Utilisation and safety of antipsychotic medicines in the young



Fariz Abdul Rani

March, 2009

The School of Pharmacy, University of London

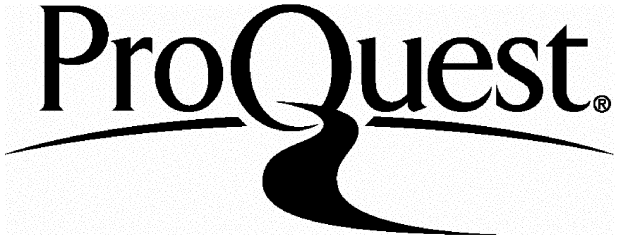
PhD Thesis

ProQuest Number: 10104767

All rights reserved

INFORMATION TO ALL USERS
The quality of this reproduction is dependent upon the quality of the copy submitted.

In the unlikely event that the author did not send a complete manuscript
and there are missing pages, these will be noted. Also, if material had to be removed,
a note will indicate the deletion.



ProQuest 10104767

Published by ProQuest LLC(2016). Copyright of the Dissertation is held by the Author.

All rights reserved.
This work is protected against unauthorized copying under Title 17, United States Code.
Microform Edition © ProQuest LLC.

ProQuest LLC
789 East Eisenhower Parkway
P.O. Box 1346
Ann Arbor, MI 48106-1346

Plagiarism statement

This thesis describes research conducted in the School of Pharmacy, University of London between October 2005 and October 2008 under the supervision of Professor Ian Wong and Dr Patrick Byrne. I certify that the research described is original and that any parts of the work that have been conducted by collaboration are clearly indicated. I also clarify that I have written all the text herein and have clearly indicated by suitable citation any part of this dissertation that has already appeared in publication.



18/03/2009

Signature

Date

Abstract

Antipsychotic medications are used for the treatment of various psychiatric disorders, including psychotic disorders such as schizophrenia. There are two main classes of antipsychotic drugs; the older, typical antipsychotics and the newer atypical antipsychotics. Studies in the USA and the Netherlands show that antipsychotic use in children is rising, primarily for 'off-label' indications. Thus, despite the evident increase in use, the safety profile of these drugs in this population is lacking. Furthermore, there is a gap in investigations of antipsychotic use and safety in the UK paediatric population. Therefore, the aim of this thesis was to investigate the utilisation and safety of antipsychotic medications in children and adolescents in the UK.

Three main studies were conducted. Firstly, the pharmacoepidemiology of antipsychotic prescribing in the paediatric population was examined using the General Practice Research Database (GPRD). Secondly, the incidences of specific serious adverse events of mortality, liver abnormalities, diabetes mellitus and extrapyramidal effects in the identified GPRD cohort exposed to antipsychotic therapy was investigated. Finally, a targeted pharmacovigilance pilot study was conducted to describe adverse reactions associated with atypical antipsychotic treatment seen in children from secondary and tertiary care settings. The feasibility of conducting the pharmacovigilance study, with the view of expanding it to a wider scale, was also explored.

The largest UK paediatric cohort exposed to antipsychotic therapy was identified from the GPRD. The overall prevalence of antipsychotic prescribing almost doubled between 1992 and 2005 (0.39 to 0.77 patients per 1,000 person-years). The greatest increase was seen in patients aged 7-12 years (0.23 patients per 1,000 person-years in 1992 and 0.61 patients per 1,000 person-years in 2005). Atypical antipsychotic agents were shown to be replacing the older, typical antipsychotics. Although there was an increasing prevalence trend, the incidence of all antipsychotic prescribing remained stable suggesting patients stay on treatment for longer durations. Results from the safety studies revealed that children exposed to antipsychotic therapy have a higher mortality rate than the general paediatric population (SMR of 4.03; 95% CI: 1.48 to 8.76). However, it was demonstrated that antipsychotic therapy was unlikely to be associated with the majority of the identified cases of death. The rate of diabetes mellitus was not significantly different compared to the general paediatric population (SIR of 1.61; 95% CI: 0.20 to 5.81) and there were also no cases of liver adverse reactions in the antipsychotic-exposed cohort. However, these results were possibly limited by the sample size of the study cohort. On the other hand, antipsychotic-exposed patients were shown to have significantly higher odds ratios of experiencing extrapyramidal symptoms compared to unexposed patients (OR of 1.88; $p < 0.05$). The targeted pharmacovigilance study on atypical antipsychotics allowed for an alternative method for investigating the safety of these drugs in children. The study revealed a high rate of adverse drug reactions with every five patients experiencing a reaction. The study also identified relevant methodological issues which need to be addressed related to expanding such a study to wider scale.

Acknowledgements

There are a number of people who I must thank for without them it would not be possible for me to complete this thesis.

I owe my deepest gratitude to my supervisor, Professor Ian Wong, for his continuous support, guidance and patience throughout the past 3 years. I would also like to thank my second supervisor, Dr Patrick Byrne for his encouragement during the PhD course, and kind aid in checking the diagnostic medical codes in Chapter 4 as well as analyses on causality assessments in Chapters 5 and 6.

Special thanks to Dr Noel Cranswick from the University of Melbourne for his kind assistance in the analysis on causality in Chapter 5.

I would also like to acknowledge Dr Angie Wade and Eirini Koutoumanou from the Institute of Child Health for their support and help with the statistical analysis in Chapters 6 and 7.

I would also like to thank members of the London Paediatric Psychopharmacology Group (PPG), notably Professor Eric Taylor and Professor Gillian Baird, who proposed the pharmacovigilance study on atypical antipsychotic agents in children (Chapter 7). I would especially like to thank Professor Eric Taylor for his support during the PAMS study.

My deepest gratitude to my fellow PhD students, Ruth Ackers, Suzanne McCarthy and Paula Thompson for their kind help and unending encouragement throughout the past 3 years. Special thanks to the Centre for Paediatric Pharmacy Research staff, Macey Murray and Yingfen Hsia for their help and advice in data programming; as well as Antje Neubert and Claire Planner for their support throughout my course of research.

I would also like to acknowledge the Ministry of Higher Education of Malaysia for providing the funds and University Malaya for sponsoring my PhD.

Finally I thank God, my parents, my family and my dear wife Jackie for their unconditional support and motivation.

Presentations and Publications

Presentations

2008

- Oral presentation 'Mortality in Children and Adolescents on Antipsychotic Medication'. European Society for Developmental Perinatal and Paediatric Pharmacology. 6th June 2008. Rotterdam, Netherlands.
- Oral presentation 'Epidemiology of Antipsychotic Prescribing for Children and Adolescents in the UK'. PhD Research Day. 2nd April 2008. The School of Pharmacy, University of London, UK.

2007

- Poster presentation 'Epidemiology of Antipsychotic Prescribing for Children and Adolescents in the UK'. 23rd International Conference on Pharmacoepidemiology and Therapeutic Risk Management. 19th – 23rd August 2007. Quebec City Convention Centre, Quebec City, Canada.

2006

- Oral presentation 'Rise in Atypical Antipsychotic Prescribing in Children and Adolescents in General Practice'. Royal College of Paediatrics and Child Health (RCPCH) 10th Spring Meeting. 5th April 2006. University of York, UK.

Publications

2008

- Rani FA, Byrne PJ, Murray ML, Carter P, Wong ICK (2008), Paediatric Atypical antipsychotic Monitoring Safety study (PAMS): Pilot study in children and adolescents in secondary- and tertiary- care settings. *Drug Safety* (Accepted 11 November 2008)
- Hsia YF, Neubert A, Rani F, Viner RM, Hindmarsh CP, Wong ICK. An increase in the prevalence of type 1 and 2 diabetes in children and adolescents: results from prescription data from a UK general practice database. *British Journal of Clinical Pharmacology* (Accepted 2008)
- Rani FA, Murray ML, Byrne PJ, Wong ICK (2008), Epidemiologic Features of Antipsychotic Prescribing to Children and Adolescents in Primary Care in the United Kingdom. *Pediatrics*, 121(5): 1002-1009.

2007

- Abstract: Rani F, Murray M, Byrne P, Wong I. Epidemiology of Antipsychotic Prescribing for Children and Adolescents in the UK. *Pharmacoepidemiology and Drug Safety* 2007; 16(S2): S216.

2006

- Abstract: Rani F, Murray M, Wong I. Rise in Atypical Antipsychotic Prescribing in Children and Adolescents in General Practice. *Archives of Disease in Childhood* 2006; 91(S1):A41.

Contents

Contents

Plagiarism statement 1

Abstract 2

Acknowledgements 3

Presentations and Publications 5

Contents 7

List of Tables 13

List of Figures 15

List of Equations 17

List of Abbreviations 18

1 Chapter ONE: Introduction 20

1.1 Background of antipsychotic drugs 20

1.1.1 Typical antipsychotic drugs 26

1.1.2 Atypical antipsychotic drugs 30

1.1.3 Atypical antipsychotics better than typical antipsychotics? 37

1.2 Antipsychotic therapy in children and adolescents 41

1.2.1 Indications of antipsychotic drugs in children and adolescents 43

1.2.2 Safety of antipsychotic drugs in children and adolescents 49

2 Chapter TWO: Aims and objectives 63

2.1 Aim: 63

2.2 Objectives: 63

3 Chapter THREE: Methodology 64

3.1 Pharmacoepidemiology 64

3.2 The General Practice Research Database (GPRD) 65

GPRD: History 65

GPRD: Population 66

GPRD: Recorded Data 66

GPRD: Quality of Data 68

GPRD: Data Extraction 71

GPRD: Study population 73

GPRD: Data analysis 75

GPRD: Strengths and limitations 75

3.3 Pharmacoepidemiological analysis 76

Adverse events and adverse drug reactions 78

Prevalence 79

Incidence 80

Person-years 80

Calculating person-years 81

Additional pharmacoepidemiological analysis 92

3.4 Pharmacovigilance 92

4 Chapter FOUR: Epidemiology of antipsychotic drug prescribing to children and adolescents in UK primary care 94

4.1 Introduction 94

4.1.1 Systematic literature review on the utilisation of antipsychotic drugs in children and adolescents 95

4.2 Methodology 110

Data source 110

Data analysis 110

Data verification 115

4.3 Results 115

Duration of prescriptions and treatment episodes 118

Prevalence and incidence 121

Verification using the IMS database 127

4.4 Discussion 130

Comparison with utilisation studies in other countries 130

Effect of restricted indications of thioridazine 133

Antipsychotic treatment in early and middle childhood 134

Rising trend of antipsychotic drug prescribing 135

Validation using the IMS database 138

Clinical Implications 139

Study limitations 139

4.5 Conclusions 141

5 Chapter FIVE: Mortality in children and adolescents on antipsychotic medication in UK primary care 143

5.1 Introduction 143

5.2 Methodology 144

Data source 144

Data extraction 145

Data analysis 147

5.3 Results 151

After exclusion of patients with pre-existing medical conditions 154

Causality assessment on the 6 patients 154

5.4 Discussion 159

Causality assessments 159

Standardised Mortality Ratios 163

Limitations 164

Clinical implications 164

5.5 Conclusions 167

6 Chapter SIX: Incidence of liver abnormalities, diabetes mellitus and extrapyramidal symptoms in a cohort of patients on antipsychotic medication 169

6.1 Introduction 169

6.2 Incidence of liver abnormalities 170

6.2.1 Systematic literature review on liver abnormalities associated with antipsychotic drug therapy in children and adolescents 170

6.2.2 Methodology 183

Data source 183

Cases of liver abnormalities 184

Data analysis 185

6.2.3 Results 187

6.2.4 Discussion 193

6.3 Incidence of diabetes mellitus 197

6.3.1 Systematic literature review on diabetes mellitus associated with antipsychotic therapy in children and adolescents 197

6.3.2 Methodology 213

Data source 213

Cases of diabetes 214

Data analysis 214

6.3.3 Results 218

6.3.4 Discussion 221

6.4 Incidence of extrapyramidal symptoms 228

6.4.1 Methodology 229

Data source 229

Cases of extrapyramidal symptoms 230

Data analysis 231

6.4.2 Results 234

6.4.3 Discussion 251

6.5 Overall discussion on the incidence of liver abnormalities, diabetes mellitus and extrapyramidal symptoms in the study cohort 255

Causality assessments 255

Clinical implications 256

Limitations 257

6.6 Conclusions 261

7 CHAPTER SEVEN: Paediatric Atypical antipsychotic Monitoring Safety study (PAMS) 263

7.1 Introduction 263

7.2 Methodology 265

Setting 265

Participants 266

Inclusion criteria 266

Exclusion criteria 266

Reporting criteria 266

Data collection 268

7.3 Results 269

7.4 Discussion 273

Methodology of PAMS 274

Adverse drug reactions reported 278

7.5 Conclusions 281

8 Chapter EIGHT: Overall conclusions 283

References 286

Appendices 331

List of Tables

Table 3.1: Antipsychotic medications in the study 72

Table 3.2: Summary of pharmacoepidemiological rates 89

Table 4.1: Keywords used in literature search on utilisation trends of antipsychotic drugs in children and adolescents 96

Table 4.2: Utilisation studies reporting rates of antipsychotic drug use in children and adolescents 98

Table 4.3: Number of patients and prescriptions in the cohort 117

Table 5.1: Categories used for the causality assessment for cases of death in the cohort 150

Table 5.2: Deceased patients 152

Table 5.3: Causality assessment on the 6 cases of death 155

Table 6.1: Keywords used in the literature search for liver abnormalities associated with antipsychotic therapy in children and adolescents 172

Table 6.2: Published studies reporting liver abnormalities associated with antipsychotic treatment in paediatric patients 173

Table 6.3: Categories used for the causality assessment for cases of liver abnormalities in the study cohort 187

Table 6.4: Causality assessment on the 6 cases of liver abnormalities 189

Table 6.5: Keywords used in the literature search for diabetes mellitus associated with antipsychotic therapy in children and adolescents 198

Table 6.6: : Published studies reporting diabetes mellitus associated with antipsychotic treatment in paediatric patients 201

List of Tables

Table 6.7: Categories used for the causality assessment for cases of diabetes mellitus in the study cohort 215

Table 6.8: Causality assessment on the 2 cases of diabetes mellitus 220

Table 6.9: Categories used for the causality assessment for cases of extrapyramidal events in the study cohort exposed to antipsychotic therapy 233

Table 6.10: Odds ratios from logistic regression analysis 236

Table 6.11: Causality assessment on the 19 cases of extrapyramidal symptoms 237

Table 7.1: Participant characteristics 270

Table 7.2: Number of Adverse Drug Reactions (ADRs) reported by category 271

Table 7.3: Reported adverse drug reactions which not included in final analysis 279

List of Figures

List of Figures

Figure 1.1: Different effects of dopamine antagonism 23

Figure 3.1: Summary of the steps taken for GPRD data extraction 74

Figure 3.2: Example of the calculation of person-years for all paediatric patients in the GPRD 83

Figure 3.3: Example of the calculation of person-years at risk when investigating the incidence of adverse events 86

Figure 3.4: Example of the calculation of person-years at risk when investigating the incidence of adverse drug reactions 88

Figure 4.1: Kaplan-Meier survival curves on drug exposure by type of antipsychotic drug 120

Figure 4.2: GPRD data: Prevalence of antipsychotic drug prescriptions 122

Figure 4.3: GPRD data: Incidence of antipsychotic drug prescriptions 123

Figure 4.4: GPRD data: Prevalence of all antipsychotic drug prescriptions by age 125

Figure 4.5: GPRD data: Percentage of patients by age group with diagnoses within 6 months of their first prescription 126

Figure 4.6: IMS Data: Prevalence of antipsychotic drug prescriptions 128

Figure 4.7: IMS Data: Incidence of antipsychotic drug prescriptions 129

Figure 4.8: IMS Data: Diagnoses of antipsychotic drug prescriptions 130

Figure 5.1: Summary of data extraction and confirmation of deceased patients 146

Figure 5.2: Summary of the results on mortality 160

Figure 6.1: Summary of the results on incidence of liver abnormalities 192

Figure 6.2: Summary of the results on incidence of diabetes mellitus 222

List of Figures

Figure 6.3: Study cohort investigating extrapyramidal symptoms 235

List of Equations

Equation 3.1: Calculation of prevalence of antipsychotic prescribing 79

Equation 3.2: General calculation of incidence 80

Equation 3.3: Calculation of the number of person-years contributed by a subject in the GPRD general paediatric population 82

Equation 3.4: Calculation of person-years at risk for an adverse event 84

Equation 3.5: Calculation of treatment-years at risk for an adverse drug reaction 87

Equation 4.1: Calculation of incidence of antipsychotic drug prescribing 111

Equation 4.2: Calculation of prevalence of antipsychotic drug prescribing 112

Equation 4.3: Calculation of antipsychotic prescription duration 112

Equation 4.4: Calculation of antipsychotic treatment episodes 113

Equation 5.1: Calculation of crude mortality rate (CMR) 148

Equation 5.2: Calculation of the expected number of deaths 148

Equation 5.3: Calculation of standardised mortality ratios (SMR) 149

Equation 6.1: Calculation of incidence of diabetes mellitus in the GPRD general paediatric population 217

Equation 6.2: Calculation of the expected number of incidence cases of diabetes mellitus 217

Equation 6.3: Calculation of standardised incidence ratios (SIR) of diabetes mellitus 218

Equation 6.4: Calculation of duration of drug exposure 232

List of Abbreviations

5-HT_{1A}	Serotonin 5-HT receptor subtype
5-HT_{2A}	Serotonin 5-HT receptor subtype
5-HT_{2c}	Serotonin 5-HT receptor subtype
AIDS	Acquired immune deficiency syndrome
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
BMI	Body mass index
BORIS	Business Objects replacement information system
BPSU	British Paediatric Surveillance Network
CAMHS	Child and Adolescent Mental Health Service
CAPTN	Child and Adolescent Psychiatry Trials Network
CMR	Crude mortality rate
D_2	Dopamine D_2 receptor subtype
EEG	Electroencephalogram
EMEA	European Medicines Agency
GGT	Gamma glutamyl transferase
GPRD	General Practice Research Database
HIV	Human immunodeficiency virus
ICD	International classification of diseases
IMS	The IMS Disease Analyser Mediplus database
ISAC	Independent Scientific Advisory Committee
LDH	Lactate dehydrogenase

List of Abbreviations

LSD	Lysergic acid diethylamide
M_1	Muscarinic acetylcholine receptor
MCA	Medicines Control Agency
MedDRA	Medical Dictionary for Regulatory Activities
MHRA	Medicines and Healthcare products Regulatory Agency
MST	Morphine sulphate
NHS	National Health Service
NICE	National Institute for Health and Clinical Excellence
NMS	Neuroleptic malignant syndrome
ONS	Office for National Statistics
OXMIS	Oxford Medical Information System
PPA	Prescription Pricing Authority
PPG	Paediatric Psychopharmacology Group
PRR	Proportional reporting ratio
RCPCH	Royal College of Paediatric and Child Health
SEAG	Scientific and Ethical Advisory Group
SGOT	Serum glutamic oxaloacetic transaminase
SGPT	Serum glutamic pyruvic transaminase
SIR	Standardised incidence ratio
SMR	Standardised mortality ratio
SSRI	Selective serotonin reuptake inhibitor
SUDEP	Sudden unexplained death due to epilepsy
UTS	Up-to-standard (date which a participating practice complied with the minimum standards for data recording quality, p 69)

1 Chapter ONE: Introduction

1.1 Background of antipsychotic drugs

Chlorpromazine is considered the prototype antipsychotic, first being introduced in 1951 (Meltzer, 2004; Bitter, 2006). The therapeutic potential of chlorpromazine originated from the discovery by a French surgeon, Laborit, who in 1947 tested the drug promethazine to alleviate signs of stress in patients undergoing surgery (Rang et al, 1999). He then concluded that promethazine had a calming effect that was dissimilar from plain sedation (Rang et al, 1999). Modifications of the phenothiazine structure of promethazine then lead to the discovery of chlorpromazine in the early 1950s (Rang et al, 1999; Meltzer, 2004; Bitter, 2006).

Since its introduction, it was found that chlorpromazine was more effective in the treatment of acute symptoms of schizophrenia compared to non-pharmacological treatment including placebo or psychotherapy (Lieberman, 2006). Chlorpromazine has also been studied in many randomised controlled trials to assess its effectiveness in the treatment of schizophrenia (Adams et al, 2005). Following its release, other antipsychotic drugs such as thioridazine, haloperidol and pimozide have been marketed for the treatment of psychotic conditions.

Clinical efficacy of antipsychotic therapy in patients suffering from psychotic disorders can be measured by investigating their effect in the clinical dimensions of schizophrenia. There are 2 main dimensions or domains of schizophrenia; positive symptoms, and negative symptoms. The concept of positive and negative symptoms

was first described by Hughlings Jackson, a 19th century neurologist. It was not until 1970 that this concept was applied to schizophrenia (Hollis, 2002). Another vital parameter in the pathology of schizophrenia is cognitive impairment. These dimensions and symptoms are explained below:

- Positive symptoms which are acute and episodic (Scahill & Lynch, 1998). These include delusions, hallucinations, and thought disorder (Jibson & Tandon, 1998; Bitter, 2006).
- Negative symptoms which are chronic and continuous (Scahill & Lynch, 1998). Negative symptoms include a lack of motivation and social drive, impaired emotional expression and experience, impoverished speech and thought, anhedonia, and a lowered social interaction (Bilder, 1997: Jibson & Tandon, 1998; Scahill & Lynch, 1998).
- Cognitive and neuropsychological impairments (Bilder, 1997; Jibson & Tandon, 1998). Cognition has been reported to progressively depreciate for several years following the onset of psychotic symptoms (Jibson & Tandon, 1998). Cognitive function in schizophrenic patients can either be improved or worsened with antipsychotic symptoms (Jibson & Tandon, 1998).

