 200mg gastro-resistant tablets
93444990	Sodium valproate 200mg gastro-resistant tablets
94409998	Sodium valproate 200mg gastro-resistant tablets
94606998	Sodium valproate 200mg gastro-resistant tablets
96977989	Sodium valproate 200mg gastro-resistant tablets
96986990	Sodium valproate 200mg gastro-resistant tablets
97721990	Sodium valproate 200mg gastro-resistant tablets
97910989	Sodium valproate 200mg gastro-resistant tablets
97911989	Sodium valproate 200mg gastro-resistant tablets
98385990	Sodium valproate 200mg gastro-resistant tablets
98929990	Sodium valproate 200mg gastro-resistant tablets
83321998	Sodium valproate 200mg modified-release tablets
92917998	Sodium valproate 200mg modified-release tablets
92918998	Sodium valproate 200mg modified-release tablets
95184979	Sodium valproate 200mg modified-release tablets

95186979 Sodium valproate 200mg modified-release tablets
95188979 Sodium valproate 200mg modified-release tablets
94408998 Sodium valproate 200mg/5ml oral solution
94568996 Sodium valproate 200mg/5ml oral solution
95160979 Sodium valproate 200mg/5ml oral solution
95163979 Sodium valproate 200mg/5ml oral solution
83766998 Sodium valproate 200mg/5ml oral solution sugar free
92802996 Sodium valproate 200mg/5ml oral solution sugar free
94408997 Sodium valproate 200mg/5ml oral solution sugar free
94568997 Sodium valproate 200mg/5ml oral solution sugar free
95164979 Sodium valproate 200mg/5ml oral solution sugar free
95165979 Sodium valproate 200mg/5ml oral solution sugar free
95810990 Sodium valproate 200mg/5ml oral solution sugar free
96159990 Sodium valproate 200mg/5ml oral solution sugar free
97911990 Sodium valproate 200mg/5ml oral solution sugar free
98929988 Sodium valproate 200mg/5ml oral solution sugar free
81955998 Sodium valproate 250mg modified-release granules sachets sugar free
83706998 Sodium valproate 250mg modified-release granules sachets sugar free
83793998 Sodium valproate 250mg modified-release granules sachets sugar free
84666998 Sodium valproate 300mg modified-release capsules
84670998 Sodium valproate 300mg modified-release capsules
88177998 Sodium valproate 300mg modified-release tablets
92345998 Sodium valproate 300mg modified-release tablets
92917997 Sodium valproate 300mg modified-release tablets
92918997 Sodium valproate 300mg modified-release tablets
95177979 Sodium valproate 300mg modified-release tablets
95180979 Sodium valproate 300mg modified-release tablets
95182979 Sodium valproate 300mg modified-release tablets
95217990 Sodium valproate 300mg modified-release tablets
84720998 Sodium valproate 300mg suppositories
82850978 Sodium valproate 400mg powder and solvent for solution for injection vials
93148998 Sodium valproate 400mg powder and solvent for solution for injection vials
94408996 Sodium valproate 400mg powder and solvent for solution for injection vials
85030998 Sodium valproate 400mg/4ml solution for injection ampoules
83479998 Sodium valproate 500mg gastro-resistant tablets
92802997 Sodium valproate 500mg gastro-resistant tablets
93443990 Sodium valproate 500mg gastro-resistant tablets
94409997 Sodium valproate 500mg gastro-resistant tablets
94606997 Sodium valproate 500mg gastro-resistant tablets
95189979 Sodium valproate 500mg gastro-resistant tablets
95190979 Sodium valproate 500mg gastro-resistant tablets
96977990 Sodium valproate 500mg gastro-resistant tablets
98084990 Sodium valproate 500mg gastro-resistant tablets
98385989 Sodium valproate 500mg gastro-resistant tablets
98929989 Sodium valproate 500mg gastro-resistant tablets
83705998 Sodium valproate 500mg modified-release granules sachets sugar free
84665998 Sodium valproate 500mg modified-release granules sachets sugar free
84669998 Sodium valproate 500mg modified-release granules sachets sugar free
88178998 Sodium valproate 500mg modified-release tablets
90505998 Sodium valproate 500mg modified-release tablets

92917996	Sodium valproate 500mg modified-release tablets
92918996	Sodium valproate 500mg modified-release tablets
95172979	Sodium valproate 500mg modified-release tablets
95175979	Sodium valproate 500mg modified-release tablets
95176979	Sodium valproate 500mg modified-release tablets
95216990	Sodium valproate 500mg modified-release tablets
60278979	Sodium valproate 500mg/5ml oral suspension
81957998	Sodium valproate 50mg modified-release granules sachets sugar free
83708998	Sodium valproate 50mg modified-release granules sachets sugar free
83709998	Sodium valproate 50mg modified-release granules sachets sugar free
65489979	Sodium valproate 600mg/5ml oral solution
65487979	Sodium valproate 60mg/5ml oral solution
81954998	Sodium valproate 750mg modified-release granules sachets sugar free
83704998	Sodium valproate 750mg modified-release granules sachets sugar free
83791998	Sodium valproate 750mg modified-release granules sachets sugar free
83792998	Sodium valproate with valproic acid 500mg modified release granules
84098998	Stiripentol 250mg capsules
84096998	Stiripentol 250mg oral powder sachets
84097998	Stiripentol 500mg capsules
84095998	Stiripentol 500mg oral powder sachets
98152992	Sulthiame 200 mg tab
98147992	Sulthiame 50 mg tab
86670998	Sultiame 200mg tablets
86669998	Sultiame 50mg tablets
86671998	Sultiame 50mg tablets
89408997	Tiagabine 10mg tablets
89409997	Tiagabine 10mg tablets
99880998	Tiagabine 10mg tablets
89408996	Tiagabine 15mg tablets
89409996	Tiagabine 15mg tablets
90858998	Tiagabine 15mg tablets
89408998	Tiagabine 5mg tablets
89409998	Tiagabine 5mg tablets
98200998	Tiagabine 5mg tablets
91050997	Topiramate 100mg tablets
91051997	Topiramate 100mg tablets
92331990	Topiramate 100mg tablets
94964979	Topiramate 100mg tablets
94971979	Topiramate 100mg tablets
65327979	Topiramate 100mg/5ml oral solution
65414979	Topiramate 100mg/5ml oral suspension
65325979	Topiramate 10mg/5ml oral solution
65412979	Topiramate 10mg/5ml oral suspension
65410979	Topiramate 12.5mg/5ml oral suspension
88868998	Topiramate 15mg capsules
91044997	Topiramate 15mg capsules
94921979	Topiramate 15mg capsules
63115979	Topiramate 15mg/5ml oral solution
63113979	Topiramate 15mg/5ml oral suspension
91050996	Topiramate 200mg tablets

91051996	Topiramate 200mg tablets
65309979	Topiramate 20mg/5ml oral suspension
57803979	Topiramate 25mg capsules
88868997	Topiramate 25mg capsules
91044996	Topiramate 25mg capsules
94914979	Topiramate 25mg capsules
57805979	Topiramate 25mg tablets
91044998	Topiramate 25mg tablets
91045998	Topiramate 25mg tablets
92298990	Topiramate 25mg tablets
92333990	Topiramate 25mg tablets
94931979	Topiramate 25mg tablets
81770998	Topiramate 25mg/5ml oral suspension
65307979	Topiramate 30mg/5ml oral solution
65305979	Topiramate 30mg/5ml oral suspension
60218979	Topiramate 50mg capsules
88396998	Topiramate 50mg capsules
88868996	Topiramate 50mg capsules
91050998	Topiramate 50mg tablets
91051998	Topiramate 50mg tablets
94972979	Topiramate 50mg tablets
81237998	Topiramate 50mg/5ml oral suspension
65303979	Topiramate 5mg/5ml oral solution
93015998	Valproic acid 150mg gastro-resistant capsules
93016998	Valproic acid 150mg gastro-resistant capsules
94068998	Valproic acid 250mg gastro-resistant tablets
97628998	Valproic acid 250mg gastro-resistant tablets
63575979	Valproic acid 250mg/5ml oral solution
93015997	Valproic acid 300mg gastro-resistant capsules
93016997	Valproic acid 300mg gastro-resistant capsules
93015996	Valproic acid 500mg gastro-resistant capsules
93016996	Valproic acid 500mg gastro-resistant capsules
94068997	Valproic acid 500mg gastro-resistant tablets
97628997	Valproic acid 500mg gastro-resistant tablets
63092979	Valproic acid 500mg/5ml oral solution
93770996	Vigabatrin 125mg capsules
93769997	Vigabatrin 500mg oral powder sachets sugar free
93770997	Vigabatrin 500mg oral powder sachets sugar free
93769998	Vigabatrin 500mg tablets
93770998	Vigabatrin 500mg tablets
66306979	Vigabatrin 500mg/5ml oral solution
95750992	Zarontin 300 mg cap
86841998	Zonisamide 100mg capsules
86844998	Zonisamide 100mg capsules
86843998	Zonisamide 25mg capsules
86846998	Zonisamide 25mg capsules
86842998	Zonisamide 50mg capsules
86845998	Zonisamide 50mg capsules
62296979	Zonisamide 50mg/5ml oral solution
62294979	Zonisamide 50mg/5ml oral suspension

81059998 Zonisamide 50mg/5ml oral suspension

C. Antipsychotics

Drug code	Generic name
91077998	Amisulpride 100mg tablets
91083998	Amisulpride 100mg tablets
94545990	Amisulpride 100mg tablets
94845990	Amisulpride 100mg tablets
90209998	Amisulpride 100mg/ml oral solution sugar free
91425998	Amisulpride 100mg/ml oral solution sugar free
64991979	Amisulpride 12.5mg/5ml oral solution
64989979	Amisulpride 12.5mg/5ml oral suspension
88383997	Amisulpride 200mg tablets
88387997	Amisulpride 200mg tablets
94544990	Amisulpride 200mg tablets
94844990	Amisulpride 200mg tablets
96360979	Amisulpride 200mg tablets
96363979	Amisulpride 200mg tablets
81131998	Amisulpride 25mg/5ml oral solution
86433998	Amisulpride 25mg/5ml oral suspension
88383996	Amisulpride 400mg tablets
88387996	Amisulpride 400mg tablets
88383998	Amisulpride 50mg tablets
88387998	Amisulpride 50mg tablets
91785990	Amisulpride 50mg tablets
94546990	Amisulpride 50mg tablets
94846990	Amisulpride 50mg tablets
81029979	Amisulpride 50mg/5ml oral suspension
94703998	Amitriptyline 10mg / perphenazine 2mg tablets
94703997	Amitriptyline 25mg / Perphenazine 2mg tablets
95574997	Amitriptyline 25mg / Perphenazine 2mg tablets
99017998	Amitriptyline 25mg / Perphenazine 2mg tablets
83620998	Amitriptyline hydrochloride & perphenazine 10mg+2mg tablets
99017997	Amitriptyline hydrochloride & perphenazine 10mg+2mg tablets
85834998	Aripiprazole 10mg orodispersible tablets sugar free
85837998	Aripiprazole 10mg orodispersible tablets sugar free
87450998	Aripiprazole 10mg tablets
87453998	Aripiprazole 10mg tablets
89524979	Aripiprazole 10mg tablets
85833998	Aripiprazole 15mg orodispersible tablets sugar free
85836998	Aripiprazole 15mg orodispersible tablets sugar free
55724978	Aripiprazole 15mg tablets
87449998	Aripiprazole 15mg tablets
87452998	Aripiprazole 15mg tablets
89520979	Aripiprazole 15mg tablets
85832998	Aripiprazole 1mg/ml oral solution
85835998	Aripiprazole 1mg/ml oral solution
39298978	Aripiprazole 30mg tablets
55056978	Aripiprazole 30mg tablets

87448998 Aripiprazole 30mg tablets
87451998 Aripiprazole 30mg tablets
39109978 Aripiprazole 400mg powder and solvent for suspension for injection vials
39110978 Aripiprazole 400mg powder and solvent for suspension for injection vials
78405978 Aripiprazole 400mg powder and solvent for suspension for injection vials
78406978 Aripiprazole 400mg powder and solvent for suspension for injection vials
39301978 Aripiprazole 5mg tablets
87089998 Aripiprazole 5mg tablets
87090998 Aripiprazole 5mg tablets
89532979 Aripiprazole 5mg tablets
83903998 Aripiprazole 9.75mg/1.3ml solution for injection vials
81170998 Asenapine 10mg sublingual tablets sugar free
81172998 Asenapine 5mg sublingual tablets sugar free
82225998 Benperidol 250microgram tablets
88885998 Benperidol 250microgram tablets
95979998 Benperidol 250microgram tablets
95980998 Benperidol 250microgram tablets
93587998 Chlorpromazine 100mg suppository
82892998 Chlorpromazine 100mg tablets
94111992 Chlorpromazine 100mg tablets
96691997 Chlorpromazine 100mg tablets
96919989 Chlorpromazine 100mg tablets
97236988 Chlorpromazine 100mg tablets
97879998 Chlorpromazine 100mg tablets
98192989 Chlorpromazine 100mg tablets
93593997 Chlorpromazine 100mg/5ml oral solution
96690998 Chlorpromazine 100mg/5ml oral solution
98062989 Chlorpromazine 100mg/5ml oral solution
64779979 Chlorpromazine 100mg/5ml oral suspension
93593998 Chlorpromazine 100mg/5ml suspension
59529979 Chlorpromazine 10mg capsules
94822992 Chlorpromazine 10mg tablets
96691998 Chlorpromazine 10mg tablets
96702979 Chlorpromazine 10mg tablets
97880998 Chlorpromazine 10mg tablets
80619979 Chlorpromazine 10mg/5ml oral suspension
97134992 Chlorpromazine 200 mg tab
97131992 Chlorpromazine 25 mg sup
94761998 Chlorpromazine 25mg tablets
94821992 Chlorpromazine 25mg tablets
95365990 Chlorpromazine 25mg tablets
96701979 Chlorpromazine 25mg tablets
97236990 Chlorpromazine 25mg tablets
97880997 Chlorpromazine 25mg tablets
98189990 Chlorpromazine 25mg tablets
98192988 Chlorpromazine 25mg tablets
85704998 Chlorpromazine 25mg/1ml solution for injection ampoules
93242998 Chlorpromazine 25mg/5ml oral solution
96673979 Chlorpromazine 25mg/5ml oral solution
96690996 Chlorpromazine 25mg/5ml oral solution

98062990 Chlorpromazine 25mg/5ml oral solution
95687990 Chlorpromazine 25mg/5ml oral solution sugar free
96674979 Chlorpromazine 25mg/5ml oral solution sugar free
96691996 Chlorpromazine 25mg/5ml oral solution sugar free
99007990 Chlorpromazine 25mg/5ml oral solution sugar free
94107992 Chlorpromazine 50mg tablets
94761997 Chlorpromazine 50mg tablets
95364990 Chlorpromazine 50mg tablets
96687979 Chlorpromazine 50mg tablets
96689979 Chlorpromazine 50mg tablets
96919990 Chlorpromazine 50mg tablets
97236989 Chlorpromazine 50mg tablets
97880996 Chlorpromazine 50mg tablets
98192990 Chlorpromazine 50mg tablets
99010990 Chlorpromazine 50mg tablets
85702998 Chlorpromazine 50mg/2ml solution for injection ampoules
93590998 Chlorpromazine 50mg/2ml solution for injection ampoules
96102992 Chlorpromazine 50mg/2ml solution for injection ampoules
97021992 Chlorpromazine 50mg/2ml solution for injection ampoules
97132992 Chlorpromazine 50mg/2ml solution for injection ampoules
97874998 Chlorpromazine 50mg/2ml solution for injection ampoules
98186990 Chlorpromazine 50mg/2ml solution for injection ampoules
96690997 Chlorpromazine 50mg/5ml oral solution
97129992 Chlorpromazine hcl 10 mg inj
96614992 Chlorpromazine hcl 100 mg mix
97871998 Chlorpromazine hydrochloride 100mg suppositories
96689996 Chlorpromazine hydrochloride 100mg tablets
95200992 Chlorpromazine hydrochloride 100mg/5ml sugar free suspension
97877998 Chlorpromazine hydrochloride 100mg/5ml sugar free suspension
96689998 Chlorpromazine hydrochloride 25mg tablets
96689997 Chlorpromazine hydrochloride 50mg tablets
96686997 Chlorprothixene 50mg tablets
99073997 Chlorprothixene 50mg tablets
87019998 Clozapine 100mg tablets
87340998 Clozapine 100mg tablets
93595997 Clozapine 100mg tablets
93596997 Clozapine 100mg tablets
82800998 Clozapine 200mg tablets
82801998 Clozapine 200mg tablets
87020998 Clozapine 25mg tablets
87341998 Clozapine 25mg tablets
93595998 Clozapine 25mg tablets
93596998 Clozapine 25mg tablets
82802998 Clozapine 50mg tablets
82803998 Clozapine 50mg tablets
82798998 Clozapine 50mg/ml oral suspension sugar free
82799998 Clozapine 50mg/ml oral suspension sugar free
94891992 Dartalan 5 mg tab
96303998 Droperidol 10mg tablets
97343998 Droperidol 10mg tablets

97343997	Droperidol 10mg/2ml injection
79122979	Droperidol 1mg capsules
93674998	Droperidol 1mg/1ml oral liquid
96303997	Droperidol 1mg/ml liquid
82873998	Droperidol 2.5mg/1ml solution for injection ampoules
97334992	Droperidol 5 mg/5ml eli
69237979	Droperidol 5mg/5ml oral solution
93675998	Droperidol 5mg/ml injection
96551998	Fentanyl with droperidol 500microgramwith2.5mg/ml injection
96504997	Flupentixol 1mg tablets
99634997	Flupentixol 1mg tablets
96503998	Flupentixol 3mg tablets
99776998	Flupentixol 3mg tablets
96504998	Flupentixol 500microgram tablets
99634998	Flupentixol 500microgram tablets
96501998	Fluphenazine 1mg tablets
99411998	Fluphenazine 1mg tablets
96501997	Fluphenazine 2.5mg tablets
96501996	Fluphenazine 5mg tablets
97466992	Fluphenazine hcl eli
97632998	Fluphenazine hydrochloride & nortriptyline 1.5mg+30mg tablets
96499998	Fluphenazine hydrochloride & nortriptyline 500mcg+10mg tablets
97634998	Fluphenazine hydrochloride & nortriptyline 500mcg+10mg tablets
99411997	Fluphenazine hydrochloride 2.5mg tablets
99411996	Fluphenazine hydrochloride 5mg tablets
96265992	Haldol 20 mg tab
95086992	Haloperidol 1.5mg tablets
96115990	Haloperidol 1.5mg tablets
96249997	Haloperidol 1.5mg tablets
96662979	Haloperidol 1.5mg tablets
97135989	Haloperidol 1.5mg tablets
97946997	Haloperidol 1.5mg tablets
98131990	Haloperidol 1.5mg tablets
98360988	Haloperidol 1.5mg tablets
98544990	Haloperidol 1.5mg tablets
67935979	Haloperidol 1.5mg/5ml oral suspension
92815998	Haloperidol 1.5mg/5ml sugar free oral solution
98080990	Haloperidol 1.5mg/5ml sugar free oral solution
96248998	Haloperidol 10mg tablets
97346997	Haloperidol 10mg tablets
97945998	Haloperidol 10mg tablets
97345997	Haloperidol 10mg/2ml injection
96242997	Haloperidol 10mg/5ml oral liquid
81467998	Haloperidol 10mg/5ml oral solution sugar free
92815996	Haloperidol 10mg/5ml oral solution sugar free
96247998	Haloperidol 10mg/5ml oral solution sugar free
96891989	Haloperidol 10mg/5ml oral solution sugar free
97346996	Haloperidol 10mg/5ml oral solution sugar free
97945996	Haloperidol 10mg/5ml oral solution sugar free
98625990	Haloperidol 10mg/5ml oral solution sugar free

96247997	Haloperidol 10mg/ml oral solution
97345998	Haloperidol 10mg/ml oral solution
81081998	Haloperidol 1mg/5ml oral solution
96247996	Haloperidol 1mg/5ml oral solution
98625988	Haloperidol 1mg/5ml oral solution
81115998	Haloperidol 1mg/5ml oral suspension
91921998	Haloperidol 1mg/ml sugar free Oral solution
96248997	Haloperidol 20mg tablets
96645979	Haloperidol 20mg tablets
97945997	Haloperidol 20mg tablets
96758992	Haloperidol 20mg/2ml injection
97944997	Haloperidol 20mg/2ml injection
93695997	Haloperidol 20mg/2ml solution for injection ampoules
87190998	Haloperidol 250micrograms/5ml oral suspension
79934979	Haloperidol 2mg/5ml oral solution
79932979	Haloperidol 2mg/5ml oral suspension
92815997	Haloperidol 2mg/5ml sugar free oral solution
96244998	Haloperidol 500mcg tablets
97946998	Haloperidol 500microgram capsules
95242990	Haloperidol 500microgram tablets
96246998	Haloperidol 500microgram tablets
96249998	Haloperidol 500microgram tablets
96889988	Haloperidol 500microgram tablets
97135990	Haloperidol 500microgram tablets
79930979	Haloperidol 500micrograms/5ml oral solution
79928979	Haloperidol 500micrograms/5ml oral suspension
96249996	Haloperidol 5mg tablets
96889990	Haloperidol 5mg tablets
97346998	Haloperidol 5mg tablets
97946996	Haloperidol 5mg tablets
98154990	Haloperidol 5mg tablets
98544988	Haloperidol 5mg tablets
83786998	Haloperidol 5mg/1ml solution for injection ampoules
83787998	Haloperidol 5mg/1ml solution for injection ampoules
97944998	Haloperidol 5mg/1ml solution for injection ampoules
98155990	Haloperidol 5mg/1ml solution for injection ampoules
67918979	Haloperidol 5mg/5ml oral solution
81468998	Haloperidol 5mg/5ml oral solution sugar free
91932990	Haloperidol 5mg/5ml oral solution sugar free
96242998	Haloperidol 5mg/5ml oral solution sugar free
96248996	Haloperidol 5mg/5ml oral solution sugar free
96389990	Haloperidol 5mg/5ml oral solution sugar free
97568992	Haloperidol 5mg/5ml oral solution sugar free
98131989	Haloperidol 5mg/5ml oral solution sugar free
98625989	Haloperidol 5mg/5ml oral solution sugar free
67916979	Haloperidol 5mg/5ml oral suspension
93695998	Haloperidol 5mg/ml injection
99112998	Isopropamide iodide with trifluoperazine tablet
95919997	Levomepromazine 25mg tablets
98853997	Levomepromazine 25mg tablets