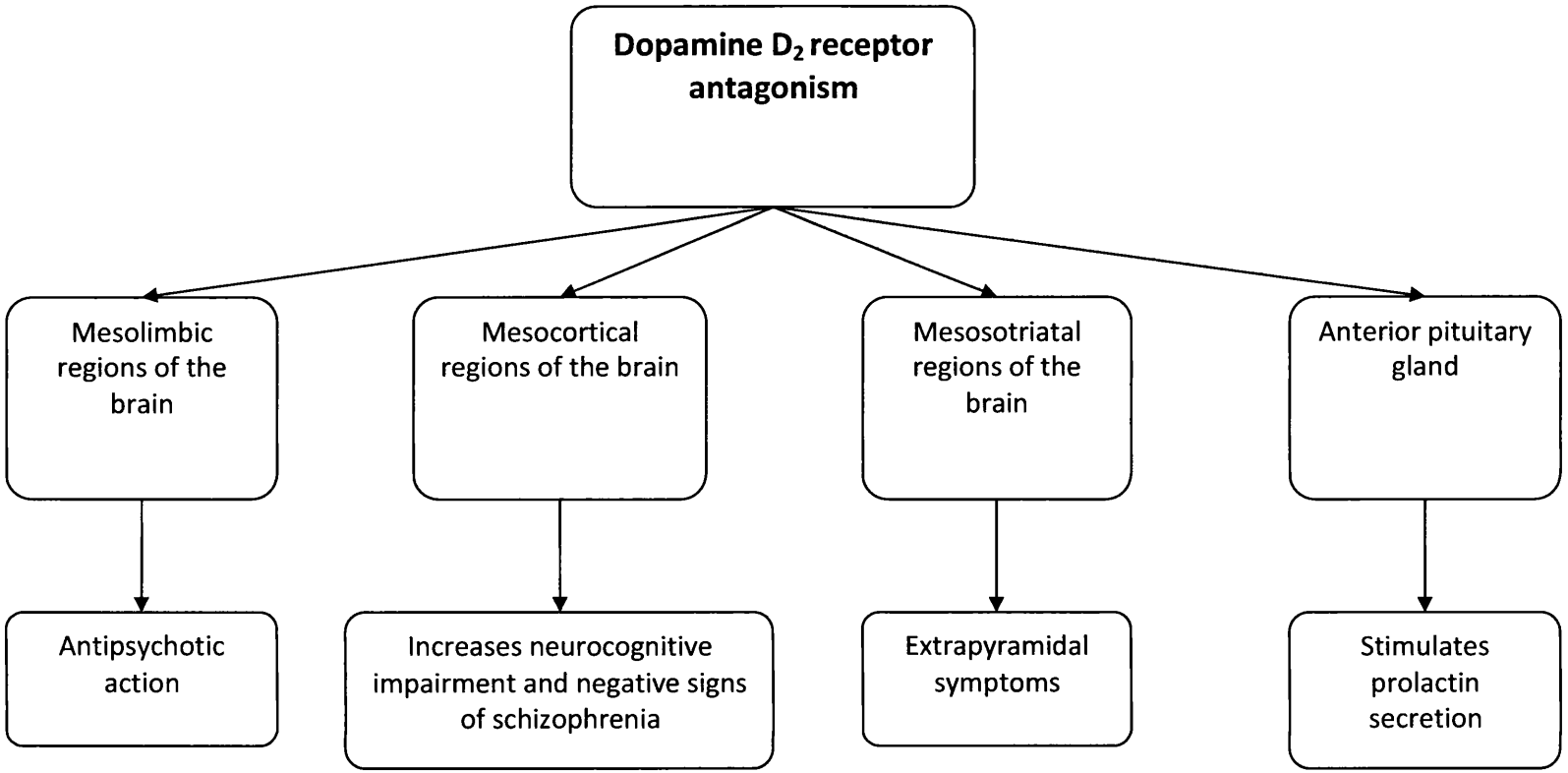
The initial hypothesis of schizophrenia proposed an overall excess of dopaminergic activity in the brain (Svensson, 2003). This suggestion was fundamentally based upon the pharmacological evidence of the antagonistic activity of antipsychotic agents in patients suffering from schizophrenia; as well as the effects of dopamine agonists such as amphetamine to induce psychosis and paranoid symptoms (Svensson, 2003). It should be noted however that the model proposed by amphetamine-induced

psychotic symptoms has a few limitations; whereby a number of core symptoms of schizophrenia including thought disorder, auditory hallucinations and anhedonia fail to manifest in psychosis induced by amphetamines (Svensson, 2003).

Dopamine is a neurotransmitter that has a role in mediating an extremely wide variety of physiological and behavioural functions such as coordinated movement, facial expression as well as complex emotional responses (Scahill & Skrypeck, 1997). From a therapeutic perspective, it is a critical property for antipsychotic drugs to have antagonistic properties on dopamine D_2 receptors to produce an antipsychotic effect (Kinon & Lieberman, 1996; Jibson & Tandon, 1998). It has also been shown that there is a direct correlation between clinical potency of antipsychotic drugs and presynaptic action on dopamine neurons (Seeman & Lee, 1975; Kapur, 1996; Kinon & Lieberman, 1996; Jibson & Tandon, 1998). In addition to receptor antagonism, interference of dopamine neurotransmission can also be achieved by impairing granular storage of dopamine within the neurons resulting in an inhibition of nerve impulse mediated release of dopamine (Ichikawa & Meltzer, 1999; Svensson, 2003).

Antagonism of dopamine D_2 receptors in different dopamine regions causes different effects (Burns, 2001). This is illustrated in Figure 1.1. Antipsychotic action is the result of dopamine D_2 antagonism at the mesolimbic regions of the brain (Meltzer, 2004). Extrapyramidal effects are caused by dopamine D_2 receptor blockade at the mesostriatal regions (Melzter, 2004). It is reported that dopamine D_2 occupancies of 75-80% are associated with extrapyramidal effects (Kapur, 1996; Horacek et al, 2006).

Figure 1.1: Different effects of dopamine antagonism



The unwanted extrapyramidal effects related to antipsychotic use comprise of symptoms such as acute dystonias and tardive dyskinesia. Acute dystonias are involuntary movements such as muscle spasms, protruding tongue, torticollis (wry neck) and Parkinson-type syndrome. They usually occur in the first few weeks of treatment and commonly decline as treatment continues. On the other hand, tardive dyskinesia develops after a period of treatment (months or years) with antipsychotic treatment. The syndrome of tardive dyskinesia consists of involuntary movements, usually of the face and tongue, but may also occur in the trunk and limbs. Tardive dyskinesia is a disabling and often irreversible condition, which may worsen when antipsychotic therapy is stopped (Rang et al, 1999).

Dopamine D_2 antagonism at the anterior pituitary gland affects prolactin pathways as dopamine is a natural inhibitor of prolactin secretion. Blockade of dopamine D_2 receptors in this region results in a raised serum prolactin which may potentially manifest as breast swelling, breast pain, and lactation; occurring in both males and females (Rang et al, 1999; Haddad & Wieck, 2004; Meltzer, 2004).

The first-generation antipsychotic drugs or typical antipsychotics such as flupenthixol, haloperidol and perphenazine are more potent in blocking the effects of dopamine action compared to chlorpromazine (Bitter, 2006). However, the increased potency in dopamine receptor antagonism was found to be related to a higher incidence of extrapyramidal side effects and not an increased efficacy in antipsychotic action (Bitter, 2006). As stated by Bitter (2006), the antipsychotic action of the typicals were "inseparable from extrapyramidal effects" associated with their use. Typical

antipsychotic drugs were found to be effective in treating the positive symptoms of schizophrenia. On the other hand, as a class, the agents have limited efficacy in treating the negative symptoms and can even potentially cause the development of negative symptoms such as anhedonia in certain patients (Borison, 1997; Bitter, 2006).

These treatment issues with typical antipsychotic therapy lead to the discovery of clozapine, which was first marketed in the late 1980s in the United Kingdom. Clozapine was the first of the atypical antipsychotics agents. It was found to be at least as effective as chlorpromazine in treating psychosis, but did not have as high an extrapyramidal side effect profile as chlorpromazine. Furthermore, it was also shown to be effective in reducing both positive and negative symptoms of schizophrenia and also useful in the management of treatment-resistant schizophrenia (Borison, 1997; Meltzer, 2004).

Despite the advantages clozapine had over the typical antipsychotic drugs, its use was found to be associated with severe blood disorders including agranulocytosis, seizures and sedation (Borison, 1997). Nevertheless, its discovery led researchers to search for newer drugs by focusing on the pharmacological similarities of clozapine but without the side effects. This then led to the discovery of other atypical antipsychotic drugs such as risperidone, olanzapine, quetiapine, and zotepine.

1.1.1 Typical antipsychotic drugs

Following the introduction of chlorpromazine in the early 1950s, other typical antipsychotic drugs such as haloperidol and thioridazine have been used in children and adolescents for various psychiatric conditions including aggression, tics, and pervasive developmental disorders (Scahill & Skrypeck, 1997; Bitter, 2006).

Despite the emergence of newer and reportedly safer and more efficacious psychopharmacological agents, chlorpromazine remains one of the most commonly used and inexpensive antipsychotic agents around the world (Adams et al, 2005). In fact chlorpromazine still remains the benchmark which other treatments are compared and evaluated with (Adams et al, 2005).

Typical antipsychotic agents are usually classified according to their chemical structure. The majority of typical antipsychotic agents are classified as phenothiazine derivatives. These can be further categorised into 3 groups (British National Formulary, 2008):

- Group 1
    - Antipsychotic drugs under this group are characterised by generally pronounced sedative effects and moderate antimuscarinic and extrapyramidal side effect profiles. Drugs under this group include chlorpromazine, levomepromazine and promazine.

- Group 2

- Antipsychotic drugs under this group are generally characterised by moderate sedative effects, marked antimuscarinic effects, and have a less severe extrapyramidal side effect profile than Groups 1 and 3. Examples of drugs in Group 2 include pericyazine.

- Group 3
  - Antipsychotic agents under this group are generally characterised by fewer sedative effects, fewer antimuscarinic effects, and a more pronounced extrapyramidal side effect profile compared to Groups 1 and 2. Examples of antipsychotic agents in this group include fluphenazine, perphenazine, prochlorperazine, and trifluoperazine.

Other typical antipsychotic agents resemble Group 3 of the phenothiazines. These include (British National Formulary, 2008):

- The butyrophenones such as benperidol and haloperidol.
- The diphenylbutylpiperidines such as pimozide.
- The thioxanthenes such as flupenthixol and zuclopenthixol.
- The substituted benzamides such as sulpiride.

Typical antipsychotic medications have been found to be beneficial in the management of various conditions. This includes controlling active psychotic symptoms, the reduction of assaultive behaviour, managing severe agitation, and reducing the risk of psychotic relapse in schizophrenic patients during maintenance therapy (Jibson & Tandon, 1998).

As mentioned earlier, the primary pharmacological activity of all antipsychotic drugs is due to the blockade of dopamine D_2 receptors in the brain (Jibson & Tandon, 1998; Horacek et al, 2006). The typical antipsychotic drugs are usually clinically effective at 70% D_2-receptor occupancy in the brain though the risks of extrapyramidal symptoms are very high above 80% occupancy (Svensson, 2003). It was found that the affinity of typical antipsychotic drugs for both the mesolimbic and mesostriatal dopamine regions was strongly correlated and therefore the desired antipsychotic effect was undividable from unwanted extrapyramidal symptoms (Meltzer, 2004).

It was estimated that 20-40% of patients treated with typical antipsychotic drugs develop extrapyramidal symptoms such as Parkinsonian syndrome, akathisia and tremor. Additionally, another 15-20% of patients who receive long term treatment with typicals develop tardive dyskinesia (Borison, 1997). Chlorpromazine and other typical antipsychotic drugs were also associated with an increased risk of elevated serum prolactin levels, sedation, cardiotoxicity, weight gain, as well as the potentially fatal neuroleptic malignant syndrome (Committee on Safety of Medicines, 2000; Meltzer, 2004).

Typical antipsychotic drugs have also been associated with cognitive dysfunction. Cognitive dysfunction in patients on typical antipsychotic therapy is directly attributed to extrapyramidal symptoms, to the drugs' anticholinergic trait, and also as the indirect

result of anticholinergic agents such as benztropine or trihexyphenidyl which are usually given as adjunctive therapy (Bilder, 1997; Jibson & Tandon, 1998)

Additionally, typical antipsychotic drugs are associated with intrinsic limitations in regards to efficacy. Up to 30% of patients exposed to typical antipsychotic medication do not experience any significant clinical improvement (Jibson & Tandon, 1998; Jones et al, 2006). In patients who do respond to treatment, the spectrum of therapeutic activity of typical antipsychotic drugs is relatively narrow (Jibson & Tandon, 1998; Jones et al, 2006). Although typical antipsychotic medicines as a class are effective in treating the positive symptoms of schizophrenia in responding patients, the drugs have limited effectiveness in treating the negative symptoms of schizophrenia and are minimally effective in treating the cognitive deficits associated with the condition (Jibson & Tandon, 1998). It was found that some of the typical antipsychotic drugs may reduce secondary negative symptoms by means of reducing psychosis, but the high incidence of extrapyramidal effects often makes the negative symptoms generally more prominent (Borison, 1997). Symptomatic relapses combined with potential adverse effects including extrapyramidal symptoms and sedation has a negative effect on adherence with these agents (Jibson & Tandon, 1998; Jones et al, 2006).

In spite of the severity of adverse effects and limited efficacy in treating specific symptoms related to schizophrenia, the typical antipsychotic drugs have been of enormous clinical significance in the treatment of psychotic disorders (Jibson & Tandon, 1998).

1.1.2 Atypical antipsychotic drugs

The atypical antipsychotic drugs were developed to either improve the treatment of adults with schizophrenia, to minimise the adverse effects seen with the older, typical antipsychotic drugs, or a combination of both (Kinon & Lieberman, 1996; Gracious & Findling, 2001; Lohr & Braff, 2003). The atypical antipsychotic drugs are thought to be a major advance in psychopharmacotherapy primarily as these drugs have been proposed to reduce the risk of developing extrapyramidal effects compared to patients exposed to the older generation drugs (Jones et al, 2006). This is considered a significant advantage especially as the lower risk of dyskinesias is more notable when taking into account the treatment of chronic conditions such as schizophrenia and pervasive developmental disorders which require long-term pharmacotherapy (Malone et al, 2001; Kumra et al, 2008). Furthermore as there is a link between extrapyramidal symptoms and the development of tardive dyskinesia, it is thought that the lower rates of extrapyramidal effects associated with atypical antipsychotic treatment compared to typical antipsychotic treatment results in a lower occurrence of tardive dyskinesia in patients exposed to the newer generation drugs (Correll & Kane, 2007).

Defining characteristics of whether an antipsychotic drug is atypical or otherwise usually includes measures of both therapeutic effects as well as adverse effects (Kinon & Lieberman, 1996). These include:

- Produces antipsychotic effects but does not produce catalepsy in animal models (Geddes et al, 2000; Meltzer, 2004).

- Possesses a unique receptor binding profile, with significantly lower affinity for dopamine D_2 receptors; with effect on other receptors including 5-HT_2 receptors (Bilder, 1997).
- Shows a clear difference i.e. a decrease or absence in causing extrapyramidal symptoms and tardive dyskinesia compared to the typical antipsychotic drugs (Kinon & Lieberman, 1996; Bilder, 1997; Scahill & Lynch, 1998; DuBois, 2005).
- Demonstrates efficacy in patients who are non-responders to typical antipsychotic treatment (Bilder, 1997).
- Increase in therapeutic efficacy towards the positive, negative, or cognitive symptoms associated with psychotic disorders (Kinon & Lieberman, 1996; Scahill & Lynch, 1998; DuBois, 2005).
- Decrease or absence in elevating serum prolactin levels (Kinon & Lieberman, 1996; Scahill & Lynch, 1998).

In 1989, the first atypical antipsychotic drug, clozapine, was marketed for the treatment of schizophrenia (Malone et al, 1999). Clozapine is a benzodiazepine with a chemical structure similar to chlorpromazine. However, clozapine did not produce signs of extrapyramidal symptoms even at doses many times higher than that produced an apparent antipsychotic effect in rats (Meltzer, 2004). The introduction of clozapine had changed the notion that extrapyramidal effects and tardive dyskinesia were unavoidable concomitants of antipsychotic therapy (Tamminga, 2003).

Clozapine has been reported to be more effective in reducing symptoms related to schizophrenia spectrum disorders in both treatment-resistant and non-treatment-resistant patients, as well as being associated with fewer extrapyramidal symptoms when compared to treatment with typical antipsychotic medication (Wahlbeck, 1999a; Wahlbeck, 1999b). Clozapine was also found useful in alleviating the negative symptoms and depression in patients suffering from schizophrenia (Bitter, 2006). However, clozapine was found to cause severe adverse effects, most notably agranulocytosis (Borison, 1997; Jones et al, 2006) which almost resulted in the withdrawal of clozapine from the market. Since then, clozapine is now reserved for patients with treatment-resistant schizophrenia (Scahill & Lynch, 1998; Stigler et al, 2001). While this has limited the use of clozapine in the treatment of psychotic patients, clozapine is considered the standard for "atypicality" to which all other atypical antipsychotics are compared (Bilder, 1997; Jibson & Tandon, 1998) and is considered to be the most "atypical" of the atypical antipsychotic drugs (Meltzer, 2004). The clinical advantages of clozapine then led to the discovery of other newer antipsychotic agents with similar efficacy such as risperidone, olanzapine, quetiapine and aripiprazole. This class of drugs was then labelled under the name 'atypical antipsychotics'.

While the typical antipsychotic agents are usually classified according to similarities in their chemical structures, the atypical antipsychotic drugs are often categorised according to their pharmacodynamic profiles, which essentially reflect their affinities for different receptors (Horacek et al, 2006). Atypical antipsychotic agents with high selectivity for

serotonin 5-HT_{2A} receptors and dopamine D_2 receptors are known as serotonin-dopamine agonists. Risperidone and sertindole are examples of this class of atypical antipsychotic agents (Horacek et al, 2006).

Atypical antipsychotic drugs which show an affinity not only for serotonin 5-HT_{2A} and dopamine D_2 receptors; but also show affinity for a wide range of receptors of other systems including cholinergic, histaminergic, and other serotonin receptor subtypes (including serotonin 5-HT_{1A} and serotonin 5-HT_{2C}) are called multi-acting receptor-targeted antipsychotics or MARTA (Bymaster et al, 1996; Horacek et al, 2006). Examples of atypical antipsychotic agents from this class include clozapine, olanzapine and quetiapine (Horacek et al, 2006).

Atypical antipsychotic agents that preferentially block dopamine D_2 and D_3 receptor subtypes are classified as combined D_2/D_3 receptor antagonists. Amisulpride is an example of an atypical antipsychotic agent from this class (Horacek et al, 2006). Lastly, atypical antipsychotic agents that also produce dopaminergic activity in addition to receptor blockade are known as the partial dopamine receptor agonists. An example of this class of drug is aripiprazole (Horacek et al, 2006).

As with the older typical antipsychotics, all atypical antipsychotic agents block the dopamine D_2 receptors (DuBois, 2005). Unlike the typical antipsychotic drugs however, where the degree of dopamine D_2 receptor antagonism is directly related to the

antipsychotic effect, it is different with the atypical antipsychotic agents (Horacek et al, 2006). It was found that clozapine has a higher affinity for dopamine D_1 receptors than D_2 receptors, whereby D_1 receptors are found in the prefrontal cortex and is often linked to negative and cognitive symptoms of schizophrenia (Horacek et al, 2006). It was also found that clozapine is clinically effective at about 45% dopamine D_2 receptor occupancy (compared to the reported 70% of dopamine occupancy with typical antipsychotic drugs), suggesting an alternative mechanism of antipsychotic action (Svensson, 2003). However as not all atypical antipsychotic drugs has the same affinity for dopamine D_1 and D_2 receptors as clozapine; this proposed an alternative theory on atypical antipsychotic drug efficacy (Svensson, 2003; Horacek et al, 2006).