53671979	Levomepromazine 25mg/1ml solution for injection ampoules
95919998	Levomepromazine 25mg/1ml solution for injection ampoules
96634979	Levomepromazine 25mg/1ml solution for injection ampoules
98853998	Levomepromazine 25mg/1ml solution for injection ampoules
95918998	Levomepromazine maleate 25mg tablets
94006998	Loxapine 10mg capsules
94007998	Loxapine 10mg capsules
94006997	Loxapine 25mg capsules
94007997	Loxapine 25mg capsules
94006996	Loxapine 50mg capsules
94007996	Loxapine 50mg capsules
68754978	Lurasidone 18.5mg tablets
68755978	Lurasidone 18.5mg tablets
68752978	Lurasidone 37mg tablets
68753978	Lurasidone 37mg tablets
68750978	Lurasidone 74mg tablets
68751978	Lurasidone 74mg tablets
94630998	Nortriptyline 10mg / fluphenazine 500microgram tablets
94630997	Nortriptyline 30mg / fluphenazine 1.5mg tablets
91618997	Olanzapine 10mg oral lyophilisates sugar free
96404979	Olanzapine 10mg oral lyophilisates sugar free
61165979	Olanzapine 10mg orodispersible tablets sugar free
61585979	Olanzapine 10mg orodispersible tablets sugar free
80976998	Olanzapine 10mg orodispersible tablets sugar free
80977998	Olanzapine 10mg orodispersible tablets sugar free
80978998	Olanzapine 10mg orodispersible tablets sugar free
81040998	Olanzapine 10mg orodispersible tablets sugar free
90659996	Olanzapine 10mg orodispersible tablets sugar free
91866990	Olanzapine 10mg orodispersible tablets sugar free
87647998	Olanzapine 10mg powder for solution for injection vials
89567996	Olanzapine 10mg tablets
89569996	Olanzapine 10mg tablets
91870990	Olanzapine 10mg tablets
60067979	Olanzapine 15mg oral lyophilisates sugar free
91364998	Olanzapine 15mg oral lyophilisates sugar free
61131979	Olanzapine 15mg orodispersible tablets sugar free
61583979	Olanzapine 15mg orodispersible tablets sugar free
61610979	Olanzapine 15mg orodispersible tablets sugar free
80972998	Olanzapine 15mg orodispersible tablets sugar free
80973998	Olanzapine 15mg orodispersible tablets sugar free
80974998	Olanzapine 15mg orodispersible tablets sugar free
91825990	Olanzapine 15mg orodispersible tablets sugar free
97995998	Olanzapine 15mg orodispersible tablets sugar free
81043998	Olanzapine 15mg tablets
91869990	Olanzapine 15mg tablets
97111998	Olanzapine 15mg tablets
97433998	Olanzapine 15mg tablets
90659998	Olanzapine 2.5mg tablets
90664998	Olanzapine 2.5mg tablets
96421979	Olanzapine 2.5mg tablets

64673979	Olanzapine 2.5mg/5ml oral suspension
85376998	Olanzapine 20mg oral lyophilisates sugar free
86324998	Olanzapine 20mg oral lyophilisates sugar free
61145979	Olanzapine 20mg orodispersible tablets
61581979	Olanzapine 20mg orodispersible tablets
80969998	Olanzapine 20mg orodispersible tablets
80970998	Olanzapine 20mg orodispersible tablets
80971998	Olanzapine 20mg orodispersible tablets
86325998	Olanzapine 20mg orodispersible tablets
91824990	Olanzapine 20mg orodispersible tablets
91864990	Olanzapine 20mg orodispersible tablets
85377998	Olanzapine 20mg tablets
90190979	Olanzapine 20mg tablets
91828990	Olanzapine 20mg tablets
91618998	Olanzapine 5mg oral lyophilisates sugar free
61166979	Olanzapine 5mg orodispersible tablets sugar free
61579979	Olanzapine 5mg orodispersible tablets sugar free
61602979	Olanzapine 5mg orodispersible tablets sugar free
80979998	Olanzapine 5mg orodispersible tablets sugar free
80980998	Olanzapine 5mg orodispersible tablets sugar free
80981998	Olanzapine 5mg orodispersible tablets sugar free
81041998	Olanzapine 5mg orodispersible tablets sugar free
90659997	Olanzapine 5mg orodispersible tablets sugar free
91827990	Olanzapine 5mg orodispersible tablets sugar free
91867990	Olanzapine 5mg orodispersible tablets sugar free
89567998	Olanzapine 5mg tablets
89569998	Olanzapine 5mg tablets
96450979	Olanzapine 5mg tablets
89567997	Olanzapine 7.5mg tablets
89569997	Olanzapine 7.5mg tablets
91871990	Olanzapine 7.5mg tablets
82202998	Olanzapine embonate 210mg powder and solvent for suspension for injection vials
82199998	Olanzapine embonate 300mg powder and solvent for suspension for injection vials
82201998	Olanzapine embonate 300mg powder and solvent for suspension for injection vials
82198998	Olanzapine embonate 405mg powder and solvent for suspension for injection vials
95650998	Oxypertine 10mg capsules
99530998	Oxypertine 10mg capsules
93699998	Oxypertine 40mg tablets
95649998	Oxypertine 40mg tablets
81419998	Paliperidone 100mg/1ml suspension for injection pre-filled syringes
81423998	Paliperidone 100mg/1ml suspension for injection pre-filled syringes
54952979	Paliperidone 100mg+150mg initial treatment set
81418998	Paliperidone 150mg/1.5ml suspension for injection pre-filled syringes
81422998	Paliperidone 150mg/1.5ml suspension for injection pre-filled syringes
54953979	Paliperidone 150mg/1.5ml suspension for injection pre-filled syringes and paliperido
30146978	Paliperidone 350mg/1.75ml prolonged-release suspension for injection pre-filled syr
84524998	Paliperidone 3mg modified-release tablets
84527998	Paliperidone 3mg modified-release tablets
81421998	Paliperidone 50mg/0.5ml suspension for injection pre-filled syringes
81425998	Paliperidone 50mg/0.5ml suspension for injection pre-filled syringes

30145978	Paliperidone 525mg/2.625ml prolonged-release suspension for injection pre-filled sy
84523998	Paliperidone 6mg modified-release tablets
84526998	Paliperidone 6mg modified-release tablets
81420998	Paliperidone 75mg/0.75ml suspension for injection pre-filled syringes
81424998	Paliperidone 75mg/0.75ml suspension for injection pre-filled syringes
84522998	Paliperidone 9mg modified-release tablets
84525998	Paliperidone 9mg modified-release tablets
83019998	Pericyazine 10mg tablets
95577997	Pericyazine 10mg tablets
99362997	Pericyazine 10mg tablets
95576998	Pericyazine 10mg/5ml oral solution
98865998	Pericyazine 10mg/5ml oral solution
97878992	Pericyazine 2.5 mg eli
83020998	Pericyazine 2.5mg tablets
95577998	Pericyazine 2.5mg tablets
99362998	Pericyazine 2.5mg tablets
95577996	Pericyazine 25mg tablet
99362996	Pericyazine 25mg tablets
95575997	Perphenazine 2mg tablets
99651998	Perphenazine 2mg tablets
95574998	Perphenazine 2mg with amitriptyline 10mg tablet
97786998	Perphenazine 2mg/5ml oral solution sugar free
95575996	Perphenazine 4mg tablets
99651997	Perphenazine 4mg tablets
97786997	Perphenazine 4mg/5ml oral solution sugar free
98587998	Perphenazine 5mg/1ml injection
95575998	Perphenazine 5mg/ml injection
97877992	Perphenazine 8 mg tab
94164992	Perphenazine 8mg tablets
95516996	Pimozide 10mg tablet
97342996	Pimozide 10mg tablets
72658978	Pimozide 1mg tablets
95516998	Pimozide 2mg tablets
97342998	Pimozide 2mg tablets
95516997	Pimozide 4mg tablets
97342997	Pimozide 4mg tablets
93476998	Promazine 100mg tablet
98786996	Promazine 100mg tablet
95386996	Promazine 12.5mg/5ml oral solution
93328990	Promazine 25mg tablets
93477998	Promazine 25mg tablets
96750992	Promazine 25mg tablets
98786998	Promazine 25mg tablets
99093990	Promazine 25mg tablets
95386997	Promazine 25mg/5ml oral solution
96950990	Promazine 25mg/5ml oral solution
98063990	Promazine 25mg/5ml oral solution
93477997	Promazine 50mg tablets
98786997	Promazine 50mg tablets
99093988	Promazine 50mg tablets

95385997	Promazine 50mg/5ml oral solution
95386998	Promazine 50mg/5ml oral solution
96950989	Promazine 50mg/5ml oral solution
98063989	Promazine 50mg/5ml oral solution
95385998	Promazine 50mg/5ml oral solution sugar free
65890979	Promazine 50mg/5ml oral suspension
93708997	Promazine 50mg/ml injection
93708998	Promazine 50mg/ml injection
97406989	Promazine 50mg/ml injection
65886979	Promazine 6.25mg/5ml oral suspension
99117998	Promazine hydrochloride 100mg/2ml injection
98783998	Promazine hydrochloride 50mg/5ml suspension
68663978	Quetiapine 100mg tablets
88734996	Quetiapine 100mg tablets
88737996	Quetiapine 100mg tablets
96395979	Quetiapine 100mg tablets
82773998	Quetiapine 100mg/5ml oral solution
82772998	Quetiapine 100mg/5ml oral suspension
81236998	Quetiapine 12.5mg/5ml oral solution
81113998	Quetiapine 12.5mg/5ml oral suspension
66395979	Quetiapine 125mg/5ml oral suspension
53079979	Quetiapine 150mg modified-release tablets
55253978	Quetiapine 150mg modified-release tablets
55254978	Quetiapine 150mg modified-release tablets
81923998	Quetiapine 150mg modified-release tablets
81924998	Quetiapine 150mg modified-release tablets
88733997	Quetiapine 150mg tablets
88736997	Quetiapine 150mg tablets
66391979	Quetiapine 150mg/5ml oral suspension
55544979	Quetiapine 200mg modified-release tablets
55703978	Quetiapine 200mg modified-release tablets
55704978	Quetiapine 200mg modified-release tablets
59369979	Quetiapine 200mg modified-release tablets
72639978	Quetiapine 200mg modified-release tablets
83492998	Quetiapine 200mg modified-release tablets
83995998	Quetiapine 200mg modified-release tablets
52736979	Quetiapine 200mg tablets
88733998	Quetiapine 200mg tablets
88736998	Quetiapine 200mg tablets
96387979	Quetiapine 200mg tablets
82888978	Quetiapine 200mg/5ml oral suspension
52738979	Quetiapine 25mg tablets
53211979	Quetiapine 25mg tablets
58638979	Quetiapine 25mg tablets
59467979	Quetiapine 25mg tablets
59468979	Quetiapine 25mg tablets
59469979	Quetiapine 25mg tablets
88734997	Quetiapine 25mg tablets
88737997	Quetiapine 25mg tablets
96402979	Quetiapine 25mg tablets

66389979	Quetiapine 25mg/5ml oral solution
81473998	Quetiapine 25mg/5ml oral suspension
88734998	Quetiapine 25mg+100mg+150mg tablets starter pack
55705978	Quetiapine 300mg modified-release tablets
55706978	Quetiapine 300mg modified-release tablets
59370979	Quetiapine 300mg modified-release tablets
72640978	Quetiapine 300mg modified-release tablets
83491998	Quetiapine 300mg modified-release tablets
83994998	Quetiapine 300mg modified-release tablets
88938979	Quetiapine 300mg modified-release tablets
58553979	Quetiapine 300mg tablets
87907998	Quetiapine 300mg tablets
87908998	Quetiapine 300mg tablets
55701978	Quetiapine 400mg modified-release tablets
55702978	Quetiapine 400mg modified-release tablets
59368979	Quetiapine 400mg modified-release tablets
68593978	Quetiapine 400mg modified-release tablets
72638978	Quetiapine 400mg modified-release tablets
83490998	Quetiapine 400mg modified-release tablets
83993998	Quetiapine 400mg modified-release tablets
88924979	Quetiapine 400mg modified-release tablets
51498978	Quetiapine 50mg modified-release tablets
55083979	Quetiapine 50mg modified-release tablets
55266978	Quetiapine 50mg modified-release tablets
55267978	Quetiapine 50mg modified-release tablets
58799979	Quetiapine 50mg modified-release tablets
64621979	Quetiapine 50mg modified-release tablets
64622979	Quetiapine 50mg modified-release tablets
64625979	Quetiapine 50mg modified-release tablets
70478978	Quetiapine 50mg modified-release tablets
83493998	Quetiapine 50mg modified-release tablets
83996998	Quetiapine 50mg modified-release tablets
63673979	Quetiapine 50mg/5ml oral solution
63671979	Quetiapine 50mg/5ml oral suspension
88737998	Quetiapine starter pack
93344998	Remoxipride 150mg capsule
93344997	Remoxipride 300mg capsule
93335998	Remoxipride hydrochloride 150mg modified release capsules
93335997	Remoxipride hydrochloride 300mg modified release capsules
90395998	Risperidone 1mg orodispersible tablets sugar free
91374998	Risperidone 1mg orodispersible tablets sugar free
92917990	Risperidone 1mg tablets
92956990	Risperidone 1mg tablets
96554979	Risperidone 1mg tablets
98585998	Risperidone 1mg tablets
99649998	Risperidone 1mg tablets
46610978	Risperidone 1mg/ml oral solution sugar free
92908990	Risperidone 1mg/ml oral solution sugar free
93240997	Risperidone 1mg/ml oral solution sugar free
99637997	Risperidone 1mg/ml oral solution sugar free