It is thought that it is the antagonistic ability of the atypical antipsychotic agents at serotonin 5-HT_2 receptors which is responsible for this class of drug's unique pharmacology (Tamminga, 2003). Historically, serotonergic regulation and its association with schizophrenia originated from the finding that serotonin 5-HT_{2A} receptor agonists such as lysergic acid diethylamide or LSD, a potent psychogenic hallucinogen, can produce psychotic symptoms (Horacek et al, 2006). Although psychotic symptoms as a result of serotonin 5-HT_{2A} agonists differ from the symptoms of schizophrenic psychosis, the serotonin 5-HT_{2A} antagonistic activity is proposed to be an additional therapeutic advantage of atypical antipsychotic drugs (Horacek et al, 2006). Furthermore, early investigations with ritanserin, a potent serotonin 5-HT_2 receptor antagonist, demonstrated a mood-elevating effect in patients suffering from depressive conditions with improved

energy, drive, and motivation. Ritanserin was also shown to reduce the negative symptoms associated with schizophrenia and improve the effects of haloperidol in schizophrenic patients resistant to treatment. Dose-dependent indirect activation of dopamine cell activity was also seen in subsequent experimentations with ritanserin (Svensson, 2003). Following these investigations, it was concluded that the addition of serotonin 5-HT_2 receptor antagonism activity to dopamine D_2 receptor blockade results in a level of limbic selectivity of a psychotropic drug. This then leads to a facilitated physiological function and transmitter output of mesocortical dopamine neurons (Svensson, 2003).

Overall, the atypical antipsychotic drugs demonstrate a high ratio of 5-HT_{2A} / D_2 receptor antagonism (Stigler et al, 2001; Svensson, 2003). The combination of dopamine D_2 and serotonin 5-HT_{2A} receptor blockade, which is one of the main defining characteristics of atypical antipsychotic action, is proposed to be beneficial in reducing extrapyramidal symptoms associated with the older generation antipsychotics (Kapur, 1996; Tamminga, 2003; Horacek et al, 2006). It has been proposed that when dopamine D_2 receptor blockade is just above the extrapyramidal symptom threshold, additional 5-HT_{2A} antagonism may delay the onset of extrapyramidal effects (Kapur, 1996). Additionally, if the dose of dopamine D_2 antagonistic agents is further increased, the concurrent serotonin 5-HT_{2A} occupancy may decrease the severity of extrapyramidal effects. Nevertheless if the dose of the dopamine D_2 antagonistic agent is raised to a

suprathreshold level, the effect of serotonin 5-HT_{2A} blockade may be inundated (Kapur, 1996).

Serotonin 5-HT_{2A} receptor blockade has also been proposed to reduce dopaminergic output into the mesolimbic system which would lead to an amplification of antipsychotic potential of atypical antipsychotic drugs with combination of 5-HT_{2A} / D_2 receptor antagonism (Horacek et al, 2006).

These apparent advantages of atypical antipsychotic drugs as a class have resulted in a treatment shift away from the older typical antipsychotic drugs in patients suffering from psychotic disorders (Meltzer, 2004; Jones et al, 2006).

However, the atypical antipsychotic agents are not totally free from unwanted effects. In addition to their therapeutic advantage via antagonism at dopamine D_2 and 5-HT_2 receptors in the limbic system, they also have varying affinities towards the histamine, adrenergic, and muscarinic receptor subtypes (Burns, 2001). It is this mechanistic difference among the atypical antipsychotic agents which leads to the individual drugs' unique efficacy and side effect profile (Tamminga, 2003). The antagonism of various receptors in different systems results in unwanted side effects such as weight gain, dizziness, blurred vision, metabolic effects including glucose dysregulation, cardiac effects such as QT prolongation, and even the rare but potentially fatal neuroleptic malignant syndrome (Burns, 2001).

1.1.3 Atypical antipsychotics better than typical antipsychotics?

A major disadvantage of typical antipsychotic drugs is the narrow therapeutic index whereby therapeutic efficacy is often achieved at doses which also cause extrapyramidal symptoms (Bryden et al, 2001). As mentioned earlier, the emergence of the newer atypical antipsychotic drugs has lead to a shift away from the older typical antipsychotics (Meltzer, 2004; Jones et al, 2006). The increase in prescribing of atypical antipsychotic medications is probably due to the assumption that the newer drugs are more effective in treating certain dimensions of schizophrenia and are better tolerated compared to the older generation drugs (Toren et al, 2004).

Many studies have been conducted to show the advantage of atypical antipsychotics over the typicals. In adults, clozapine has been found to be more effective in treatment-resistant schizophrenic patients compared to chlorpromazine (Kane et al, 1988) and has also been proven to cause fewer extrapyramidal effects than typical antipsychotic therapy (Leucht et al, 2003). The benefits of clozapine compared to conventional typical antipsychotic therapy have also been demonstrated in a Cochrane review (Wahlbeck et al, 1999b). The review stated that more patients on clozapine experienced clinical improvements compared to patients exposed to typical antipsychotic therapy. Patients on clozapine also had fewer relapses in the short term and clozapine treatment was also found to be more acceptable compared to low potency antipsychotic drugs. Overall, clozapine was confirmed to be more effective in reducing symptoms of schizophrenia,

producing clinical improvements as well as delaying relapse compared to typical antipsychotic treatment (Wahlbeck et al, 1999b).

As a class, atypical antipsychotic drugs have been shown to improve negative symptoms associated with schizophrenia in adults compared to the typical antipsychotics. This is largely due to the different mechanisms of action or by reducing secondary negative symptoms associated with extrapyramidal symptoms (Jibson & Tandon, 1998; Bryden et al, 2001). Atypical antipsychotic therapy is also found to have a reduced risk for producing tardive dyskinesia compared to the older generation antipsychotics (Correll et al, 2004). It should be noted however that this advantage was reduced when the dose of atypical antipsychotic therapy was elevated, which resulted in an increase in extrapyramidal effects (Correll et al, 2004).

The apparent advantage of atypical antipsychotic medication in children and adolescents has also been demonstrated in a number of studies. Clozapine has been found to be more effective than haloperidol in the treatment of childhood-onset schizophrenia (Kumra et al, 1996). However, approximately 30% of the study subjects experienced adverse effects, most notably neutropaenia and seizures. Although clozapine has been proven to be effective in treating early-onset schizophrenia in children and adolescents, its use similar to adults, is limited as a last resort due to the severity of adverse effects and the need for continuous blood monitoring (Malone et al, 1999).

Risperidone has been found to be more effective and better tolerated than haloperidol in the long-term maintenance treatment of children with autistic disorder (Gencer et al, 2008). It was also found that autistic children exposed to risperidone do not suffer the same language deterioration as those exposed to haloperidol (Gencer et al, 2008). Risperidone has also been found to be superior to pimozide in reducing tic symptoms in children with Tourette's disorder. However, patients exposed to risperidone experienced greater weight gain than those treated with pimozide (Gilbert et al, 2004).

Despite the various studies and reports proposing a clear clinical advantage of the atypical antipsychotic drugs over the older typical antipsychotics, a number of reviews and meta-regression analyses have refuted this claim. Systematic overviews of antipsychotic drugs reported that the dose of comparator drugs, such as haloperidol and chlorpromazine, significantly affected the apparent advantage of atypical antipsychotic therapy in the reviewed trials (Geddes et al, 2000; Leucht et al, 2003). Results from reviews and meta-analyses of published studies identified a significant advantage for atypical antipsychotic medication as the dose of comparator typical antipsychotic increased. Conversely the observed advantage of atypical antipsychotic medication disappeared as the dose of the comparator typical antipsychotic medication decreased (Geddes et al, 2000; Leucht et al, 1999; Leucht et al, 2003). One review concluded that "taking the results at face value, atypical antipsychotics are slightly more effective and better tolerated in patients with schizophrenia". However, when controlled for the "higher than recommended dose" of typical antipsychotic therapy that was used in a number of the reviewed trials, the

differences in efficacy and overall tolerability was negated (Geddes et al, 2000). This suggests that the apparent advantage of atypical antipsychotic drugs over the older generation antipsychotics is actually due to excessively high doses of comparator drugs used in the investigative trials. It must be noted however, that the review showed that atypical antipsychotic therapy was still found to have a modest advantage in the extrapyramidal side effect profile even after controlling for the high doses of conventional antipsychotic medications (Geddes et al, 2000).

A more recent randomised controlled trial investigating the quality of life, tolerability and costs of care in schizophrenic adult patients on typical versus atypical antipsychotic therapy failed to result in a significant clinical advantage or an improved quality of life favouring atypical antipsychotic treatment. In fact patients exposed to the older typical antipsychotic drugs showed a greater trend towards improvements in quality of life, although this effect was not statistically significant (Jones et al, 2006).

A number of reviews have also been conducted on studies in children and adolescents. A review and meta-analysis investigating antipsychotic treatment in children suffering from early-onset schizophrenia concluded that atypical antipsychotic drugs had no beneficial advantage in terms of efficacy when the dose of the comparator typical antipsychotic was equivalent to or less than 12mg per day of haloperidol (Armenteros & Davies, 2006). The review also found that weight gain and sedation were more pronounced in children exposed to atypical antipsychotic therapy compared to typical antipsychotics (Armenteros

& Davies, 2006). Another study comparing the clinical response and tolerability of haloperidol, risperidone, and olanzapine in the treatment of adolescents with schizophrenia, found that the atypical antipsychotic drugs were not clinically superior to haloperidol; and all 3 drugs were equally effective in treating acute symptoms of the condition (Gothelf et al, 2003).

On the other hand, there have also been published meta-analyses rebuffing these conclusions and claiming that the dose of comparator haloperidol drug did not affect the results and that a number of atypical antipsychotic drugs were significantly more effective compared to typical antipsychotic medication (Davis et al, 2003; Horacek et al, 2006).

To summarise, it can be said that despite studies with claims of atypical antipsychotic superiority over the typical antipsychotic drugs, many meta-analyses and clinical trials have questioned the size and significance of these effects (Leucht et al, 2003; Lieberman et al, 2005; Lieberman, 2006; Jones et al, 2006). These studies have found few differences favouring the newer atypical antipsychotic drugs. Whether atypical antipsychotic has an advantage over the older, typical antipsychotics in children and adolescents remains debatable.

1.2 Antipsychotic therapy in children and adolescents

Studies of antipsychotic therapy in adults with chronic schizophrenia may provide rough guidance for treatment in paediatric patients with the condition. The use of antipsychotic

therapy in the paediatric population is considered to be relatively new compared to the adult population (Erdogan et al, 2008). However, children and adolescents have unique developmental aspects which may influence the pharmacology of these drugs (Lewis, 1998; Bryden et al, 2001; Kumra et al, 2008). The developmental difference in the young population compared to adults includes changes in dopamine cell density, peaking of basal dopamine levels, dopamine turnover, and changes in dopamine D_1 and D_2 receptor concentrations in the striatum (Lewis, 1998; Kumra et al, 2008). Adolescents also have higher levels of basal dopamine levels in the prefrontal cortex of the brain. These changes during maturation could potentially affect clinical response and pharmacology of antipsychotic therapy; as well as increase the sensitivity and susceptibility of young patients to possible adverse effects associated with these drugs (Lewis, 1998; Kumra et al, 2008).

Progressively more children are being exposed to psychotropic medicines over the recent years (Jacobs et al, 2001; Wong et al, 2004). Although investigations on prescribing practices of child psychiatrists are lacking compared to those conducted from adult practices, it has been reported that as many as half of child and adolescent psychiatric inpatients and one-third of child and adolescent psychiatric outpatients are prescribed antipsychotic medication (Kaplan et al, 1994).

1.2.1 Indications of antipsychotic drugs in children and adolescents

The use of and indications of antipsychotic medications are well defined in adults but less clearly outlined for use in paediatric patients (Scahilll & Skrypeck, 1997).

Schizophrenia is considered a major indication of antipsychotic medication in children and adolescents (Lewis, 1998; Frangou & Byrne, 2000; Armenteros & Davies, 2006). This is highlighted by the general consensus that early onset-schizophrenia is more detrimental compared to adult-onset due to its potential severe effect on the developing social skills and neurocognitive functions of children (Findling & McNamara, 2004). It has also been said that antipsychotic treatment produces a better response in patients suffering from first-episode schizophrenia rather than in chronic multiepisode patients (Lieberman et al, 1993). As it has been proven that early treatment of first-episode schizophrenia generates a greater therapeutic outcome with a more complete remission of symptoms in adults, the same approach in younger patients may also substantially reduce long-term morbidity associated with these disorders. It has also been suggested that pharmacological intervention at an early stage of the disease progression may play a "neuroprotective" role (Bryden et al, 2001).

Although schizophrenic disorders in children has been reported to be a rare condition (Malone et al, 1999), it has been noted that almost half of males and about one-third of females who develop schizophrenia do so by 19 years of age, and the incidence of this condition increases dramatically during adolescence (Armenteros et al, 1997; Lewis, 1998;

Armenteros & Davies, 2006; Kumra et al, 2008). Furthermore it has been reported that the onset of psychosis after 35 years of age only occurs in 17% and 2% of women and men with schizophrenia respectively (Loranger, 1984). Both the typical antipsychotic agents including haloperidol (Scahill & Skrypeck, 1997; Spencer & Campbell, 1994; Campbell et al, 1999; Malone et al, 1999; Gillberg, 2000; Bryden et al, 2001; Gothelf et al, 2003) as well as the atypical antipsychotic drugs such as clozapine (Frazier et al, 1994; Kumra et al, 1996), risperidone (Armenteros et al, 1997; Cannon et al, 2002), olanzapine (Kumra et al, 1998; Findling et al, 2003; Ross et al, 2003) and quetiapine (Malone et al, 1999; Findling, 2002; Cheer & Wagstaff, 2004) have been shown to be efficacious in treating children and adolescents with psychotic disorders including first-episode schizophrenia.

Besides schizophrenia and psychotic disorders, other common uses of antipsychotic agents in child psychiatry include mood disorders such as bipolar disorder and major depression with psychotic features; movement disorders such as tic disorders and Tourette's syndrome; and pervasive developmental disorders such as autism (Campbell et al, 1999; Malone et al, 1999; Gracious & Findling, 2001; McClellan & Werry, 2003; Patel et al, 2006b; Correll, 2008). A survey of child psychiatry practices has even revealed that approximately two-thirds of children exposed to antipsychotic medication were prescribed these drugs for non-psychotic conditions including aggression associated with conduct disorder (Kaplan et al, 1994). The newer atypical antipsychotic agents have also been studied in many case reports and open-label trials for the treatment of a wide variety of psychiatric conditions in children and adolescents (Findling & McNamara, 2004).

Chapter ONE: Introduction

It has been reported that the best evidence for use of antipsychotic therapy in children and adolescents is probably in the treatment for autism (McClellan & Werry, 2003). Autism has also been considered among the most severe among the pervasive developmental disorders (Kemner et al, 2002). Autistic spectrum disorders comprise of 3 main areas of deficit, which are social deficits, communication deficits, and restricted repetitive behaviours (Lord & Bailey, 2002). Most children with this condition are identified by their parents as showing abnormal behaviour or delays in development by the second year of life (Lord & Bailey, 2002). Unlike schizophrenic disorders, children suffering from autistic spectrum disorders usually develop abnormalities related to the condition in the first 3 years, while children with schizophrenia often show abnormalities later in life (Lord & Bailey, 2002).

Antipsychotic therapy in children with autism is used clinically to reduce the disruptive symptoms associated with the condition such as temper tantrums, aggressiveness and hyperactivity (Campbell et al, 1999; Gencer et al, 2008). Haloperidol is considered to be the most critically studied medication in children suffering from autistic disorder (Malone et al, 2001; Coghill, 2003; Gencer et al, 2008). Haloperidol has been established to be efficacious (Perry et al, 1989), superior to placebo (Gencer et al, 2008), and comparable to olanzapine (Malone et al, 2001) in the reduction of disruptive behavioural symptoms in autistic children. Atypical antipsychotic agents such as risperidone, amisulpride and olanzapine have also been shown to be effective and well tolerated in children with

pervasive developmental disorders or autistic disorders (Potenza et al, 1999; Malone et al, 1999; Malone et al, 2001; Casaer et al, 2002; Diler et al, 2002; Kemner et al, 2002; Malone et al, 2002; McCracken et al, 2002; Gagliano et al, 2004; Gencer et al, 2008).

Haloperidol and pimozide have been studied and found to be effective in treating children with behavioural disorders (Naruse et al, 1982). Trifluoperazine has been shown to reduce hyperactivity and attention deficits, aggressive behaviour as well as behavioural symptoms in autistic children (Gillberg, 2000). The effectiveness of the atypical antipsychotic risperidone has also been demonstrated in children with behaviour disorders (Ad-Dab'bagh et al, 2000; Turgay et al, 2005; Findling et al, 2004; Croonenberghs et al, 2005).

Conduct disorders comprise of an extensive range of antisocial and aggressive behaviours which may become prominent in early childhood and may even persist into adulthood (Earls & Mezzacappa, 2002). Early recognition and management of this disorder has been reported to both reduce childhood dysfunction, and also prevent abusive and criminal behaviour that may manifest later in life (Earls & Mezzacappa, 2002). A number of antipsychotic agents including haloperidol, thioridazine, and risperidone have been investigated and found to be efficacious in the treatment of conduct disorders in children and adolescents (Campbell et al, 1997; Scahill & Skrypeck, 1997; Findling et al, 2000; Ercan et al, 2003).

Typical antipsychotic agents have been shown to be effective in reducing tic symptoms associated with Tourette's disorders (Sallee et al, 1997; Campbell et al, 1999; Gillberg, 2000). The onset of Tourette's syndrome is usually in early childhood, increases severity at puberty, and stabilises in adulthood. The severity of tics associated with the condition varies throughout this period with an average cycle of about 3 months (Coghill, 2003). Tic disorders are often associated with difficulties in self esteem, family life, social acceptance and school performance (Leckman & Cohen, 2002). In addition to tic symptoms, patients suffering from tic disorders may present with a wide range of behaviour difficulties (Leckman & Cohen, 2002). Haloperidol, pimozide and sulpiride are the typical antipsychotic agents considered to be the primary forms of pharmacotherapy in the treatment of tics (Coghill, 2003). Atypical antipsychotic drugs including risperidone have also been shown to be effective in reducing the frequency and intensity of tics in paediatric patients with tic disorders (Lombroso et al, 1995; Malone et al, 1999; Gaffney et al, 2002; Gilbert et al, 2004).

Antipsychotic agents have also been found useful in the treatment of symptoms associated with mental retardation (McClellan & Werry, 2003). Thioridazine and haloperidol have been studied and shown to be useful in treating children suffering from mental retardation and hyperactivity (Scahill & Skrypeck, 1997; Campbell et al, 1999). Chlorpromazine was also found useful in children with attention deficit hyperactivity disorders (Campbell et al, 1999). Recently antipsychotic use in the treatment of attention

deficit hyperactivity disorder is only in cases where patients are also suffering from Tourette's disorder or psychosis co-morbidities (Campbell et al, 1999).

The atypical antipsychotic agents have been proposed as part of the management strategy in the treatment of adolescents with mood disorders including bipolar illness (Clark, 2001). Bipolar disorder is characterised by a combination of depression and "distinct episodes of manic disorder" (Harrington, 2002). Even so, all patients suffering from mania are considered in the bipolar group, even in the absence of depression (Harrington, 2002). In severe cases of mania, patients may even present with symptoms of delusions, hallucinations and frenzied overactivity (Harrington, 2002). Quetiapine, an atypical antipsychotic drug, has been shown to significantly reduce symptoms of mood disorders including mania as an adjunct to divalproex (semisodium valproate) compared to divalproex with placebo (DelBello et al, 2002; Findling, 2002).

Other indications of antipsychotic agents include the treatment of anorexia nervosa. Olanzapine has been shown to be promising in treating the condition by way of its effect on weight gain (Powers et al, 2002). Clozapine has also been indicated to be effective in reducing psychiatric symptoms and risk behaviours in adolescents suffering from post traumatic stress disorder and psychotic symptoms (Wheatley et al, 2004).

In summary, the use of both typical and atypical antipsychotic agents has been studied for an extensive range of psychiatric conditions in children and adolescents. It must be noted

however, that the majority of these agents are not licensed in children, and many of the indications studied are for 'off-label' uses (Yan, 2007). Among the available typical antipsychotic agents, only haloperidol and trifluoperazine are licensed for behavioural disorders and schizophrenia in children. Pimozide and sulpiride are only licensed for patients aged 12 years and above and 14 years and above respectively for the treatment of psychotic disorders. Among the available atypical antipsychotic drugs, only amisulpride, clozapine and risperidone are licensed for use in patients aged 18 years and under. Amisulpride is licensed for patients aged 15 years and above for acute and chronic schizophrenic disorders; risperidone is licensed for the treatment of acute and chronic schizophrenic disorders as well as mania in bipolar disorders in patients aged 15 years and above whereas clozapine is only licensed in adolescents aged 16 years and above suffering from treatment-resistant schizophrenia non-responsive to other antipsychotic drugs (Electronic Medicines Compendium).

The off-label prescribing of these drugs in children and adolescents is an important issue as it demonstrates a lack of adequate investigations and experience for use in this population. This is highlighted by the fact that off-label prescribing to children may potentially increase the risk of drug toxicity (Impicciatore et al, 2001).

1.2.2 Safety of antipsychotic drugs in children and adolescents

Only in recent years has research been shifted from investigating efficacy to studying safety of medicines in children (Conroy et al, 2000). Although there have been significant

advances in the research of other areas of paediatric psychopharmacology, research on safety and efficacy on the treatment of early-onset schizophrenia has been lacking (Armenteros & Davies, 2006). The rate of prescribing of antipsychotic drugs has been increasing in children and adolescents for a rising number of psychiatric indications. Despite this, the availability of evidence for the safety and efficacy of these drugs in the young is limited, where the majority of available studies are the result of open-label trials, reviews and case reports (Malone et al, 1999; Bhana et al, 2001; Bryden et al, 2001; Laita et al, 2007). In general, the incidence of adverse drug reactions correlates with age in the general population, suggesting that paediatric patients are more susceptible to adverse effects (Impicciatore et al, 2001). The severity of potential adverse effects of antipsychotic drugs seen in adult studies (Glazer, 2000; Kane, 2004; Laita et al, 2007) further accentuates caution when prescribing these drugs to the paediatric population. Furthermore, it has been reported that adverse effects associated with moderate doses of antipsychotic medications in children are more prevalent and severe compared to the effects reported in the adult population (Sikich et al, 2004). This could possibly be due to differences in developmental pharmacokinetics such as lower proportion of adipose tissue and levels of protein binding seen in children, which may result in an increased bioavailability of antipsychotic drugs leading to increased therapeutic and adverse effects (Piscitelli et al, 1994; DuBois, 2005).

Extrapyramidal symptoms

With typical antipsychotic therapy, extrapyramidal effects manifests in the same dose range as the antipsychotic effect i.e. clinical benefit goes hand in hand with extrapyramidal symptoms. In atypical antipsychotic therapy, clinical efficacy reported to be achieved without producing extrapyramidal symptoms, or at doses less than at which causes significant extrapyramidal symptoms (Jibson & Tandon, 1998). Despite this, extrapyramidal symptoms have been reported in paediatric patients on both typical and atypical antipsychotic treatment (Armenteros & Davies, 2006; Correll, 2008). It has also been shown that high-potency atypical antipsychotic drugs such as risperidone have a "higher-than-expected" rate of producing extrapyramidal effects (Lewis, 1998). On the other hand, quetiapine has been reported to have the lowest rate of producing extrapyramidal adverse effects in children when compared to other atypical antipsychotic agents including risperidone and olanzapine (Findling, 2002).

Extrapyramidal side effects usually manifest during the initial few weeks of treatment, but can also appear much later in the course of antipsychotic treatment. The 3 most common types of these symptoms are acute dystonic reactions, akathisia, and pseudoparkinsonism (Gracious & Findling, 2001). Laryngospasm, a form of dystonic reaction can also occur in patients exposed to antipsychotic treatment, and can be potentially fatal (Gracious & Findling, 2001). Early occurrence of extrapyramidal effects during treatment with antipsychotic medication is reported to significantly increase the likelihood of developing tardive dyskinesia (Jibson & Tandon, 1998).

The impact of extrapyramidal side effects in antipsychotic-treated patients should not be overlooked as it plays an important role in compliance and adherence to therapy. As acute dystonic reactions and akathisia are common in the initial stages of antipsychotic therapy, it is associated with premature discontinuation of treatment (Jibson & Tandon, 1998). Among patients who do continue treatment, extrapyramidal symptoms can manifest as bradykinesia and rigidity which may impair social function, adding to the likelihood of non-compliance (Jibson & Tandon, 1998). Furthermore, as mentioned earlier, extrapyramidal effects are associated with cognitive dysfunction in patients suffering from psychotic disorders (Bilder, 1997). It has also been reported that poorly controlled extrapyramidal effects induced by antipsychotic therapy is a risk factor for neuroleptic malignant syndrome (Pelonero et al, 1998).

Tardive dyskinesia

Among the adverse effects seen with antipsychotic therapy, tardive dyskinesia is often regarded as the most serious (Casey, 1999). Tardive dyskinesia has been associated with poor quality of life and may even result in an increase in morbidity as well as mortality (Correll et al, 2004). Although this condition is relatively rare, it is thought that younger patients exposed to antipsychotic therapy may be more prone to developing tardive dyskinesia (Gracious & Findling, 2001). Symptoms of tardive dyskinesia include:

- Repetitive, involuntary, hyperkinetic, tic-like movements. Examples include chewing, protrusion or vermicular motion of the tongue, side-to-side jaw movements, lip smacking and lip puckering (Casey, 1999; Gracious & Findling, 2001).

- Hyperkinetic movements of the limbs and trunk (Casey, 1999).

The respiratory system has also been reported to be affected by tardive dyskinesia, resulting in irregular respiration rates. However, this clinical manifestation is not as common as the previously mentioned symptoms (Casey, 1999). Other clinical manifestations include tardive dystonia which is sustained abnormal postures and tardive akathisia which is persistent restlessness. These clinical presentations are similar to the acute extrapyramidal symptoms typically seen, but persist over a longer period of time after antipsychotic therapy has been stopped (Casey, 1999).

It has been reported that as many as half of patients have recurrent symptoms of tardive dyskinesia without prolonged remission, and between 10-50% of patients experiencing tardive dyskinesia will have a reduction in movements or full remission. Up to one-third of patients will experience worsening of symptoms (Casey, 1999).

Hyperprolactinaemia

Prolactin is responsible for stimulating lactation, developing breast tissue and also plays a role in certain aspects of gonadal function and development (Pappagallo & Silva, 2004). Prolactin is secreted by the lactotroph cells found in the anterior pituitary in the brain (Haddad & Wieck, 2004). Dopamine is the predominant inhibiting factor of prolactin secretion whereby dopamine inhibits prolactin secretion by binding to dopamine D_2 receptors found on the membrane of lactotroph cells (Haddad & Wieck, 2004). An increase in prolactin production is a common side effect associated with both typical and

atypical antipsychotic therapy (Bryden et al, 2001; Masi et al, 2001; Toren et al, 2004) as virtually all antipsychotic agents are capable of blocking dopamine D_2 receptors in the brain (Haddad & Wieck, 2004). However, the unique mechanism of action of atypical antipsychotic agents and their individual differences in receptor binding profiles may be the cause of the varying effects on prolactin for this newer class of drugs (Pappagallo & Silva, 2004). Among the atypical antipsychotic agents, risperidone has been shown to have the most effect on prolactin levels compared to olanzapine and quetiapine (Saito et al, 2004).

Hyperprolactinaemia has been associated with the development of menstrual and sexual dysfunction, breast enlargement, lactation, and reduced bone density (Haddad & Wieck, 2004; Pappagallo & Silva, 2004; Saito et al, 2004; Croonenberghs et al, 2005). Potential indirect long-term sustained effects of hyperprolactinaemia include an increased risk of impotency, cardiovascular disease, obesity, and osteoporosis which is caused by a decrease in oestrogen and testosterone (Gracious & Findling, 2001; Pappagallo & Silva, 2004; Toren et al, 2004; Correll, 2008). Hyperprolactinaemia may also potentially affect patients' compliance. For example, galactorrhoea and gynaecomastia, especially in males, may have a strong impact on self-image and may lead to premature discontinuation of treatment (Pappagallo & Silva, 2004).

It has been reported that children may be more liable and sensitive to the effects of elevations in serum prolactin than adults (Wudarsky et al, 1999; Haddad & Wieck, 2004;

Pappagallo & Silva, 2004). Furthermore, the effect of hyperprolactinaemia during the essential developmental period of puberty is currently unknown (Pappagallo & Silva, 2004).

Neuroleptic malignant syndrome

Neuroleptic malignant syndrome (NMS) is a rare but potentially fatal adverse effect of antipsychotic medication. The earliest case of NMS can probably be traced back to 1959 which occurred in a patient exposed to trifluoperazine (Brown, 1999). Practically all antipsychotic drugs are capable of producing NMS (Pelonero et al, 1998). A number of reports of NMS in children and adolescents associated with atypical antipsychotic drug treatment including risperidone (Sharma et al, 1996; Robb et al, 2000; Vercammen et al, 2003; Zalsman et al, 2004; Mané et al, 2005), olanzapine (Berry et al, 2003; Hanft et al, 2004), clozapine (Sachdev et al, 1995; Brown, 1999; Skarpathiotakis & Westreich, 2005), and aripiprazole (Spalding, 2004; Hammerman et al, 2006) have been reported as case reports and letters in scientific journals.

It is the antagonism of dopamine D_2 receptors in the hypothalamus and nigrostriatum which is the likely mechanism of NMS in antipsychotic-treated patients (Burns, 2001). There are 3 major manifestations of NMS; high fever, muscle rigidity, and elevated creatine phosphokinase (Levenson, 1985). Other characteristics of NMS include altered mental status, autonomic dysfunction including hyperthermia, cardiovascular changes and

elevated white blood cell count (Pelonero et al, 1998; Gracious & Findling, 2001; DuBois, 2005).

Weight gain

Weight gain has been reported in patients exposed to both typical and atypical antipsychotic medication (Campbell et al, 1999; Gracious & Findling, 2001; King et al, 2003; Gilbert et al, 2004; Sikich et al, 2004; Bebarta et al, 2005; Armenteros & Davies, 2006; Correll, 2007; Laita et al, 2007; Gencer et al, 2008). Increase in weight and body mass index (BMI) correlates with an increased appetite, which is one of the mechanisms of weight gain. Increase in appetite is due to the antipsychotic drugs' affinity for histaminergic and adrenergic receptors (Burns, 2001; Laita et al, 2007). Another possible mechanism for weight gain with atypical antipsychotic therapy is the disruption of the satiety centre regulation, which is mediated by serotonin 5-HT_2 receptors in the hypothalamus (Gracious & Findling, 2001).

Besides an increased appetite, many other factors including age, gender, schizophrenia sub-type, metabolic and endocrine processes, duration of treatment, as well as genetic factors may potentially have an effect on weight changes in patients exposed to antipsychotic medication (Martin et al, 2000; Lane et al, 2006). Weight gain can also be attributed to the psychiatric disorder itself as well as unhealthy lifestyles of patients (Correll, 2008).

Weight changes related to antipsychotic therapy is a cause for concern because of the known relationship between weight gain and obesity with diabetes mellitus, abnormal lipid levels and hypertension which may potentially lead to cardiovascular morbidity and mortality (Pi-Sunyer, 1993; Green et al, 2000; Armenteros & Davies, 2006; Correll, 2007). In the young, weight gain may have a particularly detrimental effect as it predicts an increased morbidity and mortality associated with obesity, cardiovascular disease and metabolic syndrome in adulthood (Stigler et al, 2004; Correll, 2007). It has also been suggested that the onset of obesity and metabolic abnormalities in childhood could lead to a faster progression of those conditions compared to patients who commence treatment later in life (Correll, 2007).

It has been shown that the younger the patient, a greater magnitude of weight gain is seen relative to baseline body weight across the age span (Woods et al, 2002; Safer, 2004; Correll, 2008). Additionally, weight gain may potentially have an effect on compliance, especially in image-conscious adolescents where an increase in body weight may distort self image (Potenza et al, 1999; Bryden et al, 2001; Ross et al, 2003; DuBois, 2005).

Diabetes mellitus

Diabetes mellitus has been reported with chlorpromazine administration, as well as other typical antipsychotic medications (Hägg et al, 1998; Mackin et al, 2005). The newer atypical antipsychotic drugs are also not free from this adverse effect. Diabetes mellitus has been linked with clozapine and olanzapine treatment in adolescents (Koller &

Malozowski, 2001) as well as in adult patients (Wirshing et al, 1998; Henderson et al, 2000; Koller et al, 2001).

The possible mechanism of antipsychotic-emergent diabetes mellitus is via the drugs' dopamine antagonistic effect on blood glucose regulation by the hypothalamus. Bromocriptine, a dopamine agonist, was shown to decrease elevated blood glucose concentrations in non-diabetic hyperinsulinaemic women. Therefore it has been postulated that the antagonistic effect of antipsychotic drugs on dopamine receptors cause dysregulation of blood glucose levels (Liebzeit et al, 2001). An additional mechanism of diabetes mellitus with atypical antipsychotic therapy is the hindering of cellular glucose uptake or the reduced response of pancreatic β-cells which is mediated by serotonin 5-HT_2 receptors (Stigler et al, 2004).

Weight gain itself and an increase in adipose tissue may lead to diminished insulin sensitivity, impaired glucose tolerance, and diabetes mellitus (Wirshing, 1998; Liebzeit et al, 2001; Stigler et al, 2004; Bebarta et al, 2005). Dyslipidaemia and increased fatty acids associated with weight gain could also potentially alter glucose metabolism (Stigler et al, 2004). However, new-onset diabetes mellitus has been reported in patients who are not overweight, suggesting a number of underlying mechanisms which increases the risk of developing diabetes mellitus in patients exposed to antipsychotic therapy (Stigler et al, 2004).

Cardiovascular effects

Both typical and atypical antipsychotic agents produce effects on the cardiovascular system (Haddad & Anderson, 2002; Labellarte et al, 2003; Brown et al, 2004). It is proposed that many antipsychotic drugs have electrophysiological effects similar to quinidine (Reilly et al, 2000; Brown et al, 2004). Examples of cardiovascular effects include tachycardia, dizziness, and orthostatic hypotension (Gracious and Findling, 2001).

Adverse cardiovascular effects may have serious consequences including prolonged QT interval and sudden death (Haddad & Anderson, 2002; Brown et al, 2004). The normal QT interval runs from the beginning of the QRS complex to the end of the T wave (Haddad & Anderson, 2002). Prolongation of the QT interval may lead to Torsade de Pointes, which is a type of arrhythmia with a twisting morphology of the QRS complexes (Haddad & Anderson, 2002; Brown et al, 2004). Torsade de Pointes may be asymptomatic, or manifest as palpitations, dizziness, or syncope. Rarely, the condition may even lead to ventricular fibrillation and sudden death (Haddad & Anderson, 2002; Bebarta et al, 2005; Correll, 2008).

The phenothiazines, including the typical antipsychotic drugs chlorpromazine, trifluoperazine, promazine and fluphenazine affect the calcium and potassium ion channels in cells thus prolonging QT intervals (Labellarte et al, 2003). Thioridazine and droperidol have been proposed to have high odds ratios of 5.4 and 6.7 respectively for causing QT prolongation in adult psychiatric patients (Reilly et al, 2000). Thioridazine has

also been the most commonly implicated antipsychotic agent in causing cardiovascular related arrhythmias and sudden death (Brown et al, 2004). This has resulted in a warning issued by the Committee on Safety of Medicines restricting its use to the second-line treatment of schizophrenia in adults (Committee on Safety of Medicines, 2000).

Prolonged QT intervals have also been reported in patients exposed to atypical antipsychotic medications (Bebarta et al, 2005). Sertindole, an atypical antipsychotic drug, was withdrawn from the market following studies reporting sudden deaths related to cardiac complications associated with its use (Brown et al, 2004).

Other potentially fatal effects are myocarditis and cardiomyopathy associated with exposure to clozapine treatment (Killian et al, 1999; La Grenade et al, 2001; DuBois, 2005).

Other cardiovascular events associated with antipsychotic therapy include tachycardia and hypotension, a result of α-adrenergic receptor antagonism (Burns, 2001; Gracious & Findling, 2001). Antipsychotic binding of the M_1 muscarinic receptors produces hypertension and tachycardia (Burns, 2001).

Liver damage

Antipsychotic drugs are extensively metabolised by the liver, primarily by cytochrome P450 enzymes. The resultant metabolites are usually in an active form (Burns, 2001). Increases in liver enzymes in patients exposed to atypical antipsychotic treatment have

been reported (Biswas et al, 2001; Holtman et al, 2003b; DuBois, 2005). This effect is shown to be dose related and reversible (DuBois, 2005). More importantly, liver toxicity manifesting as steatohepatitis have also been reported in paediatric patients exposed to atypical antipsychotic therapy (Kumra et al, 1997; Holtman et al, 2003a; Correll, 2008).

Other adverse effects

Generalised tonic-clonic seizures have been reported with atypical antipsychotic drugs including clozapine, risperidone, quetiapine, and olanzapine use (Kumra et al, 1996; Kumra et al, 1998; Bebarta et al, 2005; DuBois, 2005). Furthermore, antipsychotic drugs have also been known to lower the threshold of seizures. However, this effect is not thought to be significant except in patients with known seizure disorders (Gracious & Findling, 2001).

Other adverse effects seen in patients exposed to antipsychotic therapy include sedation, headaches, photosensitivity, drooling, fever, and enuresis (Nitenson et al, 1995; Findling, 2002; Malone et al, 2002; King et al, 2003; DuBois, 2005).

In summary, antipsychotic therapy is associated with a wide range of adverse effects. More importantly, it has been proposed that younger patients are more prone to many of these side effects including tardive dyskinesia (Gracious & Findling, 2001) and weight gain (Safer, 2004; Correll, 2008). Furthermore, many adverse effects seen with the older typical

antipsychotic drugs are also seen in patients exposed to the newer generation atypical antipsychotic agents (Cheng-Shannon et al, 2004).

2 Chapter TWO: Aims and objectives

2.1 Aim:

The aim of this PhD project was to investigate the utilisation and safety of antipsychotic medications in children and adolescents in the UK.

2.2 Objectives:

i. To investigate the epidemiology of antipsychotic prescribing to children and adolescents in the UK, using the General Practice Research Database (GPRD).

ii. To evaluate the safety of antipsychotic drugs by:
   a. Investigating the mortality rates in the cohort identified from (i).
   b. Investigating the incidence of diabetes mellitus, liver abnormalities, and extrapyramidal symptoms in the cohort of patients identified from (i).

iii. To investigate the feasibility of conducting a prospective surveillance study using consultant child and adolescent psychiatrists and consultant paediatricians as a data source to assess the safety of atypical antipsychotic agents in children and adolescents.

iv. To discuss the methodology of conducting a national surveillance system for antipsychotic drug use in children.

3 Chapter THREE: Methodology

3.1 Pharmacoepidemiology

Pharmacoepidemiology is the study of the use and the effects of drugs in large numbers of people. It combines both the fields of pharmacology i.e. the study of the effects of drugs; and epidemiology, which is the distribution of conditions or diseases in populations (Strom, 2003). This PhD project aims to describe the utilisation of antipsychotics in children and adolescents; as well as to quantify specific adverse effects that occur in terms of frequency and incidence in these patients. The fields of drug utilisation review and the surveillance of adverse drug reactions are important functions in the area of pharmacoepidemiology.

Chapter 1 has demonstrated a current gap with regards to sufficient data on the utilisation and safety of antipsychotic therapy in the paediatric population. Published studies have also identified a number of potentially serious adverse drug reactions associated with these drugs in adults as well as children. For the purpose of this PhD project, a large cohort of patients from the General Practice Research Database (GPRD) was identified. The following sections describe the GPRD, its history, data; and the basic methods used to identify the study cohort.

3.2 The General Practice Research Database (GPRD)

GPRD: History

The GPRD was established as the VAMP research database by VAMP Ltd, a commercial company in May, 1987 (The General Practice Research Database; Hollowell, 1997; Walley & Mantgani, 1997). Participating general practitioners were provided with computer equipment for submitting anonymised patient data for research use. The purpose of the database was to develop an automated clinical research database with longitudinal and continuous data on 4 million patients which are representative of the UK population (Walley & Mantgani, 1997).

The VAMP database was not commercially successful, and Reuters Health Information took over the database in 1993 (The General Practice Research Database; Hollowell, 1997). Reuters launched Vision, which was a new Windows-based practice management software and is the only practice software used by participating general practitioners in the GPRD.

The database was then subsequently donated to the Department of Health in 1994 and was renamed the GPRD (Hollowell, 1997; Wood & Martinez, 2004). The database was managed by the Department of Health's Statistics division and run by the Office for National Statistics (ONS) from 1994 until 1999. Since 1999, the database has been managed by the Medicines Control Agency (MCA), which became the Medicines and

Healthcare products Regulatory Agency (MHRA) in April 2003 (The General Practice Research Database; Wood & Martinez, 2004).

GPRD: Population

The GPRD is one of the world's largest computerised databases containing anonymised longitudinal data from patients in primary care (The General Practice Research Database; Wood & Martinez, 2004). As the National Health Service (NHS) in the UK provides complete coverage of the UK population, there is no section of the population which is omitted from the GPRD (Rodríguez & Gutthann, 1998).

Additionally, the GPRD population is widely representative of the UK population in age and gender. Comparisons of age and gender distributions in the GPRD population and the National Population Census have been shown to be closely similar (Rodríguez & Gutthann, 1998). In April 2008, there were 8.55 million patients (803,595 patients aged 19 or less) registered in the GPRD from 433 general practices around the UK (The General Practice Research Database).

GPRD: Recorded Data

Observational 'cradle to grave' patient data collected from participating general practitioners are anonymised with no patient, general practitioner, or practice identifiers presented to researchers (The General Practice Research Database; Rodríguez &

Gutthann, 1998). The general practitioners use clinical software supplied by In Practice Systems Ltd as a tool to contribute data to the GPRD, although the software is used primarily as a system for managing patients' medical records electronically. Identifiable data on patients are encrypted and unique numerical patient codes are assigned to individual patients. These encrypted codes are only deciphered by the contributing practice (Wood & Martinez, 2004). Information collected from participating general practitioners includes (The General Practice Research Database; Hollowell, 1997):

- patient demographics
- medical symptoms
- therapy details
- referrals to hospitals or specialists
- laboratory tests and pathology results
- lifestyle factors such as alcohol consumption, smoking and BMI
- patient registration details

Therapy details include data on medicines, vaccines and devices. Additional information concerning medicines prescribed such as dose, route of administration, daily quantity, number of packs and pack size are also provided by the GPRD. Dosage free text data are also easily converted into daily dose numerical values (The General Practice Research Database; Wood & Martinez, 2004).