55523979 Risperidone 25mg powder and solvent for suspension for injection vials
88164998 Risperidone 25mg powder and solvent for suspension for injection vials
91676998 Risperidone 25mg powder and solvent for suspension for injection vials
90396998 Risperidone 2mg orodispersible tablets sugar free
92107998 Risperidone 2mg orodispersible tablets sugar free
52748979 Risperidone 2mg tablets
79816978 Risperidone 2mg tablets
92955990 Risperidone 2mg tablets
98585997 Risperidone 2mg tablets
99649997 Risperidone 2mg tablets
88163998 Risperidone 37.5mg powder and solvent for suspension for injection vials
92089998 Risperidone 37.5mg powder and solvent for suspension for injection vials
85039998 Risperidone 3mg orodispersible tablets sugar free
85042998 Risperidone 3mg orodispersible tablets sugar free
92954990 Risperidone 3mg tablets
96914992 Risperidone 3mg tablets
98585996 Risperidone 3mg tablets
99649996 Risperidone 3mg tablets
85038998 Risperidone 4mg orodispersible tablets sugar free
85040998 Risperidone 4mg orodispersible tablets sugar free
92953990 Risperidone 4mg tablets
93240998 Risperidone 4mg tablets
99637998 Risperidone 4mg tablets
86983998 Risperidone 500microgram orodispersible tablets sugar free
86984998 Risperidone 500microgram orodispersible tablets sugar free
92491990 Risperidone 500microgram orodispersible tablets sugar free
92625990 Risperidone 500microgram orodispersible tablets sugar free
91968998 Risperidone 500microgram tablets
92023998 Risperidone 500microgram tablets
92957990 Risperidone 500microgram tablets
89908998 Risperidone 50mg powder and solvent for suspension for injection vials
95519998 Risperidone 50mg powder and solvent for suspension for injection vials
93240996 Risperidone 6mg tablets
99637996 Risperidone 6mg tablets
89809997 Sertindole 12mg tablets
89812997 Sertindole 12mg tablets
89809996 Sertindole 16mg tablets
89812996 Sertindole 16mg tablets
89808998 Sertindole 20mg tablets
89811998 Sertindole 20mg tablets
89809998 Sertindole 4mg tablets
89812998 Sertindole 4mg tablets
90805998 Sulpiride 200mg tablets
95226998 Sulpiride 200mg tablets
97163990 Sulpiride 200mg tablets
97176998 Sulpiride 200mg tablets
97858990 Sulpiride 200mg tablets
97966990 Sulpiride 200mg tablets
98796998 Sulpiride 200mg tablets
89497979 Sulpiride 200mg/5ml oral solution sugar free

90158998	Sulpiride 200mg/5ml oral solution sugar free
95226997	Sulpiride 200mg/5ml oral solution sugar free
95226996	Sulpiride 400mg tablets
95524990	Sulpiride 400mg tablets
97163989	Sulpiride 400mg tablets
98796997	Sulpiride 400mg tablets
98149992	Sulpiride 500 mg tab
98174992	Thiopropazate hcl 10 mg tab
98175992	Thiopropazate hcl 5 mg tab
96492992	Thioproperazine mesylate 10 mg tab
98173992	Thioproperazine mesylate 25 mg tab
95174998	Thioridazine 100mg tablets
98404988	Thioridazine 100mg tablets
99436998	Thioridazine 100mg tablets
95174996	Thioridazine 100mg/5ml oral suspension
98899997	Thioridazine 100mg/5ml oral suspension
92821997	Thioridazine 100mg/5ml sugar free oral solution
95175998	Thioridazine 10mg tablets
99437998	Thioridazine 10mg tablets
95173997	Thioridazine 10mg/5ml oral solution
98403989	Thioridazine 10mg/5ml oral solution
95175997	Thioridazine 25mg tablets
97715990	Thioridazine 25mg tablets
98003990	Thioridazine 25mg tablets
98404990	Thioridazine 25mg tablets
99437997	Thioridazine 25mg tablets
95173996	Thioridazine 25mg/5ml oral solution
95173998	Thioridazine 25mg/5ml oral solution
98003989	Thioridazine 25mg/5ml oral solution
98403990	Thioridazine 25mg/5ml oral solution
98899996	Thioridazine 25mg/5ml oral solution
95174997	Thioridazine 25mg/5ml oral suspension
98899998	Thioridazine 25mg/5ml oral suspension
95175996	Thioridazine 50mg tablets
97715989	Thioridazine 50mg tablets
98003988	Thioridazine 50mg tablets
98404989	Thioridazine 50mg tablets
99437996	Thioridazine 50mg tablets
92821998	Thioridazine 50mg/5ml oral solution
64178979	Thioridazine 50mg/5ml oral suspension
96491992	Thioridazine concentrate 750mg/5ml 750 mg eli
96570992	Thioridazine s/f 50 mg/5ml syr
99280998	Tranylcypromine & trifluoperazine 10mg+1mg tablets
95143998	Tranylcypromine with trifluoperazine tablet
99108996	Trifluoperazine 10mg modified release capsules
95119996	Trifluoperazine 10mg modified-release capsules
95119998	Trifluoperazine 10mg/ml concentrate
99108998	Trifluoperazine 10mg/ml concentrate
99107998	Trifluoperazine 15mg modified release capsules
95118998	Trifluoperazine 15mg modified-release capsules

54534979	Trifluoperazine 1mg tablets
92623998	Trifluoperazine 1mg tablets
95607992	Trifluoperazine 1mg tablets
96586979	Trifluoperazine 1mg tablets
98052989	Trifluoperazine 1mg tablets
98400990	Trifluoperazine 1mg tablets
99109998	Trifluoperazine 1mg tablets
99107997	Trifluoperazine 1mg/1ml injection
59474979	Trifluoperazine 1mg/5ml oral solution sugar free
92623997	Trifluoperazine 1mg/5ml oral solution sugar free
99109996	Trifluoperazine 1mg/5ml oral solution sugar free
95118997	Trifluoperazine 1mg/ml injection
99108997	Trifluoperazine 2mg modified release capsules
92623996	Trifluoperazine 2mg modified-release capsules
54533979	Trifluoperazine 5mg tablets
95119997	Trifluoperazine 5mg tablets
96580979	Trifluoperazine 5mg tablets
98052990	Trifluoperazine 5mg tablets
99109997	Trifluoperazine 5mg tablets
87435998	Trifluoperazine 5mg/5ml oral solution sugar free
95118996	Trifluoperazine 5mg/5ml oral solution sugar free
98203992	Trifluoperazine 5mg/5ml oral solution sugar free
98206992	Trifluoperazine tab
94626998	Trifluoperazine with tranylcypromine 1mg + 10mg tablet
95117998	Trifluperidol 0.5mg tablet
95117997	Trifluperidol 1mg tablet
95116997	Trifluperidol 1mg tablets
98204992	Trifluperidol 2 mg tab
95116998	Trifluperidol 500mcg tablets
98190996	Zotepine 100mg tablets
99337996	Zotepine 100mg tablets
98190998	Zotepine 25mg tablets
99337998	Zotepine 25mg tablets
98190997	Zotepine 50mg tablets
99337997	Zotepine 50mg tablets
96629997	Zuclopenthixol 10mg tablets
99821997	Zuclopenthixol 10mg tablets
96629996	Zuclopenthixol 25mg tablets
99821996	Zuclopenthixol 25mg tablets
96629998	Zuclopenthixol 2mg tablets
99821998	Zuclopenthixol 2mg tablets
86332998	Zuclopenthixol acetate 100mg/2ml oily injection
93519998	Zuclopenthixol acetate 100mg/2ml oily injection
86334998	Zuclopenthixol acetate 100mg/2ml solution for injection ampoules
86333998	Zuclopenthixol acetate 50mg/1ml solution for injection ampoules
86335998	Zuclopenthixol acetate 50mg/1ml solution for injection ampoules
93520998	Zuclopenthixol acetate 50mg/ml oily injection

D. Antipsychotic depots

Drug code	Generic name
39109978	Aripiprazole 400mg powder and solvent for suspension for injection vials
39110978	Aripiprazole 400mg powder and solvent for suspension for injection vials
78405978	Aripiprazole 400mg powder and solvent for suspension for injection vials
78406978	Aripiprazole 400mg powder and solvent for suspension for injection vials
86420998	Flupentixol 100mg/1ml solution for injection ampoules
86422998	Flupentixol 100mg/1ml solution for injection ampoules
86536998	Flupentixol 100mg/1ml solution for injection ampoules
96502996	Flupentixol 200mg/1ml solution for injection ampoules
97516998	Flupentixol 200mg/1ml solution for injection ampoules
85613998	Flupentixol 20mg/1ml solution for injection ampoules
85614998	Flupentixol 20mg/1ml solution for injection ampoules
86539998	Flupentixol 20mg/1ml solution for injection ampoules
96502998	Flupentixol 20mg/1ml solution for injection ampoules
98766998	Flupentixol 20mg/1ml solution for injection ampoules
94879998	Flupentixol 40mg/2ml solution for injection ampoules
98766997	Flupentixol 40mg/2ml solution for injection ampoules
86421998	Flupentixol 50mg/0.5ml solution for injection ampoules
86423998	Flupentixol 50mg/0.5ml solution for injection ampoules
86537998	Flupentixol 50mg/0.5ml solution for injection ampoules
99775998	Flupentixol 50mg/0.5ml solution for injection ampoules
96502997	Flupentixol decanoate 100mg/ml injection
85294998	Fluphenazine decanoate 100mg/1ml solution for injection ampoules
85296998	Fluphenazine decanoate 100mg/1ml solution for injection ampoules
96498997	Fluphenazine decanoate 100mg/1ml solution for injection ampoules
98668990	Fluphenazine decanoate 100mg/1ml solution for injection ampoules
98759998	Fluphenazine decanoate 100mg/1ml solution for injection ampoules
85300998	Fluphenazine decanoate 12.5mg/0.5ml solution for injection ampoules
85303998	Fluphenazine decanoate 12.5mg/0.5ml solution for injection ampoules
93032992	Fluphenazine decanoate 12.5mg/0.5ml solution for injection ampoules
96342992	Fluphenazine decanoate 12.5mg/0.5ml solution for injection ampoules
96344979	Fluphenazine decanoate 12.5mg/0.5ml solution for injection ampoules
93092998	Fluphenazine decanoate 25mg/1ml oily injection
85299998	Fluphenazine decanoate 25mg/1ml solution for injection ampoules
85302998	Fluphenazine decanoate 25mg/1ml solution for injection ampoules
96286990	Fluphenazine decanoate 25mg/1ml solution for injection ampoules
96742990	Fluphenazine decanoate 25mg/1ml solution for injection ampoules
96498998	Fluphenazine decanoate 25mg/ml injection
85295998	Fluphenazine decanoate 50mg/0.5ml solution for injection ampoules
85297998	Fluphenazine decanoate 50mg/0.5ml solution for injection ampoules
99414998	Fluphenazine decanoate 50mg/2ml prefilled syringes
85298998	Fluphenazine decanoate 50mg/2ml solution for injection ampoules
85301998	Fluphenazine decanoate 50mg/2ml solution for injection ampoules
99408998	Fluphenazine enantate 25mg/1ml injection
96500998	Fluphenazine enanthate 25mg/ml injection
99189998	Fluspirilene 12mg/6ml injection
96494998	Fluspirilene 2mg/ml injection
96245997	Haloperidol decanoate 100mg/1ml solution for injection ampoules
96307992	Haloperidol decanoate 100mg/1ml solution for injection ampoules
97344997	Haloperidol decanoate 100mg/1ml solution for injection ampoules

96245998	Haloperidol decanoate 50mg/1ml solution for injection ampoules
97344998	Haloperidol decanoate 50mg/1ml solution for injection ampoules
82202998	Olanzapine embonate 210mg powder and solvent for suspension for injection vials
82199998	Olanzapine embonate 300mg powder and solvent for suspension for injection vials
82201998	Olanzapine embonate 300mg powder and solvent for suspension for injection vials
82198998	Olanzapine embonate 405mg powder and solvent for suspension for injection vials
81419998	Paliperidone 100mg/1ml suspension for injection pre-filled syringes
81423998	Paliperidone 100mg/1ml suspension for injection pre-filled syringes
54952979	Paliperidone 100mg+150mg initial treatment set
81418998	Paliperidone 150mg/1.5ml suspension for injection pre-filled syringes
81422998	Paliperidone 150mg/1.5ml suspension for injection pre-filled syringes
54953979	Paliperidone 150mg/1.5ml suspension for injection pre-filled syringes and paliperido injectio
30146978	Paliperidone 350mg/1.75ml prolonged-release suspension for injection pre-filled syr
81421998	Paliperidone 50mg/0.5ml suspension for injection pre-filled syringes
81425998	Paliperidone 50mg/0.5ml suspension for injection pre-filled syringes
30145978	Paliperidone 525mg/2.625ml prolonged-release suspension for injection pre-filled sy
81420998	Paliperidone 75mg/0.75ml suspension for injection pre-filled syringes
81424998	Paliperidone 75mg/0.75ml suspension for injection pre-filled syringes
85411998	Pipotiazine 100mg/2ml solution for injection ampoules
85413998	Pipotiazine 50mg/1ml solution for injection ampoules
85409998	Pipotiazine palmitate 100mg/2ml oily injection
98622998	Pipotiazine palmitate 100mg/2ml oily injection
85410998	Pipotiazine palmitate 50mg/1ml oily injection
95503998	Pipotiazine palmitate 50mg/ml depot injection
86332998	Zuclopenthixol acetate 100mg/2ml oily injection
86333998	Zuclopenthixol acetate 50mg/1ml solution for injection ampoules
85607998	Zuclopenthixol decanoate 200mg/1ml solution for injection ampoules
85609998	Zuclopenthixol decanoate 200mg/1ml solution for injection ampoules
96628998	Zuclopenthixol decanoate 200mg/ml oily injection
95071998	Zuclopenthixol decanoate 500mg/1ml solution for injection ampoules
96628997	Zuclopenthixol decanoate 500mg/1ml solution for injection ampoules
98767998	Zuclopenthixol decanoate 500mg/1ml solution for injection ampoules

E. Anxiolytics

Drug code	Generic name
95051998	Alprazolam 250microgram tablets
97901998	Alprazolam 250microgram tablets
95051997	Alprazolam 500microgram tablets
97901997	Alprazolam 500microgram tablets
95945998	Bromazepam 1.5mg tablets
99476998	Bromazepam 1.5mg tablets
95945997	Bromazepam 3mg tablets
96773979	Bromazepam 3mg tablets
99476997	Bromazepam 3mg tablets
94823997	Buspirone 10mg tablets
94824997	Buspirone 10mg tablets
95498990	Buspirone 10mg tablets
96586989	Buspirone 10mg tablets
96704979	Buspirone 10mg tablets

97143989	Buspirone 10mg tablets
92212990	Buspirone 5mg tablets
94823998	Buspirone 5mg tablets
94824998	Buspirone 5mg tablets
95499990	Buspirone 5mg tablets
96586990	Buspirone 5mg tablets
96715979	Buspirone 5mg tablets
96719979	Buspirone 5mg tablets
97143990	Buspirone 5mg tablets
87286998	Chlordiazepoxide 10mg capsules
96806997	Chlordiazepoxide 10mg capsules
96809997	Chlordiazepoxide 10mg capsules
97777989	Chlordiazepoxide 10mg capsules
98190989	Chlordiazepoxide 10mg capsules
98239988	Chlordiazepoxide 10mg capsules
98248990	Chlordiazepoxide 10mg capsules
98647989	Chlordiazepoxide 10mg capsules
99300989	Chlordiazepoxide 10mg capsules
99474997	Chlordiazepoxide 10mg capsules
93774997	Chlordiazepoxide 10mg tablets
94666990	Chlordiazepoxide 10mg tablets
96805998	Chlordiazepoxide 10mg tablets
96808998	Chlordiazepoxide 10mg tablets
98647988	Chlordiazepoxide 10mg tablets
93774996	Chlordiazepoxide 25mg tablets
96808997	Chlordiazepoxide 25mg tablets
98580990	Chlordiazepoxide 25mg tablets
87287998	Chlordiazepoxide 5mg capsules
96809998	Chlordiazepoxide 5mg capsules
97777990	Chlordiazepoxide 5mg capsules
98190990	Chlordiazepoxide 5mg capsules
98239989	Chlordiazepoxide 5mg capsules
98647990	Chlordiazepoxide 5mg capsules
99300990	Chlordiazepoxide 5mg capsules
99474998	Chlordiazepoxide 5mg capsules
93774998	Chlordiazepoxide 5mg tablets
96809996	Chlordiazepoxide 5mg tablets
98580989	Chlordiazepoxide 5mg tablets
99473998	Chlordiazepoxide hydrochloride 10mg tablets
99473997	Chlordiazepoxide hydrochloride 25mg tablets
96806996	Chlordiazepoxide hydrochloride 5mg tablets
99474996	Chlordiazepoxide hydrochloride 5mg tablets
96808996	Chlordiazepozide 100mg injection
96703998	Chlormezanone 200mg tablets
99035998	Chlormezanone 200mg tablets
86457998	Clobazam 10mg/5ml oral suspension
81126998	Clobazam 5mg/5ml oral solution
86161998	Clobazam 5mg/5ml oral suspension
99032997	Clorazepate dipotassium 15mg capsules
99032998	Clorazepate dipotassium 7.5mg capsules

92901998 Diazepam 10mg suppositories
96408997 Diazepam 10mg suppositories
98648990 Diazepam 10mg suppositories
98995997 Diazepam 10mg suppositories
91282998 Diazepam 10mg tablets
95520990 Diazepam 10mg tablets
96242988 Diazepam 10mg tablets
96311988 Diazepam 10mg tablets
96560988 Diazepam 10mg tablets
97193996 Diazepam 10mg tablets
97216996 Diazepam 10mg tablets
98680988 Diazepam 10mg tablets
98996996 Diazepam 10mg tablets
99631988 Diazepam 10mg tablets
99632988 Diazepam 10mg tablets
99633988 Diazepam 10mg tablets
99634989 Diazepam 10mg tablets
99645988 Diazepam 10mg tablets
89501998 Diazepam 10mg/2.5ml rectal solution tube
94664990 Diazepam 10mg/2.5ml rectal solution tube
96407997 Diazepam 10mg/2.5ml rectal solution tube
97291992 Diazepam 10mg/2.5ml rectal solution tube
97533997 Diazepam 10mg/2.5ml rectal solution tube
98649988 Diazepam 10mg/2.5ml rectal solution tube
99705997 Diazepam 10mg/2.5ml rectal solution tube
92858998 Diazepam 10mg/2ml emulsion for injection ampoules
97282992 Diazepam 10mg/2ml emulsion for injection ampoules
99761998 Diazepam 10mg/2ml emulsion for injection ampoules
96546992 Diazepam 10mg/2ml injection
97532998 Diazepam 10mg/2ml injection
98999998 Diazepam 10mg/2ml injection
92858997 Diazepam 10mg/2ml solution for injection ampoules
96195992 Diazepam 10mg/2ml solution for injection ampoules
97259990 Diazepam 10mg/2ml solution for injection ampoules
98570989 Diazepam 10mg/2ml solution for injection ampoules
85019978 Diazepam 10mg/5ml oral solution
79132979 Diazepam 10mg/5ml oral suspension
92814996 Diazepam 10mg/5ml oral suspension
79130979 Diazepam 1mg/5ml oral solution
92814998 Diazepam 1mg/5ml suspension
96407996 Diazepam 2.5mg/1.25ml rectal solution tube
99705996 Diazepam 2.5mg/1.25ml rectal solution tube
79128979 Diazepam 2.5mg/5ml oral solution
92814997 Diazepam 2.5mg/5ml oral suspension
98079989 Diazepam 2.5mg/5ml oral suspension
97290992 Diazepam 20 mg inj
91354998 Diazepam 20mg rectal tubes
92573998 Diazepam 20mg rectal tubes
96504992 Diazepam 20mg/4ml injection
88944979 Diazepam 25mg/5ml oral solution

96409997 Diazepam 2mg capsules
98998998 Diazepam 2mg capsules
94382990 Diazepam 2mg tablets
94737990 Diazepam 2mg tablets
95997990 Diazepam 2mg tablets
96119990 Diazepam 2mg tablets
96242990 Diazepam 2mg tablets
96311990 Diazepam 2mg tablets
96560990 Diazepam 2mg tablets
97216998 Diazepam 2mg tablets
97766990 Diazepam 2mg tablets
98680990 Diazepam 2mg tablets
98996998 Diazepam 2mg tablets
99631990 Diazepam 2mg tablets
99632990 Diazepam 2mg tablets
99645990 Diazepam 2mg tablets
98997998 Diazepam 2mg/5ml oral solution
30273978 Diazepam 2mg/5ml oral suspension
31208978 Diazepam 2mg/5ml oral suspension
51907978 Diazepam 2mg/5ml oral suspension
61561979 Diazepam 2mg/5ml oral suspension
86049998 Diazepam 2mg/5ml oral suspension
89770979 Diazepam 2mg/5ml oral suspension
93849990 Diazepam 2mg/5ml oral suspension
97215998 Diazepam 2mg/5ml oral suspension
98649989 Diazepam 2mg/5ml oral suspension
99634988 Diazepam 2mg/5ml oral suspension
96409996 Diazepam 5mg
97192997 Diazepam 5mg capsules
98998997 Diazepam 5mg capsules
96408998 Diazepam 5mg suppository
98995998 Diazepam 5mg suppository
95469990 Diazepam 5mg tablets
95996990 Diazepam 5mg tablets
96242989 Diazepam 5mg tablets
96311989 Diazepam 5mg tablets
96560989 Diazepam 5mg tablets
96790979 Diazepam 5mg tablets
96791979 Diazepam 5mg tablets
97216997 Diazepam 5mg tablets
98680989 Diazepam 5mg tablets
98996997 Diazepam 5mg tablets
99235989 Diazepam 5mg tablets
99631989 Diazepam 5mg tablets
99632989 Diazepam 5mg tablets
99633989 Diazepam 5mg tablets
99634990 Diazepam 5mg tablets
99645989 Diazepam 5mg tablets
94837979 Diazepam 5mg/2.5ml rectal solution tube
96407998 Diazepam 5mg/2.5ml rectal solution tube