GPRD: Quality of Data

The GPRD is a database which provides a high level of quality data (The General Practice Research Database; Jick et al, 1991; Jick et al, 1992; Nazareth et al, 1993). The quality of data from the GPRD is maintained at the practice and patient level. Data from both practices and patients seen at individual practices undergo stringent quality checks before being included in the database, and subsequently before being available for use in different studies.

All patients included in studies where the GPRD was used as the data source were 'acceptable' patients. For a patient to be 'acceptable', patients' data were assessed against 4 criteria regarding gender, age, registration details and event dates. Acceptability flags are given to each of the criteria where all 4 flags need to be set to 'Yes' for the patient to be 'acceptable'. Details of the 4 criteria are given below (Medicines and Healthcare Products Regulatory Agency, 2005):

- Acceptable event record flag
    - Set to 'Yes' when no event record exists prior to the patient birth year.
- Acceptable patient age flag
    - Set to 'Yes' when the patient is less than 115 years old.
- Acceptable patient gender flag
    - Set to 'Yes' when the patient is recorded as being either 'Male', 'Female' or 'Indeterminate'.
- Acceptable registration details

- Set to 'Yes' when the patient is registered as 'Applied', 'Permanent' or 'Transferred Out' **AND**
- The patient registration year is after or equal to the patient birth year **AND**
- For a patient registered as 'Permanent' or 'Applied' there is no Transferred Out Date and Reason **OR** For a patient registered as 'Transferred Out' there is a valid Transferred Out Reason and the Transferred Out Date is after the registration date.

Additionally, at the practise level, specific practice-based measurements are applied as a quality marker for participating practices; where the practice up-to-standard (UTS) date is the first date at which a participating practice complied with the GPRD-defined minimum standards for data recording quality (The General Practice Research Database; Wood & Martinez, 2004). The generation of the UTS date is based on an evaluation of the "completeness, continuity and plausibility of data recording in key areas, in accordance with the GPRD Recording Guidelines" (The General Practice Research Database). The completeness of data is assessed as a minimum value from ten variables (Medicines and Healthcare Products Regulatory Agency, 2005):

- The percentage of patients which are defined as acceptable (minimum value: 80%).
- The percentage of prescriptions patients which are defined as an acceptable registration status (minimum value: 80%).
- The number of prescriptions per patient by month (minimum value: 0.33).

- The percentage of new prescriptions for which a medical indication has been recorded (minimum value: 70%).
- The percentage of deaths for which a transfer out reason of 'death', and a transfer out date which is after the date of death have been recorded (minimum value: 70%).
- The percentage of deaths for which the cause of death has been recorded (minimum value: 80%).
- The percentage of pregnancies for which an outcome has been recorded (minimum value: 70%).
- The number of contraception events per 100 women by month (minimum value: 6).
- The percentage of referrals for which the clinical speciality has been recorded (minimum value: 38%).
- The referral rate per 100 patients (minimum value: 0.23).
- The number of deaths in a 12 month period (minimum value: 15% of maximum)*.

*Refers to first of 12 calendar months for which the minimum of 15% was achieved

It has been shown that there is good correlation between prescribing data from the GPRD and national dispensing data from the Prescription Pricing Authority (PPA) (Hollowell 1997). Medical symptoms and medical events are Read/OXMIS (Oxford Medical Information System) coded and presented as Read/OXMIS terms. Medical events are also

presented according to MedDRA (Medical Dictionary for Regulatory Activities) (The General Practice Research Database; Wood & Martinez, 2004).

Participating practices are required to record a minimum of 95% of completeness, with regards to prescribing and relevant patient-encounter data (Wood & Martinez 2004; Walley & Mantgani, 1997). Data from practices are routinely checked and validated, and feedback is provided on the level of completeness and quality of data recording after each contribution (Wood & Martinez, 2004). Several studies have also been published validating the database quality and completeness (Nazareth et al 1993; Jick et al 1991; Jick et al 1992, Van Staa & Abenheim, 1994).

The GPRD contains data from as early as 1987, though most participating practices have been providing complete quality data required for research starting in 1991 (Rodríguez & Gutthann, 1998).

GPRD: Data Extraction

Firstly, a list of antipsychotic drugs was generated according to the British National Formulary (Table 3.1) (British National Formulary, 2008). The corresponding list of product codes based on type of drug was then obtained using the GPRD Product Dictionary (Appendix A).

Table 3.1: Antipsychotic medications in the study

Antipsychotic medications investigated
Atypical antipsychotics
Amisulpride
Aripiprazole
Clozapine
Olanzapine
Quetiapine
Risperidone
Typical antipsychotics
Thioridazine
Haloperidol
Chlorpromazine
Sulpiride
Trifluoperazine
Flupenthixol
Zuclopenthixol
Promazine
Pimozide
Pericyazine
Methotrimeprazine
Droperidol
Benperidol
Perphenazine
Fluphenazine
Fluspirilene
Remoxipride
Loxapine

The relevant product codes were then applied in the data extraction using Business Objects™ (Business Objects, France). Business Objects™ is a software package supplied by the GPRD which is designed for the extraction of data from the database. The software allows for complex and flexible extraction of data without expert knowledge on the

database (Medicines and Healthcare Products Regulatory Agency, 2005). All subjects aged 18 years and under who received at least one prescription for an antipsychotic agent from the list of products previously acquired were identified using Business Objects™. The resultant data was known as Therapy file. A screen-shot example of a query using Business Objects™ is illustrated in Appendix B.

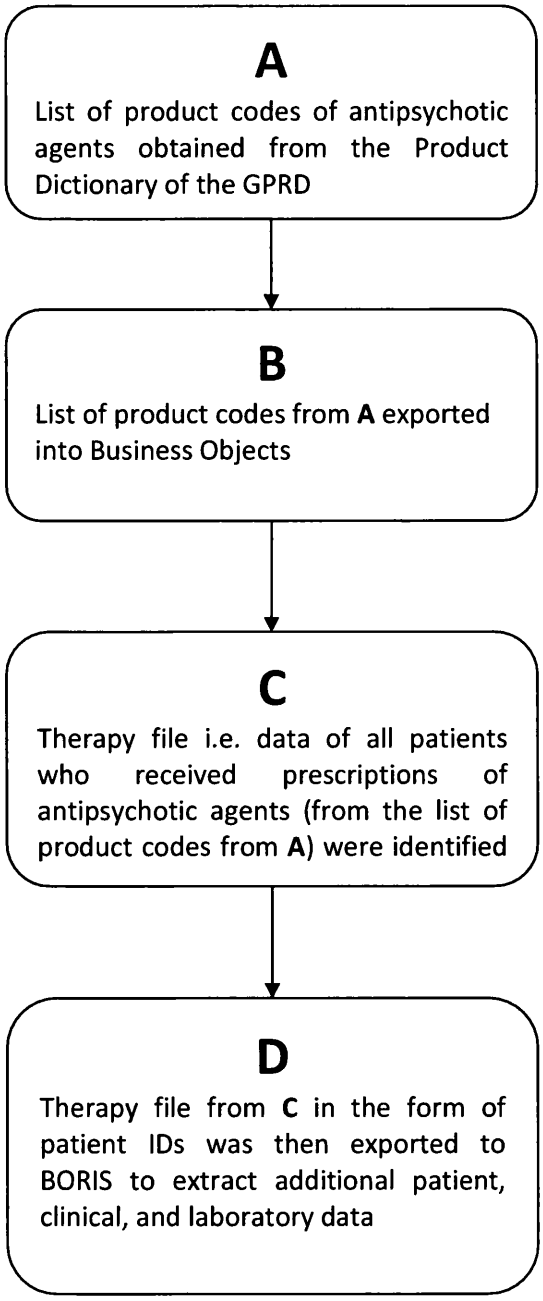
Once the subjects were identified in the Therapy file from Business Objects™, additional patient, clinical, and laboratory data for these patients in the database were extracted using BORIS (Business Objects Replacement Information System) which is a supplementary extraction tool provided by the GPRD. A screen shot example of data extraction using BORIS is shown in Appendix C. A summary of the data extraction process is illustrated in Figure 3.1.

Data retrieved was then exported to other applications including Microsoft Excel (Microsoft, United States) and Stata/SE version 9.1 (StataCorp, College Station, Texas, United States) for analysis.

GPRD: Study population

Patients included in the study population had at least one year of research standard data available, a known gender, and an acceptable patient registration status from a participating practice with a suitable UTS date. The availability of at least one year of

Figure 3.1: Summary of the steps taken for GPRD data extraction



research standard data criteria was implemented to avoid the inclusion of patients who are temporarily registered with a practice into the study. Additionally, subjects who had a registration status as "Temporary" with a practice were also excluded. The defined study period for studies using the GPRD was between 01/01/1992 and 31/12/2005 (except for Chapter 6; the study investigating the incidence of extrapyramidal symptoms).

GPRD: Data analysis

All data analysis was carried out using Stata/SE version 9.1 (StataCorp, College Station, Texas, United States). Specific methods and steps of analyses were carried out based on the type and design of individual studies. More detailed descriptions on methods of analysis are given in the individual study chapters.

GPRD: Strengths and limitations

As the GPRD is one of the largest computerised databases available, it allows for a large number of patients to be studied. Furthermore, the availability and high level of demographic, therapy and clinical data provides the capability of investigating drug utilisation and pharmacovigilance studies on adverse events to be conducted in a large number of subjects. This is a major advantage when conducting studies involving the paediatric population as sample size is a recognised problem.

Despite its many apparent advantages, the GPRD is also subject to a number of limitations. Firstly, the GPRD lacks data on the filling of prescriptions and compliance of patients. Secondly, the GPRD does not provide a direct link between diagnoses or indications and the prescribed drugs. As the GPRD is a database focused on primary care, it does not provide any direct evidence on the pathway into care that patients follow; including secondary and tertiary care, which results in prescription of an antipsychotic. Furthermore, unlike clinical trials, the number of study subjects cannot be increased as there is a finite number of subjects in the database.

However, data from the GPRD has been well validated with a large number of studies using the database as a data source that have been conducted and published in scientific journals (The General Practice Research Database). And although it is impossible to increase sample size by recruiting more patients (as done in clinical trials), the database allowed the study of a much larger study sample size of paediatric patients exposed to antipsychotic medication compared to any other known study set in real-life settings where recruitment of such a large number of exposed patients is probably difficult.

3.3 Pharmacoepidemiological analysis

The cohort identified from the GPRD was used as a data source to conduct descriptive pharmacoepidemiological analysis of antipsychotic prescribing (Chapter 4), as well as to quantify specific adverse events and adverse drug reactions within the identified cohort (Chapters 5 and 6). As previously stated in Chapter 1, a number of serious adverse effects

associated with antipsychotic agents are potentially fatal, or may have long-term consequences affecting patients' morbidity. This includes rare events such as liver abnormalities, diabetes mellitus and even mortality. Even extrapyramidal symptoms, which are considered a common side effect of antipsychotic therapy, may also have serious consequences to patients', and may also have an effect on patients' morbidity.

Liver abnormalities, diabetes mellitus and mortality are considered rare, albeit serious adverse effects associated with antipsychotic treatment. It has been recommended that larger child populations, i.e. in the thousands, should be used to obtain data to investigate and detect such adverse events (Greenhill et al, 2003). Therefore, this large population extracted from the GPRD was useful in investigating these conditions. Extrapyramidal symptoms associated with antipsychotic treatment are more common compared to liver damage, diabetes mellitus and mortality. Extrapyramidal symptoms are seen in patients exposed to both typical and atypical antipsychotic therapy and are a major cause for non-compliance and may even lead to more serious events such as tardive dyskinesia (Chapter 1). Therefore, the rate and likelihood of developing this adverse effect was also investigated using the identified cohort.

Descriptive pharmacoepidemiological studies describe general characteristics of a distribution of a disease or condition (in this case the distribution of antipsychotic prescribing and specific adverse effects related to antipsychotic use) in relation to population and time. Descriptive data has allowed healthcare providers to allocate

resources and plan effective measures in the management of conditions in the population (Hennekens & Buring, 1987). Descriptive pharmacoepidemiological data has also provided the first clues about determinants of a disease (Hennekens & Buring, 1987). Two important forms of measurements in descriptive pharmacoepidemiology are the measurements of prevalence and incidence.

Adverse events and adverse drug reactions

As previously mentioned, the incidence of mortality, liver abnormalities, diabetes mellitus and extrapyramidal symptoms was investigated in a cohort of children on antipsychotic therapy. The incidences of these conditions were described in two ways, as adverse events and adverse drug reactions.

Adverse events were defined as conditions of interest experienced by patients who received prescriptions for antipsychotic therapy, regardless of whether the event occurred while the patient was exposed to therapy, which occurred during the course of the study. Therefore if a subject experiences a condition of interest which occurs during the course of the study, it is considered an adverse event regardless of causality.

On the other hand, an event is considered as an adverse drug reaction if the condition of interest is related to antipsychotic therapy from the results of the causality assessment. Important elements when categorising an event as an adverse drug reaction include a plausible time relationship, i.e. whether or not the patient is exposed to the antipsychotic

agent at the time of experiencing an event, as well as any other concurrent therapy or other medical conditions the subject may have experienced during the time of the event of interest.

Consequently, the equations for determining the incidence of the evens of interest are influenced on whether it is adverse events or adverse drug reactions which is being analysed. This will be further described in later sections.

Prevalence

Prevalence can be defined as the number of subjects who experience an event in a population at a specific point in time (Hennekens & Buring, 1987). Prevalence provides a measure of the status of how widespread an event is occurring in a population at given time points. Measures of prevalence were used in Chapter 4 to determine the proportion of patients aged 18 years and below who received prescriptions for antipsychotic medications in the general paediatric population during the defined study period. The equation to calculate prevalence is given in Equation 3.1.

Equation 3.1: Calculation of prevalence of antipsychotic prescribing

$$\text{Prevalence} = \frac{N^P}{K} \times 1000$$

Where N^P = Number of patients with a prescription of an antipsychotic in a particular year

And K = Total number of person-years in the general population in the GPRD aged 18

years and younger in a particular year

Incidence

Unlike prevalence, incidence measures the number of new events occurring in the population. Therefore, incidence only quantifies the number of subjects who newly experience the event of interest rather than the number of all subjects who experience the event in the population. Incidence calculation was used to investigate the number of new starters of antipsychotic drugs (Chapter 4), as well as to investigate the incidence rates of adverse events and adverse drug reactions of interest associated with antipsychotic medication (Chapters 5 and 6). The general equation for calculating incidence is given in Equation 3.2.

Equation 3.2: General calculation of incidence

Incidence of an event $= \frac{N^I}{K^R} \times 1000$

Where N^I = Number of patients with a new event of interest

And K^R = Total number of person-years at risk

Person-years

Person-years is the main unit for the denominator used in the calculations of prevalence and incidence in this study. As opposed to using 'total number of patients' as a denominator, person-years takes into account the period of time subjects were at risk to develop or experience the event of interest (Webb et al, 2005). This unit of calculation

takes into consideration that not all subjects contribute the same amount of follow-up time during the study period. This is particularly true in large scale studies and studies investigating the occurrence of relatively rare events whereby subjects do not contribute to the whole follow-up period of the total study duration. Subjects often do not enter a study at the same time, and for those that do, there will most likely be a varying period of follow-up among the study subjects (Hennekens & Buring, 1987). A simple example of person-years would be if 100 subjects each present in the GPRD for a full year, this would equate to 100 person-years.

Calculating person-years

For the purpose of this thesis, the calculation of person-years was conducted using a number of methods. This was depending on the nature of the event of interest and whether it is the incidence or prevalence that was being calculated.

When investigating the epidemiology of antipsychotic prescribing to children and adolescents in the general population (Chapter 4), the cumulative person-years of all subjects in the GPRD aged 18 years and below during the study period of 01 January 1992 until 31 December 2005 were determined (all subjects in the GPRD, not just those prescribed antipsychotic agents). The resulting total number of person-years for all subjects was then used as the denominator when calculating the prevalence and incidence of antipsychotic prescribing in Chapter 4. The number of person-years

contributed by a subject in the general paediatric population in the GPRD was calculated using the equation illustrated in Equation 3.3.

Equation 3.3: Calculation of the number of person-years contributed by a subject in the GPRD general paediatric population

K = xend – xstart

Where;

K = Total person-years of a subject

xend = The earliest date of either the subject's transferred out date (date the subject transferred out of the practice), subject's date of death, or the end of the study period

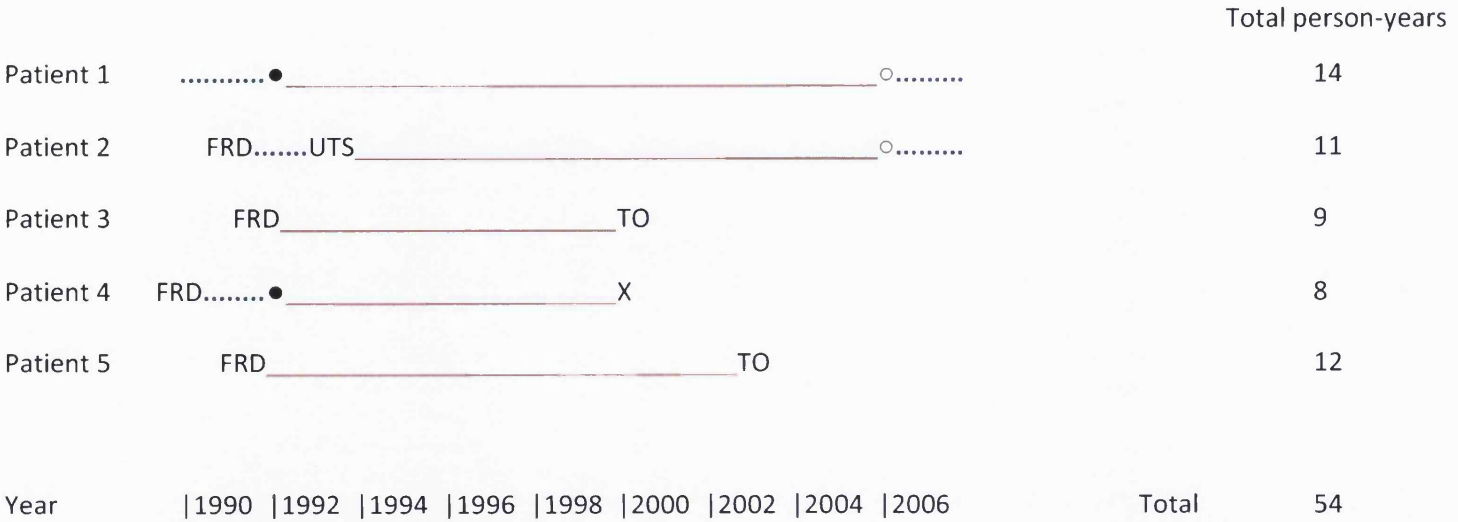
xstart = The latest date of either the subject's first registration date with the practice, the 'Up-to-standard'* date of the practice, or the start of the study period

*See previous section on GPRD: Quality of Data

A brief example for the calculation of person-years for all paediatric patients in the GPRD when investigating the prevalence and incidence of antipsychotic prescribing in Chapter 4 is shown in Figure 3.2. This example illustrates how the number of person-years from a theoretical sample of 5 patients is determined.

For studies investigating the safety of antipsychotic medication in children (Chapters 5 and 6), 2 different methods were used for calculating person-years. Firstly, the person-years at

Figure 3.2: Example of the calculation of person-years for all paediatric patients in the GPRD



___	=	Follow-up time contributing to person-years	TO	=	Transferred out
.....	=	Time in database not contributing to person-years	X	=	Death
●	=	Start of study	○	=	End of study
FRD	=	First registration date of patient			
UTS	=	'Up-to-standard' date of practice			

risk for a subject to experience an adverse event was calculated. The person-years at risk was defined as the time contributed by a subject from the date of the first antipsychotic drug prescription until the earliest occurrence of either the date of the event of interest, date the subject transferred out of the practice, subject's date of death or the end of the study period.

The equation used for the calculation of person-years at risk for a subject when investigating the incidence of adverse events is shown below in Equation 3.4.