97292992	Diazepam 5mg/2.5ml rectal solution tube
97533998	Diazepam 5mg/2.5ml rectal solution tube
98135990	Diazepam 5mg/2.5ml rectal solution tube
99705998	Diazepam 5mg/2.5ml rectal solution tube
30258978	Diazepam 5mg/5ml oral suspension
31085978	Diazepam 5mg/5ml oral suspension
85206978	Diazepam 5mg/5ml oral suspension
93848990	Diazepam 5mg/5ml oral suspension
96409998	Diazepam 5mg/5ml oral suspension
98649990	Diazepam 5mg/5ml oral suspension
94354992	Diazepam 5mg/ml rectal solution tube
97293992	Diazepam s/r 10 mg cap
96627997	Dipotassium clorazepate 15mg capsules
96627998	Dipotassium clorazepate 7.5mg capsules
62719979	Generic Kalms tablets
62720979	Generic kalms tablets
81201998	Generic Kalms tablets
85659998	Generic Kalms tablets
96040998	Ketazolam 15mg capsule
99946998	Ketazolam 15mg capsules
96040997	Ketazolam 30mg capsule
99946997	Ketazolam 30mg capsules
94223992	Lorazepam .5 mg tab
97679992	Lorazepam 1 mg sus
47289978	Lorazepam 1mg tablets
59477979	Lorazepam 1mg tablets
92951990	Lorazepam 1mg tablets
93795990	Lorazepam 1mg tablets
95193990	Lorazepam 1mg tablets
96603990	Lorazepam 1mg tablets
97213998	Lorazepam 1mg tablets
98501990	Lorazepam 1mg tablets
99168990	Lorazepam 1mg tablets
99370990	Lorazepam 1mg tablets
99932998	Lorazepam 1mg tablets
84132998	Lorazepam 1mg/5ml oral solution
84134998	Lorazepam 1mg/5ml oral suspension
96603989	Lorazepam 2.5mg tablets
97213997	Lorazepam 2.5mg tablets
99168989	Lorazepam 2.5mg tablets
99370989	Lorazepam 2.5mg tablets
99932997	Lorazepam 2.5mg tablets
79571979	Lorazepam 2mg/5ml oral suspension
99933998	Lorazepam 4mg/1ml injection
95993998	Lorazepam 4mg/1ml solution for injection ampoules
94222992	Lorazepam 5 mg tab
81114998	Lorazepam 500micrograms/5ml oral solution
86430998	Lorazepam 500micrograms/5ml oral suspension
79567979	Lorazepam 5mg/5ml oral solution
79565979	Lorazepam 5mg/5ml oral suspension

95915997	Medazepam 10mg capsule
99349997	Medazepam 10mg capsules
95915998	Medazepam 5mg capsule
99349998	Medazepam 5mg capsules
95898998	Meprobamate 200mg tablet
97302998	Meprobamate 200mg tablets
95898997	Meprobamate 400mg tablets
97302997	Meprobamate 400mg tablets
97716992	Meprobamate 400mg tablets
94335992	Oxazepam 10mg tablets
95666998	Oxazepam 10mg tablets
97013998	Oxazepam 10mg tablets
97549989	Oxazepam 10mg tablets
98241990	Oxazepam 10mg tablets
99713990	Oxazepam 10mg tablets
99716990	Oxazepam 10mg tablets
96374992	OXAZEPAM 15 MG CAP
95578992	Oxazepam 15mg tablets
97013997	Oxazepam 15mg tablets
97549990	Oxazepam 15mg tablets
98241989	Oxazepam 15mg tablets
99713989	Oxazepam 15mg tablets
99716989	Oxazepam 15mg tablets
95667998	Oxazepam 30mg capsule
97013996	Oxazepam 30mg tablet
95666996	Oxazepam 30mg tablets
99843998	Prazepam 10mg tablets
93722992	Serenid forte 30 mg cap
87308998	Valerian 62.5mg / Hops extract 33.4mg tablets

F. Hypnotics

Drug code	Generic name
97113992	Chloral 100 mg eli
98072998	Chloral 200mg/5ml paediatric oral solution
94548998	Chloral 500mg capsules
92874998	Chloral hydrate 143.3mg/5ml oral solution BP
97274997	Chloral hydrate 143.3mg/5ml oral solution BP
80662979	Chloral hydrate 1g/5ml oral solution bp
98073997	Chloral hydrate 1g/5ml oral suspension
80660979	Chloral hydrate 200mg/5ml oral solution bp
59517979	Chloral hydrate 250mg suppositories
80656979	Chloral hydrate 300mg/5ml oral solution bp
68065979	Chloral hydrate 400mg/5ml oral solution bp
97112992	Chloral hydrate 500 mg cap
99347998	Chloral hydrate 500mg capsules
79141979	Chloral hydrate 500mg suppositories
96875979	Chloral hydrate 500mg/5ml mixture bp 2000
98073998	Chloral hydrate 500mg/5ml mixture bp 2000
98087990	Chloral hydrate 500mg/5ml mixture bp 2000

80654979	Chloral hydrate 500mg/5ml oral solution
76368978	Chloral hydrate 500mg/5ml oral solution sugar free
98073996	Chloral hydrate 500mg/5ml oral suspension
80648979	Chloral hydrate 600mg/5ml oral solution bp
59515979	Chloral hydrate 750mg suppositories
85436998	Chloral hydrate oral solution
84686998	Chloral hydrate suppository
97114992	Chloral mix
93586992	Chloral syr
96705998	Clomethiazole 157.5mg/5ml oral solution sugar free
99567998	Clomethiazole 157.5mg/5ml oral solution sugar free
96706998	Clomethiazole 192mg capsules
96873979	Clomethiazole 192mg capsules
99568998	Clomethiazole 192mg capsules
58281979	Clomethiazole 250mg/5ml oral solution
98719998	Clomethiazole 8mg/ml iv infusion
72737978	Cloral betaine 707mg tablets
72738978	Cloral betaine 707mg tablets
72739978	Cloral betaine 707mg tablets
87293998	Cloral betaine 707mg tablets
93577998	Cloral betaine 707mg tablets
97274998	Cloral betaine 707mg tablets
99032997	Clorazepate dipotassium 15mg capsules
99032998	Clorazepate dipotassium 7.5mg capsules
96404997	Dichloralphenazone 225mg/5ml oral solution
96404997	Dichloralphenazone 225mg/5ml oral solution
96404998	Dichloralphenazone 650mg tablets
96404998	Dichloralphenazone 650mg tablets
96520998	Flunitrazepam 1mg tablets
99170998	Flunitrazepam 1mg tablets
96497998	Flurazepam 15mg capsules
97464992	Flurazepam 15mg capsules
99789998	Flurazepam 15mg capsules
97465992	Flurazepam 30 mg tab
96497997	Flurazepam 30mg capsules
99789997	Flurazepam 30mg capsules
95994998	Loprazolam 1mg tablets
96653990	Loprazolam 1mg tablets
97638998	Loprazolam 1mg tablets
95992996	Lormetazepam 1mg Capsule
98790998	Lormetazepam 1mg capsule
95992997	Lormetazepam 1mg tablets
96821989	Lormetazepam 1mg tablets
96853989	Lormetazepam 1mg tablets
97742989	Lormetazepam 1mg tablets
99167989	Lormetazepam 1mg tablets
99348998	Lormetazepam 1mg tablets
99530989	Lormetazepam 1mg tablets

99531989	Lormetazepam 1mg tablets
79563979	Lormetazepam 1mg/5ml oral suspension
95331992	Lormetazepam 500mcg tablets
95992998	Lormetazepam 500microgram tablets
96821990	Lormetazepam 500microgram tablets
96853990	Lormetazepam 500microgram tablets
99167990	Lormetazepam 500microgram tablets
95244992	Mandrax tab
86716998	Melatonin 10mg capsules
63826979	Melatonin 10mg/5ml oral solution
63824979	Melatonin 10mg/5ml oral suspension
90967998	Melatonin 1mg capsules
86721998	Melatonin 1mg tablets
55647979	Melatonin 1mg/1ml oral liquid sugar free
55648979	Melatonin 1mg/1ml oral liquid sugar free
63822979	Melatonin 1mg/5ml oral solution
63820979	Melatonin 1mg/5ml oral suspension
86682998	Melatonin 1mg/ml sugar free oral solution
91804998	Melatonin 2.5mg capsules
56946978	Melatonin 2.5mg/5ml oral solution
86715998	Melatonin 2.5mg/5ml oral suspension
81720979	Melatonin 20mg capsules
70694979	Melatonin 2mg capsules
83492978	Melatonin 2mg capsules
91860998	Melatonin 2mg capsules
55129978	Melatonin 2mg modified-release capsules
63287979	Melatonin 2mg modified-release tablets
83927998	Melatonin 2mg modified-release tablets
83928998	Melatonin 2mg modified-release tablets
67238979	Melatonin 2mg/5ml oral solution
67236979	Melatonin 2mg/5ml oral suspension
78078978	Melatonin 3mg capsules
91803998	Melatonin 3mg capsules
71249979	Melatonin 3mg lozenges sugar free
86679998	Melatonin 3mg modified-release capsules
46052978	Melatonin 3mg modified-release tablets
78368978	Melatonin 3mg orodispersible tablets
81678998	Melatonin 3mg tablets
86676998	Melatonin 3mg tablets
87755998	Melatonin 3mg tablets
67234979	Melatonin 3mg/5ml oral solution
67232979	Melatonin 3mg/5ml oral suspension
64511979	Melatonin 4mg capsules
67230979	Melatonin 4mg/5ml oral solution
67228979	Melatonin 4mg/5ml oral suspension
81714979	Melatonin 500microgram capsules
81323979	Melatonin 500microgram tablets
85429998	Melatonin 5mg capsules
93198990	Melatonin 5mg capsules
63285979	Melatonin 5mg tablets

64610979	Melatonin 5mg/5ml oral solution
81620998	Melatonin 5mg/5ml oral solution
64609979	Melatonin 5mg/5ml oral suspension
81623998	Melatonin 5mg/5ml oral suspension
63465979	Melatonin 6mg capsules
63358979	Melatonin 6mg/5ml oral solution
63356979	Melatonin 6mg/5ml oral suspension
30564978	Melatonin 7.5mg capsules
47970978	Melatonin 8mg capsules
85390998	Melatonin capsule
85392998	Melatonin tablet
99346998	Methyprylon 200mg tablets
95845998	Methyprylone 200mg tablet
96364992	Nitrados 10 mg tab
95720998	Nitrazepam 10mg tablet
68938979	Nitrazepam 10mg/5ml oral suspension
55127978	Nitrazepam 2.5mg/5ml oral suspension
95720997	Nitrazepam 2.5mg/5ml oral suspension
99125998	Nitrazepam 2.5mg/5ml oral suspension
68963979	Nitrazepam 2mg/5ml oral suspension
95721998	Nitrazepam 5mg capsule
97205998	Nitrazepam 5mg capsules
97268998	Nitrazepam 5mg capsules
87289998	Nitrazepam 5mg tablets
95995990	Nitrazepam 5mg tablets
96932990	Nitrazepam 5mg tablets
97227998	Nitrazepam 5mg tablets
98470990	Nitrazepam 5mg tablets
98675990	Nitrazepam 5mg tablets
99142990	Nitrazepam 5mg tablets
99354998	Nitrazepam 5mg tablets
99404998	Nitrazepam 5mg tablets
99717990	Nitrazepam 5mg tablets
99718990	Nitrazepam 5mg tablets
99719990	Nitrazepam 5mg tablets
99720990	Nitrazepam 5mg tablets
95720996	Nitrazepam 5mg/5ml oral suspension
98088990	Nitrazepam 5mg/5ml oral suspension
95978992	Potassium bromide & chloral mix
98256990	Potassium bromide & chloral mixture
97922992	Potassium bromide & valerian mix
98255990	Potassium bromide & valerian mxtire
99974990	Potassium bromide crystals
99974988	Potassium bromide mixture
99974989	Potassium bromide powder
90126998	Promethazine hydrochloride 10mg tablets
93739998	Promethazine hydrochloride 20mg tablets
93740998	Promethazine hydrochloride 20mg tablets
91249998	Promethazine hydrochloride 25mg tablets
86210998	Sodium oxybate 500mg/ml oral solution sugar free