Equation 3.4: Calculation of person-years at risk for an adverse event

$K^{AE} = xend^{AE} - xstart^{AE}$

Where;

K^{AE} = Total person-years at risk for a subject to experience an adverse event

$Xend^{AE}$ = The earliest date of either the event of interest, the subject's transferred out date (date the subject transferred out of the practice), subject's date of death, or the end of the study period

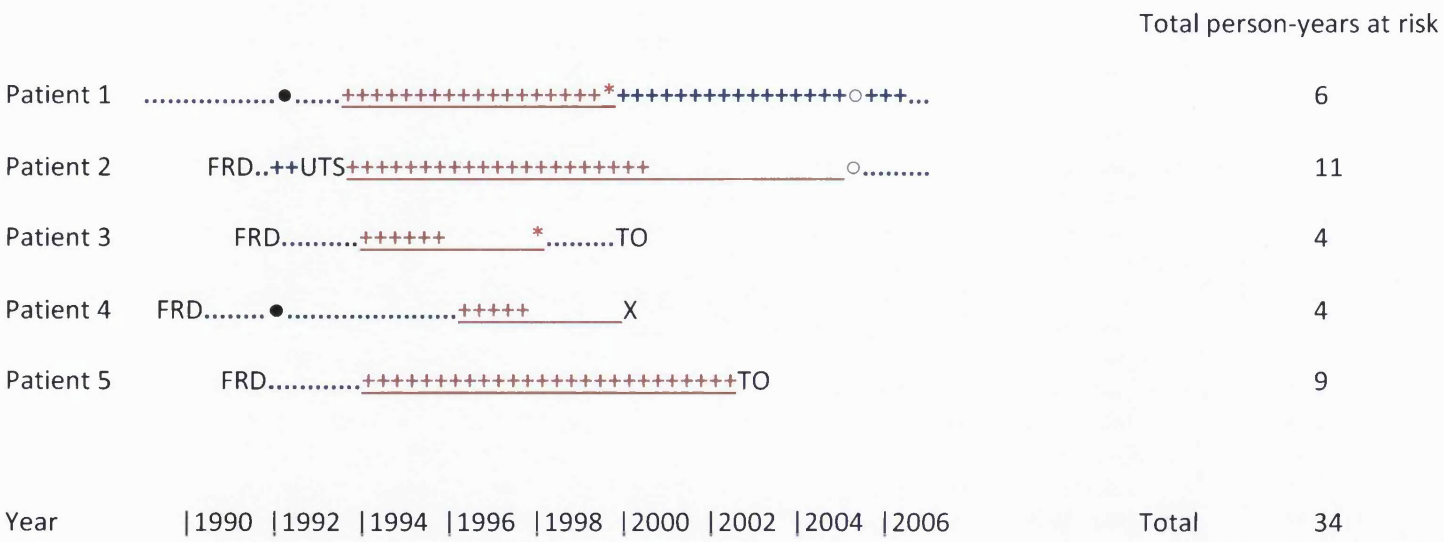
$Xstart^{AE}$ = The latest date of either the subject's first registration date with the practice, the 'Up-to-standard'* date of the practice, the date of first antipsychotic prescription, or the start of the study period

* See previous section on GPRD: Quality of Data

A brief example on how the calculation of person-years at risk for experiencing an adverse event is illustrated in Figure 3.3. In this example, 2 patients have experienced an adverse event of interest (Patients 1 and 3) during the person-years at risk. The incidence of adverse events based on this example is then 2 adverse events per 34 person-years at risk.

The calculation for person-years at risk when investigating incidence depends on the nature of incidence being reported, i.e. whether it is the incidence of adverse events, or the incidence of adverse drug reactions. The main difference between the 2 forms of calculation is whether or not the event was associated with antipsychotic therapy, based on the measure of causality. As previously mentioned, one of the main criteria when determining causality is the exposure status of the patient to the drug at the time the subject experienced the event of interest. The calculation of person-years at risk for adverse events assumes patients to be at risk at any time after the first prescription, regardless whether or not they were exposed to antipsychotic therapy at the time of the event. For the calculation of person-years at risk for the incidence of adverse drug reactions, the total person-years at risk depends on whether or not the subject was exposed to antipsychotic treatment, i.e. the subject is not at risk for developing an adverse drug reaction if the subject is not exposed to therapy. Therefore, the person-years of exposure, or treatment-years, is calculated for all patients who received antipsychotic therapy. This number will then be used as the denominator when investigating the incidence of adverse drug reactions. The equation used for the calculation of treatment-years is shown in Equation 3.5.

Figure 3.3: Example of the calculation of person-years at risk when investigating the incidence of adverse events



___	=	Follow-up time contributing to person-years at risk for an adverse event	TO	=	Transferred out
			X	=	Death
+++	=	Person-years of drug exposure (treatment-years) contributing to person-years at risk for an adverse event	●	=	Start of study
			○	=	End of study
.....	=	Time in database not contributing to person-years at risk for an adverse event	*	=	Event of interest
			FRD	=	First registration date of patient
+	=	Person-years of drug exposure (treatment-years) not contributing to person-years at risk for an adverse event	UTS	=	'Up-to-standard' date of practice

Equation 3.5: Calculation of treatment-years at risk for an adverse drug reaction

$K^{ADR} = xend^{ADR} - xstart^{ADR}$

Where;

K^{ADR} = Total treatment-years at risk for a subject to experience an adverse drug reaction

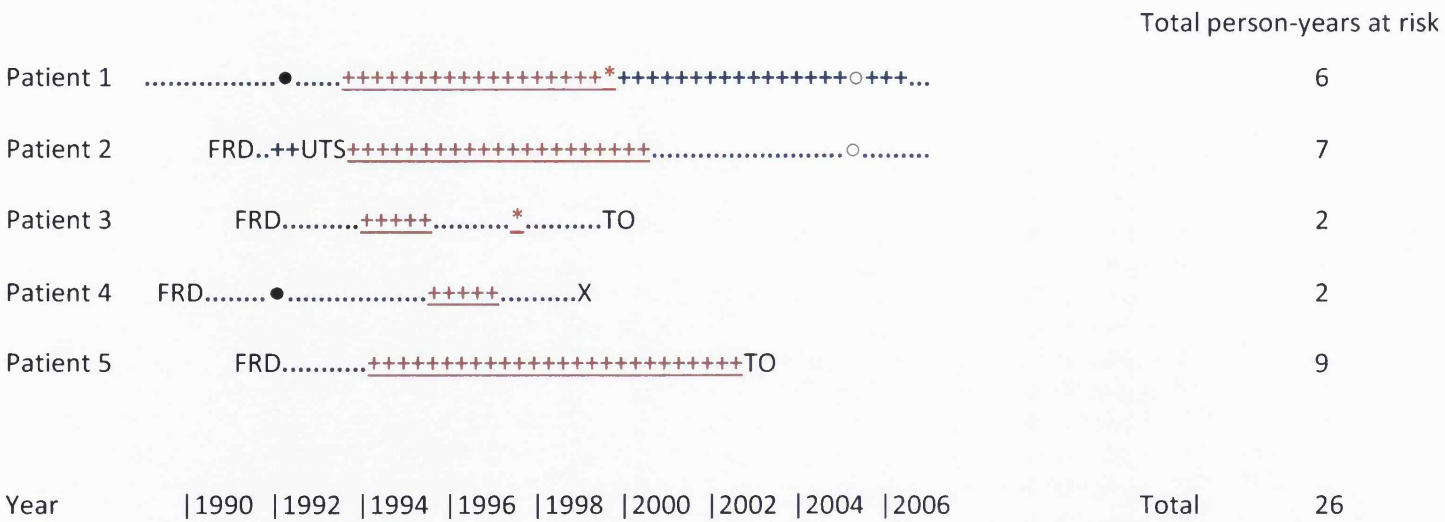
$Xend^{ADR}$ = The earliest date of either the event of interest, subject's transferred out date (date the subject transferred out of the practice), subject's date of death, end of the exposure to drug duration, or the end of the study period

$Xstart^{ADR}$ = The latest date of either the subject's first registration date with the practice, the 'Up-to-standard'* date of the practice, the date of first antipsychotic prescription, or the start of the study period

*See previous section on GPRD: Quality of Data

An example on how the calculation of treatment-years risk for experiencing an adverse drug reaction (using the same sample illustrated in Figure 3.3) is shown in Figure 3.4. Only one of the 5 patients experienced the adverse reaction while being exposed to the drug (Patient 1). The total person-years at risk is also reduced compared to the previous example, which is the reflection of the cumulative treatment-years. Therefore, the incidence of adverse reactions based on this example is 1 adverse reaction per 26 treatment-years at risk. A summary of the epidemiological rates, the type, as well as the numerators and denominators used in its calculation are shown in Table 3.2.

Figure 3.4: Example of the calculation of person-years at risk when investigating the incidence of adverse drug reactions



___	=	Follow-up time contributing to person-years at risk for an adverse event	TO	=	Transferred out
+++	=	Person-years of drug exposure (treatment-years) contributing to person-years at risk for an adverse event	X	=	Death
.....	=	Time in database not contributing to person-years at risk for an adverse event	●	=	Start of study
+	=	Person-years of drug exposure (treatment-years) not contributing to person-years at risk for an adverse event	○	=	End of study
			*	=	Event of interest
			FRD	=	First registration date of patient
			UTS	=	'Up-to-standard' date of practice

Table 3.2: Summary of pharmacoepidemiological rates

Epidemiological rate	Type	Numerator	Denominator
Prevalence of antipsychotic prescribing (Chapter 4)	Prevalence	Number of all patients (both new and existing) who received prescriptions for antipsychotic medication.	Total person-years of all patients aged 18 years and under in the GPRD.
Incidence of antipsychotic prescribing (Chapter 4)	Incidence	Number of patients who newly received prescriptions for antipsychotic medication.	Total person-years of all patients aged 18 years and under in the GPRD.
Crude Mortality Rate, for cases which are not necessarily antipsychotic-induced fatalities (Chapter 5)	Incidence	Number of patients who received antipsychotic prescriptions, who experience a fatal outcome.	Total person-years at risk for patients who received antipsychotic medication.
Crude Mortality Rate, for cases which are suspected to be antipsychotic-induced fatalities (Chapter 5)	Incidence	Number of deceased patients who experienced the fatal outcome while exposed to antipsychotic therapy; whereby the event was either *possibly*, *probably*, or *certainly* associated with antipsychotic therapy from the causality assessment.	Total treatment-years at risk for subjects exposed to antipsychotic drug therapy to experience an adverse drug reaction related to death.
Incidence of liver adverse events which are not necessarily antipsychotic-induced	Incidence	Number of patients who received prescriptions for antipsychotic therapy, who newly experience a	Total person-years at risk for patients who received antipsychotic medication to

(Chapter 6)		clinical event related to liver abnormalities.	experience an adverse event related to liver abnormalities (regardless of drug exposure status).
Incidence of liver adverse drug reactions for cases which are suspected to be antipsychotic-induced (Chapter 6)	Incidence	Number of patients who newly experience a clinical event related to liver abnormalities while exposed to antipsychotic therapy; whereby the event was either *possibly*, *probably*, or *certainly* associated with antipsychotic therapy from the causality assessment.	Total treatment-years at risk for subjects exposed to antipsychotic drug therapy to experience an adverse drug reaction related to liver abnormalities.
Incidence of diabetes mellitus adverse events which are not necessarily antipsychotic-induced (Chapter 6)	Incidence	Number of patients who received prescriptions for antipsychotic therapy, who newly experience a clinical event related to diabetes mellitus.	Total person-years at risk for patients who received antipsychotic medication to experience an adverse event related to diabetes mellitus (regardless of drug exposure status).
Incidence of diabetes mellitus adverse drug reactions for cases which are suspected to be	Incidence	Number of patients who newly experience a clinical event related to diabetes mellitus while	Total treatment-years at risk for subjects exposed to antipsychotic drug therapy to experience an

antipsychotic-induced (Chapter 6)		exposed to antipsychotic therapy; whereby the event was either *possibly*, *probably*, or *certainly* associated with antipsychotic therapy from the causality assessment.	adverse drug reaction related to diabetes mellitus.
Incidence of extrapyramidal symptoms adverse events which are not necessarily antipsychotic-induced (Chapter 6)	Incidence	Number of patients who received prescriptions for antipsychotic therapy, who newly experience a clinical event related to extrapyramidal symptoms.	Total person-years at risk for patients who received antipsychotic medication to experience an adverse event related to extrapyramidal symptoms (regardless of drug exposure status).
Incidence of extrapyramidal symptoms adverse drug reactions (Chapter 6)	Incidence	Number of patients who newly experience a clinical event related to extrapyramidal symptoms while exposed to antipsychotic therapy; whereby the event was either *possibly*, *probably*, or *certainly* associated with antipsychotic therapy from the causality assessment.	Total treatment-years at risk for subjects exposed to antipsychotic drug therapy to experience an adverse drug reaction related to extrapyramidal symptoms.

Additional pharmacoepidemiological analysis

Additional analysis was conducted when investigating the rates of diabetes mellitus and mortality in the cohort. For these 2 events, the standardised incidence ratio (for the incidence of diabetes) and standardised mortality ratio (for mortality) were investigated. This method of analysis involves calculating the overall incidence or mortality rate that would be expected in the 'standard' population if the population had the same age-specific rates as the study cohort (Webb et al, 2005). The methods for calculation and the populations used as comparators are described in more detail in Chapters 5 and 6.

Furthermore, when investigating the incidence of liver injury, diabetes mellitus and mortality, causality assessments were conducted to determine the likelihood of an association between exposure to antipsychotic medication and the event of interest (Uppsala Monitoring Centre). For this purpose, additional data was obtained and scrutinised from electronic patient profiles available from the GPRD. This is described in more detail in later sections (Chapters 5 and 6). An example of an electronic patient profile is shown in Appendix D.

3.4 Pharmacovigilance

In addition to the pharmacoepidemiological methods using the GPRD, a pharmacovigilance study (Chapter 7) was conducted to investigate the incidence of adverse drug reactions associated with atypical antipsychotic medication. The feasibility of conducting such a study was also investigated.

Chapter THREE: Methodology

For this section of the thesis, a targeted pharmacovigilance approach was taken. Targeted pharmacovigilance is focused on monitoring the safety profiles of specific groups of drugs in relation to specific adverse reactions. This method has led to the development of evidence based guidelines to reduce drug toxicity with regards to particular groups of drugs (Royal College of Paediatrics and Child Health, 2004; Choonara, 2006).

The participants in this study were clinicians from secondary and tertiary care who reported all patients aged 18 years and below under their care who were exposed to antipsychotic medication; and any adverse drug reactions experienced by these patients. The number of patients on treatment was used as the denominator when determining rates of adverse drug reactions.

In-depth data from participating clinicians was also obtained when an adverse drug reaction was reported. This included patient age, type of antipsychotic and duration of treatment, symptoms of the adverse drug reaction, as well as any concurrent medication the patient was taking at the time of the event.

Data collection was conducted from September 2005 until September 2006. A more detailed methodology for the study is described in Chapter 7.

Chapter FOUR: Epidemiology of antipsychotic drug prescribing in UK primary care

4 Chapter FOUR: Epidemiology of antipsychotic drug prescribing to children and adolescents in UK primary care

4.1 Introduction

General practitioners in the UK play an important role in prescribing and monitoring antipsychotic drugs for children with emotional and behavioural problems in the community. Antipsychotic drug prescriptions for children are usually initiated by specialists in secondary care such as child psychiatrists and behavioural paediatricians; however, general practitioners continue to monitor and prescribe these drugs (Bramble, 2003).

Studies in the USA and the Netherlands show that antipsychotic drug use in children is rising. In the Netherlands, there was a 1.5 fold increase between 1995 and 1999 of new users (1.1 to 1.7 per 1,000 children) of antipsychotic drugs. Prevalence of antipsychotic drug use also increased 2-fold in the same period (1.6 to 3.4 per 1,000 children) (Schirm et al, 2001). A more recent study in the Netherlands demonstrated over a 2-fold increase in the prevalence of all antipsychotic agents from 1997 and 2005 (3.0 to 6.8 per 1,000 children) (Kalverdijk et al, 2008). A study in the USA showed the number of new users (aged 2 to 18 years) of antipsychotic treatment almost doubled (23 to 45 per 10,000 children) from 1996 to 2001 (Cooper et al, 2004). In the USA a recent study estimated a 6-fold increase in the number of "office-based visits by youth that included antipsychotic

treatment" from 1993 to 2002 (Olfson et al, 2006). This rapid rise in antipsychotic drug prescribing is a concern as there is little robust evidence of a corresponding increased prevalence of psychotic illness in young people (Sutcliffe & Wong, 2006). However, a previous study suggests that the number of psychotropic drug prescriptions to children in the UK has increased by 68% between 2000 and 2002, and is much higher than the rate of increment in the USA and other countries (Wong et al, 2004). Following this, a systematic literature review using the Medline database (1950 to 08/08/2008) was conducted to evaluate studies which have investigated the utilisation trends of antipsychotic agents, and to identify any studies which have possibly been conducted in the UK paediatric population.

4.1.1 Systematic literature review on the utilisation of antipsychotic drugs in children and adolescents

4.1.1.1 Aim of the literature review

To review published studies which have reported utilisation trends of antipsychotic drugs in children and adolescent patients.

4.1.1.2 Methodology of the literature review

A keyword search on published studies was conducted using the keywords shown in Table 4.1

Inclusion criteria

Studies reporting the utilisation or prescribing rates of antipsychotic medication in children and adolescents were included in the review.

Table 4.1: Keywords used in literature search on utilisation trends of antipsychotic drugs in children and adolescents

Antipsychotic drug keywords		Population keywords	Utilisation keywords
atypical	typical	paediatric$	drug utilisation
antipsychotic$	antipsychotic$	adolescent$	drug utilization
atypical	typical	adolescence	prescribing pattern$
neuroleptic$	neuroleptic$	school child$	pharmacoepidemiology
new$	first generation	juvenile$	pharmacovigilance
antipsychotic$	antipsychotic$	infant$	prescribing trend$
new$	benperidol	child$	prescribing epidemiology
neuroleptic$	chlorpromazine	neonate$	
second	chlorprothixene	baby	
generation	droperidol	babies	
antipsychotic$	flupentixol	pediatric$	
amisulpride	flupenthixol	young people	
amisulpiride	fluphenazine	young person$	
aripiprazole	fluspirilene		
clozapine	haloperidol		
olanzapine	levomepromazine		
quetiapine	loxapine		
risperidone	methotrimeprazine		
	pericyazine		
	perphenazine		
	pimozide		
	promazine		
	remoxipride		
	sulpiride		
	thioridazine		
	trifluoperazine		
	zuclopenthixol		

Exclusion criteria

For the purpose of this review, interventional studies such as trials, published reviews and meta-analyses, studies that were not in the English language, and studies that did not report on antipsychotic drugs in children and adolescents were excluded.

4.1.1.3 Results of the literature review

The search resulted in 33 published papers. After removing duplicates and reviewing the titles and abstracts of the articles, a total of 15 papers were deemed relevant (Table 4.2). Ten out of the 15 publications were studies derived from paediatric populations in the USA (Kaplan et al, 1994; Zito et al, 2000; Patel et al, 2002; Martin & Leslie, 2003; Lekhwani et al, 2004; Lyons et al, 2004; Najjar et al, 2004; Staller et al, 2005; Patel et al, 2006a; Aparasu & Bhatara, 2007) , 2 in Australia (Efron et al, 2003; Dean et al, 2006) , and one in Canada (Doey et al, 2007), Italy (Alacqua et al, 2008) and UK (Clark, 2004) respectively. Only 5 of the 15 publications reported prescribing or utilisation trends over periods of time (Zito et al, 2000; Patel et al, 2002; Martin & Leslie, 2003; Najjar et al, 2004; Patel et al, 2006a), while the remaining 10 only reported a rate of antipsychotic drug prescribing at a specific point in time (Kaplan et al, 1994; Efron et al, 2003; Clark, 2004; Lekhwani et al, 2004; Lyons et al, 2004; Staller et al, 2005; Dean et al, 2006; Aparasu & Bhatara, 2007; Doey et al, 2007; Alacqua et al, 2008).

Table 4.2: Utilisation studies reporting rates of antipsychotic drug use in children and adolescents

Author	Country	Data and Setting	Result Summary
Alacqua et al, 2008	Italy	• Chart reviews from children and adolescents seen in 2 Child Neurology and Psychiatry Divisions of Southern Italy. • All paediatric patients aged 18 years and below who newly start treatment with atypical antipsychotic agents or SSRIs as monotherapy from 1 January 2002 until 31 December 2003.	• Out of 97 patients' charts reviewed, 75 (75%) were newly started on atypical antipsychotic treatment. • Risperidone was the most frequently prescribed drug (62%), followed by olanzapine (32%).
Aparasu & Bhatara, 2007	USA	• Data obtained from the 2003-2004 National Ambulatory Medical Care Survey (NAMCS) and the Outpatient Department of the 2003-2004 National Hospital Ambulatory Medical Care Survey (NHAMCS). • Patients aged 20 years and under were included in the analysis.	• Antipsychotic drugs were prescribed in 2.08 (95% CI: 1.46 to 2.70) million outpatient visits, representing 0.99% (95% CI: 0.71 to 1.06) of all visits involving children and adolescents. • The most prescribed atypical antipsychotic agent was risperidone (43.81%), followed by quetiapine (26.97%) and aripiprazole (16.79%).

Clark, 2004	UK	• Data was obtained from 21 child and adolescent mental health services (CAMHS) in England. • All new incidences of prescribing for patients within the CAMHS within 12 months (September 1999 to February 2000; and September 2000 to February 2001) were included in the study.	• Typical and atypical antipsychotic drugs were the fourth and fifth most commonly prescribed psychotropic drug respectively. • Typical antipsychotic drugs were the most commonly prescribed drug (22% of patients) in in-patient or day-patient units. • Atypical antipsychotic drugs were the third most commonly prescribed drug (15% of patients) in in-patient or day-patient units. • Antipsychotic drugs were prescribed for 10% of new cases in outpatient units. • Four percent of these were for typical antipsychotic prescriptions and 6% were for atypical antipsychotic prescriptions.
Dean et al, 2006	Australia	• Data obtained from inpatient and outpatient child and youth mental health services (CYMHS) between	• Atypical antipsychotic agents were the second most frequently used class of drug (23% of inpatients)

		April 2002 and September 2003. • Charts of all paediatric patients who received psychotropic drug therapy were reviewed during the study duration.	• Typical antipsychotic therapy was used in 9.8% of inpatients. • Antipsychotic therapy was given for a variety of indications, most of which were for off-label uses.
Doey et al, 2007	Canada	• Data was obtained from a survey of members of the Canadian Academy of Child and Adolescent Psychiatry and the Developmental Paediatrics Section of the Canadian Paediatric Society. • Child psychiatrists and paediatricians provided data on whether they prescribed atypical antipsychotic treatment to patients under their care, as well as type and frequency of drug, and frequencies of monitoring.	• Ninety-four percent of child psychiatrists and 89% of paediatricians prescribed atypical antipsychotic treatment to their patients. • The most commonly prescribed atypical antipsychotic agent was risperidone (69%). • Participating clinicians prescribed atypical antipsychotic therapy to patients under their care for a wide range of off-label psychiatric indications.
Efron et al, 2003	Australia	• A postal survey of general paediatricians and child psychiatrists was conducted in the year 2000. • Clinicians were asked to provide data on prescribing of psychotropic medications to patients under their	• Typical antipsychotic medications were the seventh most prescribed psychotropic drug prescribed by paediatricians and the fifth most common psychotropic drug prescribed by child psychiatrists.

		care.	• Atypical antipsychotic medications were the sixth most commonly prescribed psychotropic drug prescribed by paediatricians and the third most common psychotropic drug prescribed by child psychiatrists. • Typical antipsychotic therapy was prescribed by 4.9% of paediatricians and 28% of child psychiatrists. • Atypical antipsychotic therapy was prescribed by 6.3% of paediatricians and 46% of child psychiatrists.
Kaplan et al, 1994	USA	• Data was obtained from 2 sites; an outpatient service of a university-affiliated children's psychiatric center in New York and a child psychiatry service of a university-based outpatient clinic in Ohio. • Questionnaires were sent out to psychiatrists from both sites requesting. Among the information requested were data on medications prescribed as well as rationale for	• Thirty-seven percent of the patients in the medicated sample in the New York site and 18% of the medicated patients in the Ohio site received prescriptions for antipsychotic drugs. • The majority of patients (65% of patients in the New York site and 67% of patients in the Ohio site) who received antipsychotic drug therapy were prescribed these

		prescribing and target symptoms the psychiatrists were attempting to treat.	drugs for essentially non-psychotic disorders.
Lekhwani et al, 2004	USA	• Prescribed psychotropic drugs upon admission and discharge for patients aged 9 years and below seen in child inpatient psychiatric units of a university hospital between the years 1998 and 2001 were investigated.	• Atypical and typical antipsychotic drugs were the third and sixth highest type of psychotropic medication prescribed. • Antipsychotic therapy was consistently given for non-psychotic disorders in children.
Lyons et al, 2004	USA	• Clinical records of a sample of paediatric patients aged 5 to 17 years who received state (Office of Mental Health) or federal (Medicaid) funding for mental health services from ten different random sites were reviewed. • A duration of 12 months was reviewed for each case regardless if the patient was still receiving care or discharged.	• Antipsychotic medications were most commonly prescribed in more intensive services including state-operated inpatient units and residential programs. • Risperidone was the most commonly prescribed antipsychotic agent. • The majority of children who received antipsychotic drug treatment (64%) did not have any signs of psychotic disorders.
Martin & Leslie, 2003	USA	• Pharmacy claims from a research	• Antipsychotic drugs were the third most commonly prescribed class

		database as a data source. • All patients aged 17 years and younger between the years 1997 and 2000 were included in the study.	of drugs in the database. • Overall prevalence of antipsychotic agents increased by 57.6% between 1997 and 2000. • The prevalence of atypical antipsychotic agents increased by 138.4% during the study duration; and was also the highest increase among all drugs. • The prevalence of typical antipsychotic drugs reduced by 58.4% between 1997 and 2000.
Najjar et al, 2004	USA	• Data obtained from the pharmacy dispensing database of a private child psychiatric hospital. • The number and type of admissions and medication status of all patients aged 18 years and younger between the years 1991 and 1998 were investigated.	• Antipsychotic drug prescribing was stable from 1991 (19.2% of patients) to 1998 (21.0% of patients). • The number of patients who received typical antipsychotic therapy declined from 1991 (19.2% of patients) to 1998 (3.3% of patients). • The number of patients who received prescriptions for atypical antipsychotic agents increased

			from 1991 (0% of patients) to 1998 (17.7%).
Patel et al, 2002	USA	• Data was obtained from the Texas Medicaid program. • All patients aged 20 years and under between the years 1996 and 2000 were included in the analysis.	• Overall prevalence of all antipsychotic medications increased from 7.63 per 1,000 children in 1996 to 19.88 per 1,000 children in 2000. • The prevalence of typical antipsychotic medications reduced from 4.94 per 1,000 children in 1996 to 3.87 per 1,000 children in 2000. • The prevalence of atypical antipsychotic medications increased from 2.69 per 1,000 children in 1996 to 15.98 per 1,000 children in 2000. • Risperidone was the most commonly prescribed atypical antipsychotic agent during the study period.
Patel et al, 2006a	USA	• Data obtained from all paid prescription claims for antipsychotic drug therapy from the Texas	• The number of paediatric patients prescribed any antipsychotic drug increased from 7,240 patients (6.33 per 1,000 patients) in 1996

		Medicaid Vendor Drug database. • Prescriptions for children and adolescents aged 19 years and below from 1 January 1996 and 31 December 2001 were included in the analysis.	to 17,790 patients (15.53 per 1,000 patients) in 2001. • The number of youths prescribed typical antipsychotic agents decreased from 5200 patients (4.55 per 1,000 patients) in 1996 to 1753 patients (1.53 per 1,000 patients) in 2001. • The number of youths prescribed atypical antipsychotic drugs increased from 2841 patients (2.49 per 1,000 patients) in 1996 to 17,034 patients (14.9 per 1,000 patients) in 2001.
Staller et al, 2005	USA	• Data obtained from 8 child and adolescent outpatient treatment sites in the year 2002. • Patients aged 1 to 18 years from 3 private child psychiatrists' office practices, a county outpatient mental health clinic, a state psychiatric hospital outpatient mental health clinic, a state university hospital outpatient clinic, a community hospital outpatient clinic and a county day treatment centre were	• Antipsychotic agents were the third highest prescribed class of psychotropic drugs to the paediatric patients in the study. • Patients aged 10 to 14 years were more likely to receive antipsychotic therapy compared to patients aged 5 to 9 years; while there was no difference in likelihood for teenage patients to receive antipsychotic therapy

		included in the analysis.	compared to younger children. • The majority of patients who received antipsychotic treatment did not have a diagnosis related to psychotic disorders.
Zito et al, 2000	USA	• Data was obtained from 3 large data sets; the Midwestern state Medicaid population, the mid-Atlantic state Medicaid population, and the health maintenance organisation (HMO). • Patients aged 19 years and below between the years 1991 and 1995 were included in the study.	• The prevalence of all antipsychotic medications increased throughout all 3 datasets during the study period. • There was a 1.3-fold, 1.2-fold and a 1.5-fold increase in the prevalence of antipsychotic medications in the Midwestern state Medicaid program, mid-Atlantic state Medicaid program, and the HMO program respectively.

Among the 5 studies which reported prescribing trends over periods of time, 4 studies demonstrated an increase in the overall prescribing of antipsychotic medications (Zito et al, 2000; Patel et al, 2002; Martin & Leslie, 2003; Patel et al, 2006a) while one study (Najjar et al, 2004) reported a stable antipsychotic prescribing trend during the study period. Although this study demonstrated a stable prescribing trend of all antipsychotic medications, the individual prescribing trend of typical antipsychotic medications decreased while the atypical antipsychotic prescribing trend increased during the study period (Najjar et al, 2004). This trend whereby atypical antipsychotic prescribing was seen to replace typical antipsychotic prescribing was also shown in 3 other studies (Patel et al, 2002; Martin & Leslie, 2003; Patel et al, 2006a).

Studies which did not investigate prescribing trends demonstrated high numbers of paediatric patients being prescribed antipsychotic treatment (Kaplan et al, 1994; Clark et al, 2004; Lekhwani et al, 2004; Lyons et al, 2004; Staller et al, 2005; Dean et al, 2006; Aparasu & Bhatara, 2007; Alacqua et al, 2008); or showed a high number of clinicians prescribing these medications to paediatric patients under their care (Efron et al, 2003; Doey et al, 2007). Five studies reported risperidone to be the most commonly prescribed antipsychotic agent in the study populations (Patel et al, 2002; Lyons et al, 2004; Aparasu & Bhatara, 2007; Doey et al, 2007; Alacqua et al, 2008).

There was only one study conducted using data obtained from UK paediatric populations (Clark, 2004). The study investigated all new incidences of antipsychotic drug prescribing in inpatient and outpatient units in 21 Child and Adolescent Mental

Health Services (CAMHS) in England over a 12 month period. Although the authors reported the number of new prescribing for inpatients and outpatients, they did not report on utilisation trends over duration of time.

4.1.1.4 Discussion of the literature review

Investigations on drug utilisation and prescribing patterns are an important element in pharmacoepidemiological studies (Stolley & Laporte, 2003). The majority of published studies used data obtained based on paediatric populations in the USA. Additionally, only 5 of the 15 studies investigated prescribing trends over a period of time, and all 5 were studies based on USA populations. Most of these studies have shown an obvious rise in the utilisation of antipsychotic drugs, specifically the newer atypical antipsychotic agents in the young. This increase in atypical antipsychotic drug prescribing in the paediatric population is most probably due to the claims of enhanced safety and improved efficacy of these drugs (Findling et al, 1998). Furthermore, a number of the published studies showed that the antipsychotic drugs were prescribed for essentially non-psychotic indications, thereby highlighting the issue of appropriateness for use of these drugs in paediatric populations (Lekhwani et al, 2004; Lyons et al, 2004; Staller et al, 2005; Dean et al, 2006; Doey et al, 2007).

It should be noted also that the results from the literature review indicate an obvious gap in studies investigating the prescribing trends and utilisation of antipsychotic drugs in the UK paediatric population. It is still not known if the trends of antipsychotic

prescribing in children from the UK mirror the trends demonstrated from studies conducted from the USA.

Investigations on prescribing patterns and drug utilisation are a recognised important function of pharmacoepidemiology (Stolley & Laporte, 2003). It has been reported that there is much room for improvement in prescribing patterns and utilisation of specific drugs even in developed countries where dependable prescribing information is provided (Stolley & Laporte, 2003). As the majority of antipsychotic agents are used for off-label indications outside their product license in the paediatric population (Chapter 1), the gap in knowledge regarding the distribution of prescribing and utilisation patterns of these drugs in children in the UK are further intensified. Additionally, the fact that off-label prescribing to children may potentially increase the risk of drug toxicity (Impicciatore et al, 2001) further highlights the importance of investigating the prescribing trends of antipsychotic agents to children to determine the extent of how much these agents are used in the paediatric population.

As the majority of antipsychotic agents are prescribed for essentially off-label indications to children (Chapter 1), the lack of studies investigating the distribution of prescribing and patterns of drug utilisation in the UK paediatric population is further highlighted.

Chapter FOUR: Epidemiology of antipsychotic drug prescribing in UK primary care

Following the results of the literature review, the aim of this chapter was to investigate the trends in antipsychotic drug prescribing to children and adolescents in using a large database of general practices around the UK.

4.2 Methodology

Data source

The data for this study were obtained from the General Practice Research Database (GPRD). The history of the GPRD and validation of its data is described in more detail in Chapter 3.

The study population, inclusion and exclusion criteria, and data extraction and analysis are described in detail in Chapter 3. Patients who received at least one prescription for an antipsychotic medication during the defined study period between 1 January 1992 and 31 December 2005 were classified as cases in the study (i.e. the numerator).

Ethics approval was granted by the GPRD's Scientific and Ethical Advisory Group (SEAG) and the Independent Scientific Advisory Committee (ISAC) for Medicines & Healthcare products Regulatory Agency (MHRA) database research (Appendix E).

Data analysis

Data analysis was carried out using Stata/SE version 9.1 (StataCorp, College Station, Texas, United States). Once all patients in the study population were identified,

prescribing data for the first year of each patient was screened for type of prescription. If a patient received their first antipsychotic drug prescription after this screening period, they were classified as a new starter and counted as an incident case. Incidence was defined as the frequency of new starters of an antipsychotic in the general pediatric population. The calculation for incidence of antipsychotic drug prescribing is given below in Equation 4.1.

Equation 4.1: Calculation of incidence of antipsychotic drug prescribing

Incidence of an event = $\frac{N^I}{K} \times 1000$

Where;

N^I = Number of patients with a new prescription for an antipsychotic drug in a particular year

And K^R = Total number of patient years in GPRD population aged 18 years and younger in a particular year

Prevalence was defined as the number of patients who were prescribed antipsychotic treatment in the general paediatric population. Prevalence was calculated using the equation illustrated in Equation 4.2.

Equation 4.2: Calculation of prevalence of antipsychotic drug prescribing

$$\text{Prevalence} = \frac{N^P}{K} \times 1000$$

Where;

N^P = Number of patients with a prescription of an antipsychotic drug in a particular year

And K = Total number of person-years in the general population aged 18 years and younger in a particular year

The prevalences were stratified by 6-year age bands (0 to 6, 7 to 12, and 13 to 18 years of age). A chi-square test (Cochran-Armitage test for trend) was used to examine the yearly trend of antipsychotic drug prescribing.

The duration of each prescription for an antipsychotic drug was calculated from the prescribed quantity and daily dosage. The prescription duration was calculated using Equation 4.3.

Equation 4.3: Calculation of antipsychotic prescription duration

$$\text{Prescription duration} = \frac{Q}{D}$$

Where;

Q = Quantity of drug prescribed

And D = Daily dosage of the prescribed drug

For example, a patient who was prescribed 56 tablets with a daily dose of 2 tablets a day would have a prescription duration of 28 days. After prescription durations were calculated, the durations of treatment episodes were determined. Treatment episodes were defined as the duration of time when the patient was exposed to antipsychotic therapy. The duration of treatment episodes were calculated using the equation shown in Equation 4.4.

Equation 4.4: Calculation of antipsychotic treatment episodes

Episode duration = $E^{epis} - S^{epis} + L$

Where;

E^{epis} = Episode end date

And S^{epis} = Episode start date

And L = Latency period of 30 days

A latency period of 30 days was added to the episode duration to allow for non-compliance or delays in drug dispensing. If a gap of > 90 days is present between treatment episodes for a patient, then a treatment gap was presumed. In this case, a new treatment episode start date was determined for the subsequent treatment episode. The exposure duration for incidence patients were calculated and the time to discontinuation was investigated using Kaplan-Meier survival estimates.

Patients were censored if the subject was still on antipsychotic medication by the close of the study period; or if the calculated exposure episode for a subject runs beyond the

'transferred-out' date (date the subject transfers out of a practice); therefore implying the subject is lost to follow-up (Clark et al, 2003). The survival analysis was conducted using SPSS version 14.0.

For psychiatric conditions, general practitioners are usually informed of a diagnosis requiring specialist medications from secondary or tertiary care. Unfortunately, there is no direct link between medical diagnoses and prescriptions in the GPRD. Therefore all clinical records for patients in the study cohort were screened for possible diagnoses associated with antipsychotic drug prescriptions. The clinical codes were presented as Read and OXMIS codes which consist of syndromal, symptom, and clinical event descriptors. The codes were mapped onto 5 different syndromal categories derived from the International Classification of Diseases (ICD) 10. The classification of codes was checked by Dr Patrick Byrne[1], a consultant adolescent psychiatrist, for accuracy. The 5 categories were: 1: Psychosis/ Schizophrenia/ Hallucinations/ Delusions/ Paranoia; 2: Behaviour/ Conduct/ Personality Disorders; 3: Autism/ Asperger's Syndrome; 4: Depression/ Mood/ Affective disorders; and 5: Tics/ Tourette's syndrome. The number of patients with diagnoses based on the different categories within 6 months of their first prescription was then investigated. As there is no direct link between diagnoses and prescriptions, the first prescription of each subject may be associated with more than one diagnosis.

[1] Dr Patrick Byrne MMedSci FRCPsych
Consultant in Adolescent Psychiatry & Hon Research Associate IoP
Bethlem Adolescent Unit
South London & Maudsley NHS Trust

Data verification

The IMS Disease Analyser-Mediplus database was used as a source of data to verify the findings from the GPRD. Like the GPRD, the IMS database is a primary care database which collects practice records from over 500 general practitioners in the UK. There are more than 3 million active patients registered with the contributing general practitioners in the IMS database. An advantage of the IMS database is that it links prescriptions to diagnoses. The distribution of participating general practitioners is broadly representative of the UK population, although there is under-representation of smaller practices and practices from Scotland and Northern Ireland (Wong & Murray, 2005).

For verification purposes, analysis on prevalence, incidence as well as diagnoses was carried out using the IMS database and compared with findings obtained from the GPRD. Ethics approval was granted by the IMS's Independent Scientific and Ethics Committee (Appendix F).

4.3 Results

During the study period, 16,497 patients received a total of 38,286 prescriptions for antipsychotic drugs. However, prescriptions for prochlorperazine were subsequently excluded from the analysis as prochlorperazine is often prescribed for the treatment of nausea and vertigo, and not usually given for psychotic disorders in UK primary care. After excluding prescriptions for prochlorperazine, a total of 2,767 patients received

21,089 prescriptions for antipsychotic drugs. There were 1,871 patients who received a total of 10,135 prescriptions for typical antipsychotic treatment with a median of 2 prescriptions per patient (inter quartile range 1-4) and 1,103 patients who received 10,954 prescriptions for atypical antipsychotic treatment with a median of 5 prescriptions per patient (inter quartile range 2-12). There were 207 patients who were prescribed both an atypical and a typical antipsychotic drug (Table 4.3). The most commonly prescribed atypical antipsychotic agent was risperidone (73% of all prescriptions for atypical antipsychotic agents), followed by olanzapine (16%) and quetiapine (7.3%). The most commonly prescribed typical antipsychotic agent was thioridazine (27% of all prescriptions for typical antipsychotic agents), followed by haloperidol (26%) and chlorpromazine (19%). The overall percentage of antipsychotic drug prescribing by type of drug and number of patients is given in Table 4.3.

Table 4.3: Number of patients and prescriptions in the cohort

Atypical antipsychotic drugs			Typical antipsychotic drugs*			All antipsychotic drugs**	
Drug	Number of prescriptions (% of total)	Number of patients (% of total)	Drug	Number of prescriptions (% of total)	Number of patients (% of total)	Number of prescriptions (% of total)	Number of patients (% of total)
Risperidone	8,039 (38.12)	799 (28.88)	Thioridazine	2,721 (12.90)	532 (19.23)		
Olanzapine	1,727 (8.19)	282 (10.19)	Haloperidol	2,654 (12.58)	304 (10.99)		
Quetiapine	800 (3.80)	83 (3.00)	Chlorpromazine	1,927 (9.14)	438 (15.83)		
Amisulpride	326 (1.55)	40 (1.45)	Sulpiride	759 (3.60)	114 (4.12)		
Clozapine	12 (0.06)	4 (0.15)	Trifluoperazine	657 (3.12)	234 (8.46)		
Aripiprazole	50 (0.24)	11 (0.40)	Flupenthixol	524 (2.50)	280 (10.12)		
			Zuclopenthixol	206 (0.98)	21 (0.76)		
			Promazine	196 (0.93)	91 (3.29)		
			Pimozide	160 (0.76)	25 (0.90)		
			Pericyazine	115 (0.55)	31 (1.12)		
			Methotrimeprazine	133 (0.63)	39 (1.41)		
			Droperidol	25 (0.12)	11 (0.40)		
			Benperidol	30 (0.14)	4 (0.15)		
			Perphenazine	19 (0.09)	2 (0.07)		
			Fluphenazine	2 (0.01)	2 (0.07)		
			Fluspirilene	2 (0.01)	1 (0.04)		
			Remoxipride	4 (0.02)	1 (0.04)		
			Loxapine	1 (0.005)	1 (0.04)		
All atypicals	10,954 (52)	1,103 (38.86)	All typicals	10,135 (48)	1,871 (67.61)	21,089 (100)	2,767 (100)
Male/female	781/322		1001/870			1651/1116	
Mean age at study entry (SD), years	14.6 (3.3)		14.6 (4.1)			14.5 (3.9)	

*Prochlorperazine has been excluded

** Total number is less than the sum of atypical & typical patients as there are patients who were prescribed more than one type of antipsychotic

Duration of prescriptions and treatment episodes

Duration analysis was conducted on 98.8% (N=2,733 out of 2,767 patients) of the identified cohort. The remaining 1.2% of patients was excluded in the duration analysis due to incomplete data on amount of drug prescribed and daily dose of drug.