86211998	Sodium oxybate 500mg/ml oral solution sugar free
93416998	Temazepam 10mg capsules
94220998	Temazepam 10mg capsules
95215998	Temazepam 10mg capsules
99339998	Temazepam 10mg capsules
99358990	Temazepam 10mg capsules
93418998	Temazepam 10mg gel-fill capsules
99359990	Temazepam 10mg gel-fill capsules
94811997	Temazepam 10mg tablets
95230990	Temazepam 10mg tablets
96424990	Temazepam 10mg tablets
96700990	Temazepam 10mg tablets
97173990	Temazepam 10mg tablets
97684989	Temazepam 10mg tablets
97720990	Temazepam 10mg tablets
98022990	Temazepam 10mg tablets
98514990	Temazepam 10mg tablets
98606988	Temazepam 10mg tablets
98607988	Temazepam 10mg tablets
99319989	Temazepam 10mg tablets
99357988	Temazepam 10mg tablets
94811998	Temazepam 10mg/5ml oral solution sugar free
95231990	Temazepam 10mg/5ml oral solution sugar free
96840979	Temazepam 10mg/5ml oral solution sugar free
97427990	Temazepam 10mg/5ml oral solution sugar free
97708990	Temazepam 10mg/5ml oral solution sugar free
97950990	Temazepam 10mg/5ml oral solution sugar free
98606989	Temazepam 10mg/5ml oral solution sugar free
99047988	Temazepam 10mg/5ml oral solution sugar free
93416997	Temazepam 15mg capsules
95215996	Temazepam 15mg capsules
93416996	Temazepam 20mg capsules
95215997	Temazepam 20mg capsules
98870998	Temazepam 20mg capsules
99339997	Temazepam 20mg capsules
99358989	Temazepam 20mg capsules
93418996	Temazepam 20mg gel-fill capsules
94811996	Temazepam 20mg tablets
95229990	Temazepam 20mg tablets
96616990	Temazepam 20mg tablets
96700989	Temazepam 20mg tablets
97173989	Temazepam 20mg tablets
97684988	Temazepam 20mg tablets
97720989	Temazepam 20mg tablets
97913990	Temazepam 20mg tablets
98022989	Temazepam 20mg tablets
98514989	Temazepam 20mg tablets
99319988	Temazepam 20mg tablets
99357989	Temazepam 20mg tablets
93415998	Temazepam 30mg capsules

93485998	Temazepam 30mg capsules
93417998	Temazepam 30mg gel-fill capsules
93083992	Temazepam ud 10ml 10 mg/5ml eli
93087992	Temazepam ud 5ml 10 mg/5ml eli
84620998	Triazolam (roi) 125microgram tablet
84619998	Triazolam (roi) 250microgram tablet
95087992	Triazolam 125mcg tablets
97908998	Triazolam 125mcg tablets
95121998	Triazolam 125microgram tablet
94473992	Triazolam 250mcg tablets
95121997	Triazolam 250microgram tablet
98919989	Triazolam 250microgram tablet
98074998	Triclofos 500mg/5ml oral solution
99343990	Triclofos 500mg/5ml oral solution
88274997	Zaleplon 10mg capsules
88275997	Zaleplon 10mg capsules
88274998	Zaleplon 5mg capsules
88275998	Zaleplon 5mg capsules
92703997	Zolpidem 10mg tablets
92704997	Zolpidem 10mg tablets
95197990	Zolpidem 10mg tablets
95462990	Zolpidem 10mg tablets
95506990	Zolpidem 10mg tablets
95808990	Zolpidem 10mg tablets
95874990	Zolpidem 10mg tablets
96036989	Zolpidem 10mg tablets
96816979	Zolpidem 10mg tablets
92703998	Zolpidem 5mg tablets
92704998	Zolpidem 5mg tablets
95463990	Zolpidem 5mg tablets
95507990	Zolpidem 5mg tablets
95646990	Zolpidem 5mg tablets
95809990	Zolpidem 5mg tablets
95875990	Zolpidem 5mg tablets
96036990	Zolpidem 5mg tablets
96819979	Zolpidem 5mg tablets
88458998	Zopiclone 3.75mg tablets
89703998	Zopiclone 3.75mg tablets
93638997	Zopiclone 3.75mg tablets
95587990	Zopiclone 3.75mg tablets
96826979	Zopiclone 3.75mg tablets
96857990	Zopiclone 3.75mg tablets
97027989	Zopiclone 3.75mg tablets
97076990	Zopiclone 3.75mg tablets
97155990	Zopiclone 3.75mg tablets
97162989	Zopiclone 3.75mg tablets
61598979	Zopiclone 3.75mg/5ml oral solution
81097998	Zopiclone 3.75mg/5ml oral solution
85902998	Zopiclone 3.75mg/5ml oral suspension
88458997	Zopiclone 7.5mg tablets

93638998	Zopiclone 7.5mg tablets
93641998	Zopiclone 7.5mg tablets
95677990	Zopiclone 7.5mg tablets
96070990	Zopiclone 7.5mg tablets
96160990	Zopiclone 7.5mg tablets
96340990	Zopiclone 7.5mg tablets
96833979	Zopiclone 7.5mg tablets
96857989	Zopiclone 7.5mg tablets
97027990	Zopiclone 7.5mg tablets
97076989	Zopiclone 7.5mg tablets
97155989	Zopiclone 7.5mg tablets
97162990	Zopiclone 7.5mg tablets
73352978	Zopiclone 7.5mg/5ml oral solution
79049979	Zopiclone 7.5mg/5ml oral suspension

G. Stimulants

Drug code	Generic name
99788992	Amphetamine 5 mg tab
99736992	Ascorbic ac./cyanocob/ fencamfamin hyd/ 100 mg tab
53163979	Atomoxetine 100mg capsules
53164979	Atomoxetine 100mg capsules
87478998	Atomoxetine 10mg capsules
87483998	Atomoxetine 10mg capsules
87477998	Atomoxetine 18mg capsules
87482998	Atomoxetine 18mg capsules
87476998	Atomoxetine 25mg capsules
87481998	Atomoxetine 25mg capsules
68712978	Atomoxetine 25mg/5ml oral suspension
87475998	Atomoxetine 40mg capsules
87480998	Atomoxetine 40mg capsules
46039978	Atomoxetine 4mg/1ml oral solution sugar free
46040978	Atomoxetine 4mg/1ml oral solution sugar free
87474998	Atomoxetine 60mg capsules
87479998	Atomoxetine 60mg capsules
82832998	Atomoxetine 80mg capsules
82833998	Atomoxetine 80mg capsules
97019992	Caffeine 15 mg tab
97020992	Caffeine 50 mg tab
97034998	Caffeine iodide liquid
96127992	Caffeine/dextrose 30 mg tab
86042998	Dexamfetamine 15mg modified-release capsules
86043998	Dexamfetamine 15mg modified-release capsules
86933998	Dexamfetamine 1mg/ml oral liquid
70168979	Dexamfetamine 2.5mg/5ml oral suspension
83316998	Dexamfetamine 5mg modified-release capsules
46008978	Dexamfetamine 5mg tablets
96422998	Dexamfetamine 5mg tablets
97254992	Dexamfetamine 5mg tablets
97260992	Dexamfetamine 5mg tablets

99765998	Dexamfetamine 5mg tablets
69993979	Dexamfetamine 5mg/5ml oral solution
72858978	Dexamfetamine 5mg/5ml oral solution sugar free
81273998	Dexamfetamine with amfetamine 10mg with 10mg modified-release capsules
81304998	Dexamfetamine with amfetamine 10mg with 10mg modified-release capsules
97255992	Dexamphetamine sulphate 10 mg cap
96180992	Dexamphetamine sulphate 15 mg cap
97253992	Dexamphetamine sulphate 15 mg spa
97252992	Dexamphetamine sulphate/amphetamine 20 mg cap
96184992	Dexbrompheniramine/pseudoephedrine sulph 6 mg tab
94910992	Dexedrine 2.5 mg tab
39101978	Guanfacine 1mg modified-release tablets
39102978	Guanfacine 1mg modified-release tablets
39099978	Guanfacine 2mg modified-release tablets
39100978	Guanfacine 2mg modified-release tablets
39097978	Guanfacine 3mg modified-release tablets
39098978	Guanfacine 3mg modified-release tablets
39095978	Guanfacine 4mg modified-release tablets
39096978	Guanfacine 4mg modified-release tablets
37591978	Lisdexamfetamine 20mg capsules
88903979	Lisdexamfetamine 20mg capsules
47646978	Lisdexamfetamine 30mg capsules
52331979	Lisdexamfetamine 30mg capsules
85158978	Lisdexamfetamine 30mg capsules
88934979	Lisdexamfetamine 30mg capsules
37590978	Lisdexamfetamine 40mg capsules
88901979	Lisdexamfetamine 40mg capsules
47647978	Lisdexamfetamine 50mg capsules
52332979	Lisdexamfetamine 50mg capsules
88936979	Lisdexamfetamine 50mg capsules
37589978	Lisdexamfetamine 60mg capsules
88899979	Lisdexamfetamine 60mg capsules
47645978	Lisdexamfetamine 70mg capsules
52330979	Lisdexamfetamine 70mg capsules
88932979	Lisdexamfetamine 70mg capsules
96330992	Methylperidate 10 mg tab
82176978	Methylphenidate 10mg modified-release capsules
84740998	Methylphenidate 10mg modified-release capsules
86947998	Methylphenidate 10mg modified-release capsules
86949998	Methylphenidate 10mg modified-release capsules
89167979	Methylphenidate 10mg modified-release capsules
89168979	Methylphenidate 10mg modified-release capsules
84744998	Methylphenidate 10mg tablets
88229998	Methylphenidate 10mg tablets
90590997	Methylphenidate 10mg tablets
91448998	Methylphenidate 10mg tablets
91449998	Methylphenidate 10mg tablets
95065990	Methylphenidate 10mg tablets
59245978	Methylphenidate 18mg modified-release tablets
68600978	Methylphenidate 18mg modified-release tablets

89549998 Methylphenidate 18mg modified-release tablets
91480998 Methylphenidate 18mg modified-release tablets
58057979 Methylphenidate 20mg modified-release capsules
84739998 Methylphenidate 20mg modified-release capsules
86946998 Methylphenidate 20mg modified-release capsules
89495979 Methylphenidate 20mg modified-release capsules
91844998 Methylphenidate 20mg modified-release capsules
94309998 Methylphenidate 20mg modified-release capsules
89165979 Methylphenidate 20mg modified-release tablets
89166979 Methylphenidate 20mg modified-release tablets
84743998 Methylphenidate 20mg tablets
90590996 Methylphenidate 20mg tablets
91448996 Methylphenidate 20mg tablets
91759998 Methylphenidate 20mg tablets
68981979 Methylphenidate 20mg/5ml oral solution
31600978 Methylphenidate 27mg modified-release tablets
84732998 Methylphenidate 27mg modified-release tablets
84733998 Methylphenidate 27mg modified-release tablets
58051979 Methylphenidate 30mg modified-release capsules
84738998 Methylphenidate 30mg modified-release capsules
86945998 Methylphenidate 30mg modified-release capsules
86948998 Methylphenidate 30mg modified-release capsules
89159979 Methylphenidate 30mg modified-release capsules
68599978 Methylphenidate 36mg modified-release tablets
70240978 Methylphenidate 36mg modified-release tablets
89425979 Methylphenidate 36mg modified-release tablets
91237998 Methylphenidate 36mg modified-release tablets
92441998 Methylphenidate 36mg modified-release tablets
84736998 Methylphenidate 40mg modified-release capsules
84737998 Methylphenidate 40mg modified-release capsules
74435978 Methylphenidate 50mg modified-release capsules
74436978 Methylphenidate 50mg modified-release capsules
42537978 Methylphenidate 54mg modified-release tablets
51111978 Methylphenidate 54mg modified-release tablets
70239978 Methylphenidate 54mg modified-release tablets
89161979 Methylphenidate 54mg modified-release tablets
89162979 Methylphenidate 54mg modified-release tablets
81465998 Methylphenidate 5mg modified-release capsules
81466998 Methylphenidate 5mg modified-release capsules
84745998 Methylphenidate 5mg tablets
90590998 Methylphenidate 5mg tablets
91448997 Methylphenidate 5mg tablets
92102998 Methylphenidate 5mg tablets
95066990 Methylphenidate 5mg tablets
68113979 Methylphenidate 5mg/5ml oral solution
73363978 Methylphenidate 60mg modified-release capsules
73364978 Methylphenidate 60mg modified-release capsules
88198998 Modafinil 100mg tablets
88200998 Modafinil 100mg tablets
89223998 Modafinil 200mg tablets

89619998	Modafinil 200mg tablets
97801992	Nicotin./prolintane hyd/pyridox.hyd/ribo 5 mg eli
94717998	Pemoline 20mg tablets
98957998	Pemoline 20mg tablets
98966998	Prolintane hydrochloride & vitamins b & c 2.5mg/5ml liquid
93760997	Prolintane hydrochloride with vitamins liquid
98270998	Prolintane hydrochloride with vitamins liquid
93967992	Reactivan tab
95555992	Ronyl 20 mg tab
86210998	Sodium oxybate 500mg/ml oral solution sugar free
86211998	Sodium oxybate 500mg/ml oral solution sugar free
85252978	Tafamidis 20mg capsules

Appendix (9): IMRD-UK ethical approval letter for the analytical studies

SRC Feedback

Researcher Name: Basmah Alfageh
Organisation: University College London
SRC Reference Number: 18THIN044
Date: 19th June 2018
Study title: Risk of neurological and cardiovascular events in people with autism spectrum disorder (ASD) using antipsychotic medication: a population based study.

Committee opinion: Approved

The following feedback has been supplied by the SRC.

Notes from the Chair:

Approved documents:

Approved document	Version	Date
SRC_Protocol_18THIN044_v1_27-04-2018	1	27/04/2018

We are pleased to inform that you can proceed with the study as this is now approved. IQVIA will let the relevant Ethics committee know this study has been approved by the SRC.

Once the study has been completed and published, it is important for you to inform IQVIA in order for us to advise the SRC and your reference number to be closed.

References to all published studies are added to our website enabling other researchers to become aware of your work. In order to identify your study as using the THIN database, we recommend that you include the words "The Health Improvement Network (THIN)" within your title. Copies of publication(s), where available, will be appreciated.

I wish you and your team all the best with the study progression.

[redacted]

Mustafa Dungarwalla
Consultant

Appendix (10): Seizure read codes list

Read code	Description
1B63.00	Had a fit
1B63.11	Fit - had one, symptom
1B64.00	Had a convulsion
1B64.11	Convulsion - symptom
282..00	O/E - fit/convulsion
282..11	O/E - a convulsion
282..12	O/E - a fit
282..13	O/E - a seizure
2822	O/E - grand mal fit
2823	O/E - petit mal fit
2824	O/E - focal (Jacksonian) fit
2824.11	O/E - Jacksonian fit
2824.12	O/E - focal fit
2825	O/E - psychomotor fit
2828	Absence seizure
282Z.00	O/E - fit/convulsion NOS
Eu44500	[X]Dissociative convulsions
F132y00	Other specified myoclonus
F132z00	Myoclonus NOS
F132z12	Myoclonic seizure
F251600	Grand mal seizure
F252.00	Petit mal status
F253.00	Grand mal status
F253.11	Status epilepticus
F25C.00	Drug-induced epilepsy
F25y300	Complex partial status epilepticus
Fyu5200	[X]Other status epilepticus
Fyu5900	[X]Status epilepticus, unspecified
R003.00	[D]Convulsions
R003100	[D]Convulsions, infantile
R003200	[D]Fit
R003211	[D]Fit (in non epileptic) NOS
R003400	[D]Nocturnal seizure
R003y00	[D]Other specified convulsion
R003z00	[D]Convulsion NOS
R003z11	[D]Seizure NOS
Ryu7100	[X]Other and unspecified convulsions

Appendix (11): Cardiac outcomes Read codes lists

A. Arrhythmia

Read code	Description
3272.00	ECG: atrial fibrillation
3273.00	ECG: atrial flutter
3282.00	ECG: ventricular tachycardia
14AN.00	H/O: atrial fibrillation
14AR.00	History of atrial flutter
212R.00	Atrial fibrillation resolved
327..00	ECG: supraventricular arrhythmia
328..00	ECG: ventricular arrhythmia
328Z.00	ECG: ventricular arrhythmia NOS
662S.00	Atrial fibrillation monitoring
6A9..00	Atrial fibrillation annual review
7936A00	Implant intravenous pacemaker for atrial fibrillation
8CMW200	Atrial fibrillation care pathway
8HTy.00	Referral to atrial fibrillation clinic
9hF..00	Exception reporting: atrial fibrillation quality indicators
9hF1.00	Excepted from atrial fibrillation qual indic: Inform dissent
9Os..00	Atrial fibrillation monitoring administration
9Os0.00	Atrial fibrillation monitoring first letter
9Os1.00	Attends clinic A monitoring
9Os2.00	Atrial fibrillation monitoring third letter
9Os3.00	Atrial fibrillation monitoring verbal invite
9Os4.00	Atrial fibrillation monitoring telephone invite
G559.00	Arrhythmogenic right ventricular cardiomyopathy
G55A.11	Tachycardia-induced cardiomyopathy
G56..00	Conduction disorders
G56..11	Conduction disorders of heart
G567400	Wolff-Parkinson-White syndrome
G56y.00	Other conduction disorders
G56y000	Lown-Ganong-Levine syndrome
G56zz00	Conduction disorders NOS
Gyu5a00	[X]Aortic valve disorders in diseases classified elsewhere
G57..00	Cardiac dysrhythmias
G57..11	Cardiac arrhythmias
G570.00	Paroxysmal supraventricular tachycardia
G570000	Paroxysmal atrial tachycardia
G570100	Paroxysmal atrioventricular tachycardia
G570200	Paroxysmal junctional tachycardia
G570300	Paroxysmal nodal tachycardia
G570z00	Paroxysmal supraventricular tachycardia NOS
G571.00	Paroxysmal ventricular tachycardia
G571.11	Ventricular tachycardia
G572.00	Paroxysmal tachycardia unspecified
G572000	Essential paroxysmal tachycardia
G572100	Bouveret-Hoffmann syndrome
G572z00	Paroxysmal tachycardia NOS

G573.00	Atrial fibrillation and flutter
G573000	Atrial fibrillation
G573100	Atrial flutter
G573200	Paroxysmal atrial fibrillation
G573300	Non-rheumatic atrial fibrillation
G573400	Permanent atrial fibrillation
G573500	Persistent atrial fibrillation
G573600	Paroxysmal atrial flutter
G573700	Chronic atrial fibrillation
G573800	Typical atrial flutter
G573900	Atypical atrial flutter
G573z00	Atrial fibrillation and flutter NOS
G574.00	Ventricular fibrillation and flutter
G574000	Ventricular fibrillation
G574011	Cardiac arrest-ventricular fibrillation
G574100	Ventricular flutter
G574z00	Ventricular fibrillation and flutter NOS
G575.00	Cardiac arrest
G575.11	Cardio-respiratory arrest
G575.12	Asystole
G575000	Cardiac arrest with successful resuscitation
G575100	Sudden cardiac death, so described
G575200	Electromechanical dissociation with successful resuscitation
G575300	Electromechanical dissociation
G575z00	Cardiac arrest, unspecified
G576.00	Ectopic beats
G576.11	Premature beats
G576000	Ectopic beats unspecified
G576011	Extrasystoles
G576100	Supraventricular ectopic beats
G576200	Ventricular ectopic beats
G576300	Atrial premature depolarization
G576400	Junctional premature depolarization
G576500	Ventricular premature depolarization
G576z00	Ectopic beats NOS
G577.00	Sinus arrhythmia
G578.00	Atrial standstill
G57y.00	Other cardiac dysrhythmias
G57y.11	Pulsus alternans
G57y.12	Pulse missed beats
G57y.13	Skipped beat
G57y.14	Heart beats irregular
G57y000	Persistent sinus bradycardia
G57y100	Severe sinus bradycardia
G57y200	Brugada syndrome
G57y300	Sick sinus syndrome
G57y400	Sinoatrial node dysfunction NOS
G57y500	Wandering atrial pacemaker
G57y600	Nodal rhythm disorder
G57y700	Sinus tachycardia

G57y800	Bigeminal pulse
G57y900	Supraventricular tachycardia NOS
G57yA00	Re-entry ventricular arrhythmia
G57yz00	Other cardiac dysrhythmia NOS
G57z.00	Cardiac dysrhythmia NOS

B. Heart failure

Read Code	Description
1O1..00	Heart failure confirmed
8B29.00	Cardiac failure therapy
G58..00	Heart failure
G58..11	Cardiac failure
G580.00	Congestive heart failure
G580.11	Congestive cardiac failure
G580.12	Right heart failure
G580.13	Right ventricular failure
G580.14	Biventricular failure
G580000	Acute congestive heart failure
G580100	Chronic congestive heart failure
G580200	Decompensated cardiac failure
G580300	Compensated cardiac failure
G580400	Congestive heart failure due to valvular disease
G581.00	Left ventricular failure
G581.11	Asthma - cardiac
G581.12	Pulmonary oedema - acute
G581.13	Impaired left ventricular function
G581000	Acute left ventricular failure
G582.00	Acute heart failure
G583.00	Heart failure with normal ejection fraction
G583.11	HFNEF - heart failure with normal ejection fraction
G583.12	Heart failure with preserved ejection fraction
G584.00	Right ventricular failure
G58z.00	Heart failure NOS
G58z.11	Weak heart
G58z.12	Cardiac failure NOS

C. Myocardial infarction

Read code	Description
323..00	ECG: myocardial infarction
3233.00	ECG: antero-septal infarct.
3234.00	ECG: posterior/inferior infarct
3235.00	ECG: subendocardial infarct
3236.00	ECG: lateral infarction
323Z.00	ECG: myocardial infarct NOS
889A.00	Diab mellit insulin-glucose infus acute myocardial infarct
G30..00	Acute myocardial infarction
G30..11	Attack - heart

G30..12	Coronary thrombosis
G30..13	Cardiac rupture following myocardial infarction (MI)
G30..14	Heart attack
G30..15	MI - acute myocardial infarction
G30..16	Thrombosis - coronary
G30..17	Silent myocardial infarction
G300.00	Acute anterolateral infarction
G301.00	Other specified anterior myocardial infarction
G301000	Acute anteroapical infarction
G301100	Acute anteroseptal infarction
G301z00	Anterior myocardial infarction NOS
G302.00	Acute inferolateral infarction
G303.00	Acute inferoposterior infarction
G304.00	Posterior myocardial infarction NOS
G305.00	Lateral myocardial infarction NOS
G306.00	True posterior myocardial infarction
G307.00	Acute subendocardial infarction
G307000	Acute non-Q wave infarction
G307100	Acute non-ST segment elevation myocardial infarction
G308.00	Inferior myocardial infarction NOS
G309.00	Acute Q-wave infarct
G30A.00	Mural thrombosis
G30B.00	Acute posterolateral myocardial infarction
G30X.00	Acute transmural myocardial infarction of unspecif site
G30X000	Acute ST segment elevation myocardial infarction
G30y.00	Other acute myocardial infarction
G30y000	Acute atrial infarction
G30y100	Acute papillary muscle infarction
G30y200	Acute septal infarction
G30yz00	Other acute myocardial infarction NOS
G30z.00	Acute myocardial infarction NOS
G310.11	Dressler's syndrome
G31y100	Microinfarction of heart
G35..00	Subsequent myocardial infarction
G350.00	Subsequent myocardial infarction of anterior wall
G351.00	Subsequent myocardial infarction of inferior wall
G353.00	Subsequent myocardial infarction of other sites
G35X.00	Subsequent myocardial infarction of unspecified site
G36..00	Certain current complication follow acute myocardial infarct
G360.00	Haemopericardium/current comp folow acut myocard infarct
G361.00	Atrial septal defect/curr comp folow acut myocardal infarct
G362.00	Ventric septal defect/curr comp fol acut myocardal infarctn
G363.00	Ruptur cardiac wall w'out haemopericard/cur comp fol ac MI
G364.00	Ruptur chordae tendinae/curr comp fol acute myocard infarct
G365.00	Rupture papillary muscle/curr comp fol acute myocard infarct
G366.00	Thrombosis atrium,auric append&vent/curr comp foll acute MI
G38..00	Postoperative myocardial infarction
G380.00	Postoperative transmural myocardial infarction anterior wall
G381.00	Postoperative transmural myocardial infarction inferior wall
G384.00	Postoperative subendocardial myocardial infarction

G38z.00	Postoperative myocardial infarction, unspecified
G501.00	Post infarction pericarditis
Gyu3400	[X]Acute transmural myocardial infarction of unspecif site