The median prescription duration for all antipsychotic drugs was 28 days per prescription (inter quartile range 23-30 days for all antipsychotic drugs; 20-33 days for typical antipsychotic drugs and 28-30 days for atypical antipsychotic drugs).

Treatment episodes were defined as the duration of time a patient is exposed to antipsychotic therapy. If a gap of > 90 days is present between treatment episodes for a patient, then a treatment gap was presumed. There were 3,323 treatment episodes from the 2,733 patients for patients exposed to antipsychotic treatment (either typical, atypical or both antipsychotic drugs). The majority of patients had only one treatment episode (N=2,286, 83.6%), 361 patients (13.2%) experienced 2 treatment episodes and 86 patients (3.2%) experienced 3 or more treatment episodes during the study period. The median exposure duration for all antipsychotic drugs was 86 days (inter quartile range 53-226 days).

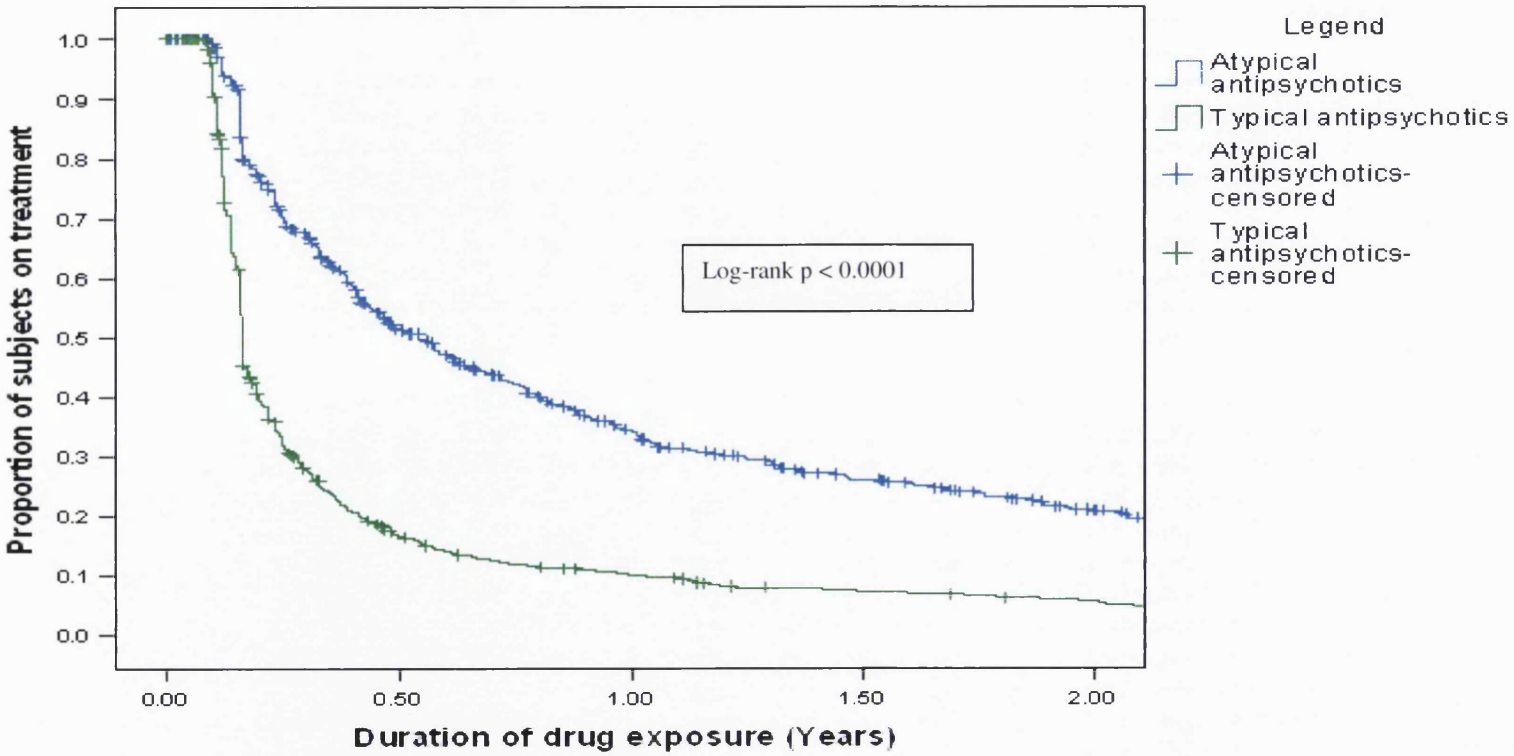
Additional analysis on drug exposure was conducted for all incidence patients on their first episode. A higher proportion of patients on atypical antipsychotic treatment were on treatment for significantly longer durations ($p < 0.0001$) compared to patients on typical antipsychotic agents as illustrated as Kaplan-Meier survival estimates in Figure

4.1. Fifty percent of incidence patients exposed to typical antipsychotic treatment stopped treatment after approximately 2 months of therapy, where as 50% of patients on atypical antipsychotic agents stopped treatment after about 6 months of therapy.

There were 1,793 patients with 2,114 treatment episodes for patients taking typical antipsychotic drugs. Among these patients, 1546 (86.2%) had only one treatment episode, 200 patients (11.2%) had 2 treatment episodes and 47 patients (2.3%) experienced 3 or more treatment episodes during the study period. The median exposure duration for patients on typical antipsychotic therapy was 60 days (inter quartile range 45-141 days).

There were 972 patients with 1,157 treatment episodes for patients taking atypical antipsychotic drugs. Among these patients, 824 (84.8%) had only one treatment episode, 123 (12.7%) experienced 2 treatment episodes and 25 (2.5%) experienced 3 or more treatment episodes during the study period. The median exposure duration for patients on atypical antipsychotic therapy was 152 days (inter quartile range 65-353 days).

Figure 4.1: Kaplan-Meier survival curves on drug exposure by type of antipsychotic drug



Chapter FOUR: Epidemiology of antipsychotic drug prescribing in UK primary care

Prevalence and incidence

Figure 4.2 shows the overall prevalence of all antipsychotic drugs (either atypical or typical) almost doubled ($p < 0.01$) from 1992 to 2005 (0.39 patients to 0.77 patients per 1,000 person-years respectively). Typical antipsychotic drug prescribing was stable from 1992 to 2000 before decreasing significantly ($p < 0.01$) in 2000 (0.44 patients per 1,000 person-years; 95% CI: 0.38 to 0.49 patients per 1,000 person-years) to 2005 (0.18 patients per 1,000 person-years; 95% CI: 0.15 to 0.21 patients per 1,000 person-years). On the other hand, Figure 4.2 shows the prevalence of atypical antipsychotic drug prescriptions rising steadily from 0.006 patients per 1,000 person-years (95% CI: 0.002 to 0.02 patients per 1,000 person-years) in 1994 (when the first atypical antipsychotic drug prescription was recorded) to 0.61 patients per 1,000 person-years (95% CI: 0.55 to 0.67 patients per 1,000 person-years) in 2005 ($p < 0.01$).

Figure 4.3 shows the incidence (new starters) of both typical and atypical antipsychotic drugs mirroring the prevalence in Figure 1 whereby there is a steady increase in new starters of atypical antipsychotic agents and a decline in new starters of typical antipsychotic agents. However, unlike the prevalence of all antipsychotic drugs seen in Figure 4.2, the overall incidence of all antipsychotic agents is stable without a significant increase ($p > 0.10$) between 1992 (0.30 patients per 1,000 person-years; 95% CI: 0.24 to 0.37 patients per 1,000 person- years) to years) to 2005 (0.33 patients per 1,000 person-years; 95% CI: 0.29 to 0.37 patients per 1,000 person-years).

Figure 4.2: GPRD data: Prevalence of antipsychotic drug prescriptions

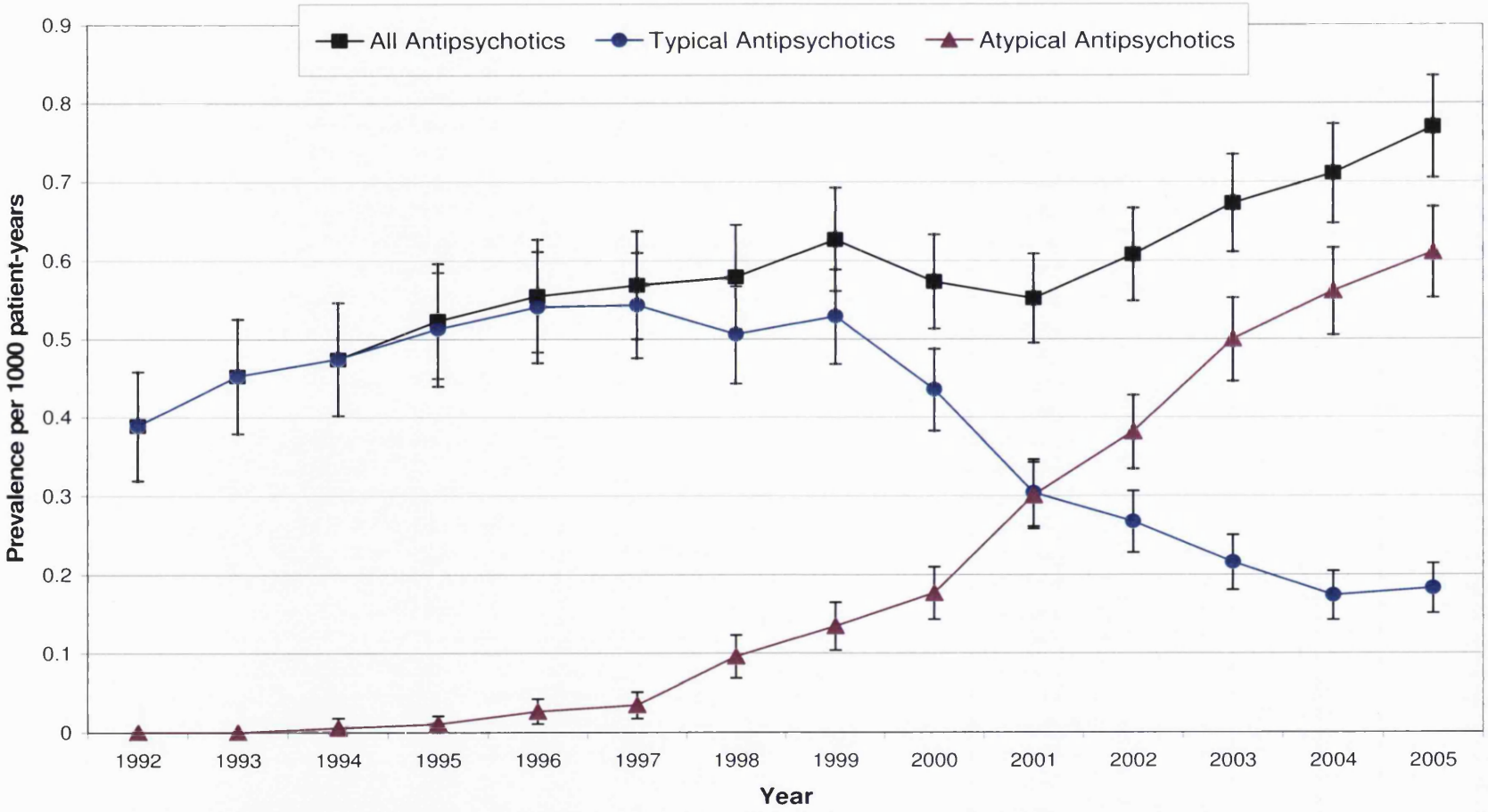


Figure 4.3: GPRD data: Incidence of antipsychotic drug prescriptions

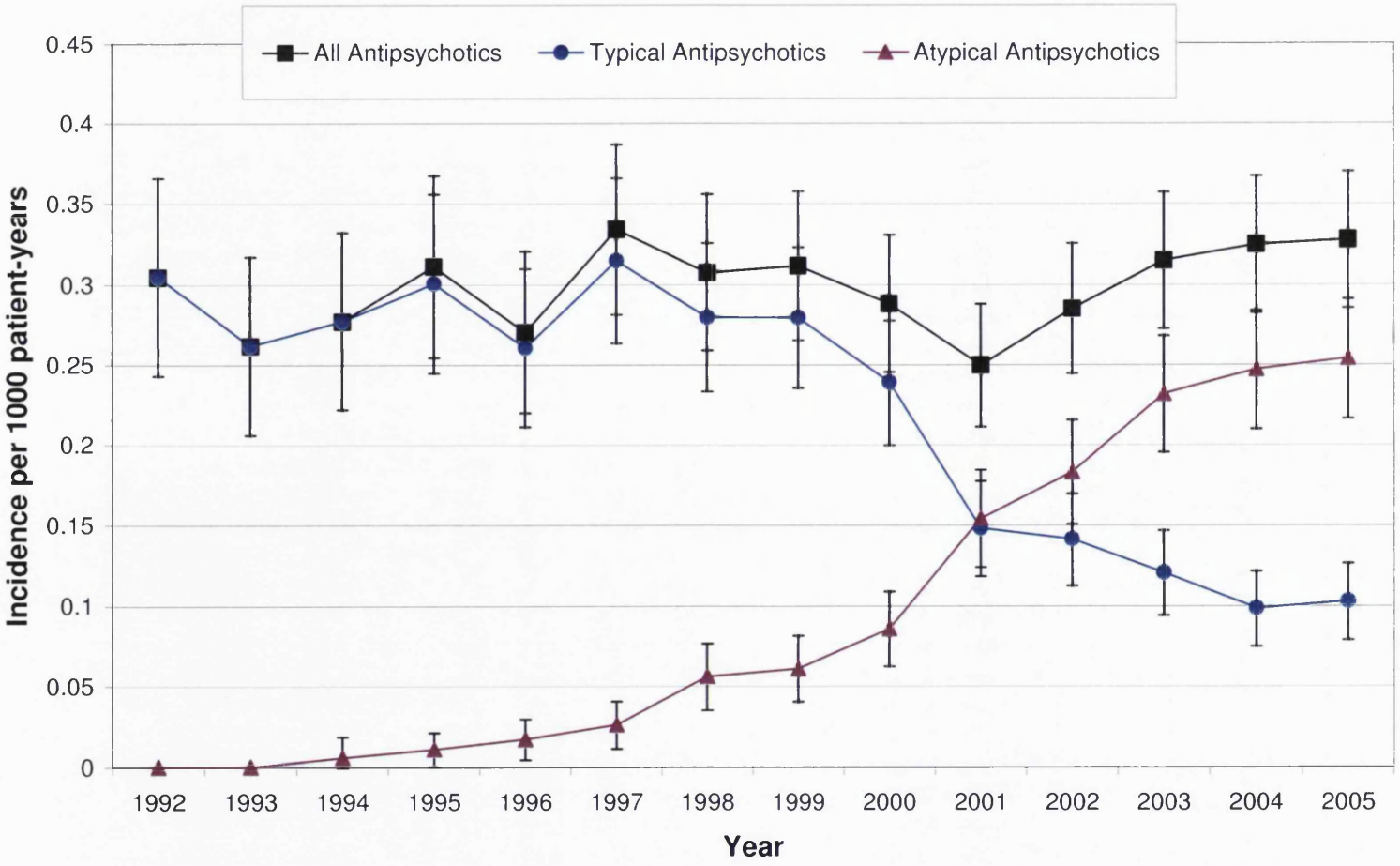


Figure 4.4 shows the prevalence of all antipsychotic agents by 6 year age bands (0 to 6, 7 to 12, and 13 to 18 years of age). The prevalence of antipsychotic agents for teenagers (13 to 18 years) increased significantly ($p < 0.001$) from 1992 (1.09 patients per 1,000 person-years; 95% CI: 0.87 to 1.31 patients per 1,000 person-years) to 2005 (1.57 patients per 1,000 person-years; 95% CI: 1.41 to 1.73 patients per 1,000 person-years). However, the prescribing of antipsychotic agents to patients in middle childhood aged 7 to 12 years shows the most significant increase ($p < 0.0001$) throughout the study period from 1992 (0.23 patients per 1,000 person-years; 95% CI: 0.15 to 0.34 patients per 1,000 person-years) to 2005 (0.61 patients per 1,000 person-years; 95% CI 0.51 to 0.71 patients per 1,000 person-years).

A total of 1557 patients (56% of all patients) had diagnoses in at least one of the 5 categories within 6 months of their first prescription. The distribution of patients with diagnoses by different age bands is reflected in Figure 4.5.

There was a higher proportion of patients with a diagnoses from categories 2 (Behaviour/ Conduct/ Personality Disorders) and 3 (Autism/ Asperger's Syndrome) in early childhood (2 to 6 years of age) and middle childhood (7 to 12 years of age) compared to adolescent patients (13 to 18 years of age). On the other hand, adolescent patients had a higher proportion of diagnoses from category 1 (Psychosis/ Schizophrenia/ Hallucinations/ Delusions/ Paranoia) and category 4 (Depression/ Mood/ Affective disorders) compared to patients in the other age groups. There were 17% of patients in the 13 to 18 year age band who had a diagnosis related

Figure 4.4: GPRD data: Prevalence of all antipsychotic drug prescriptions by age

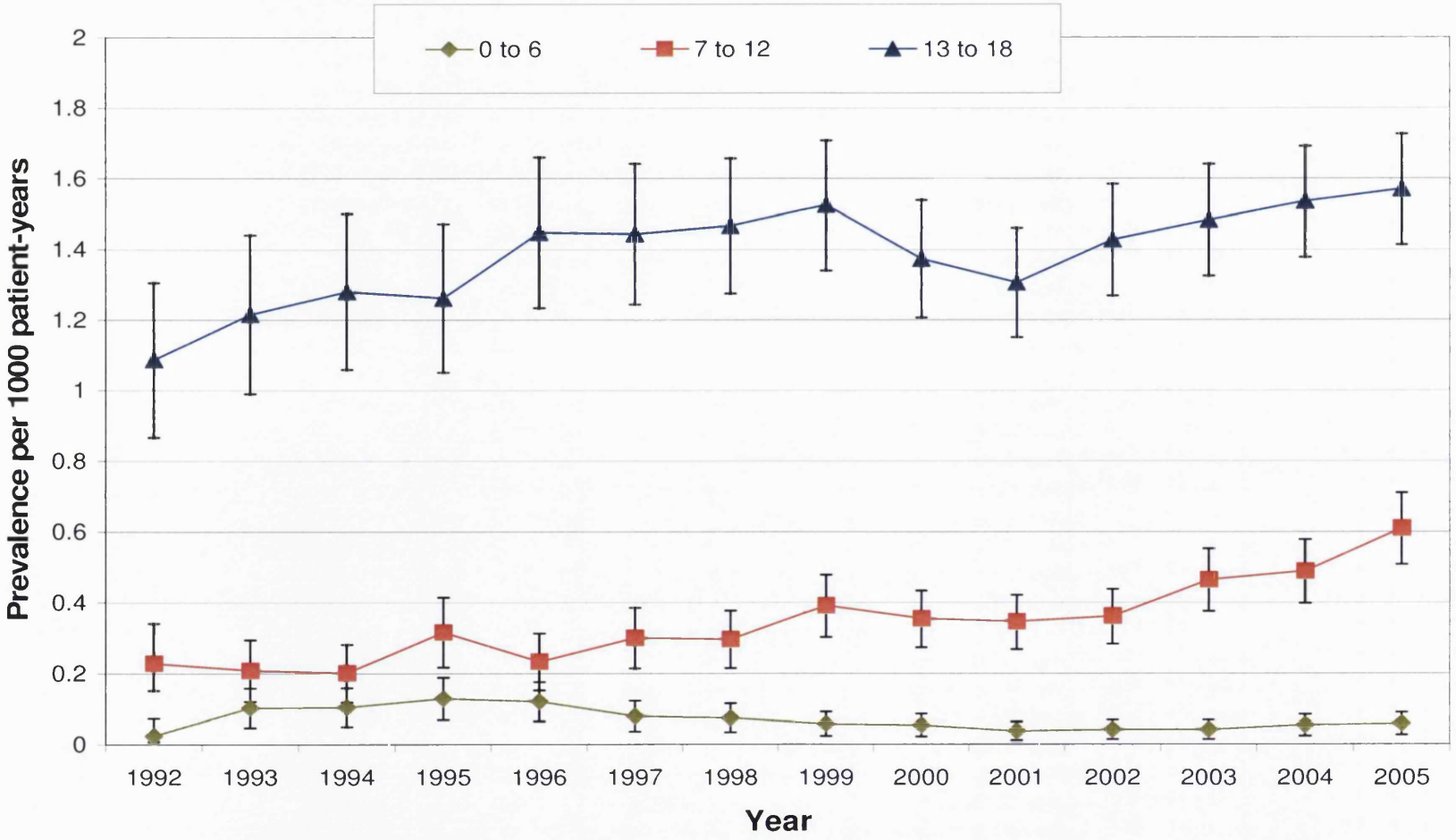
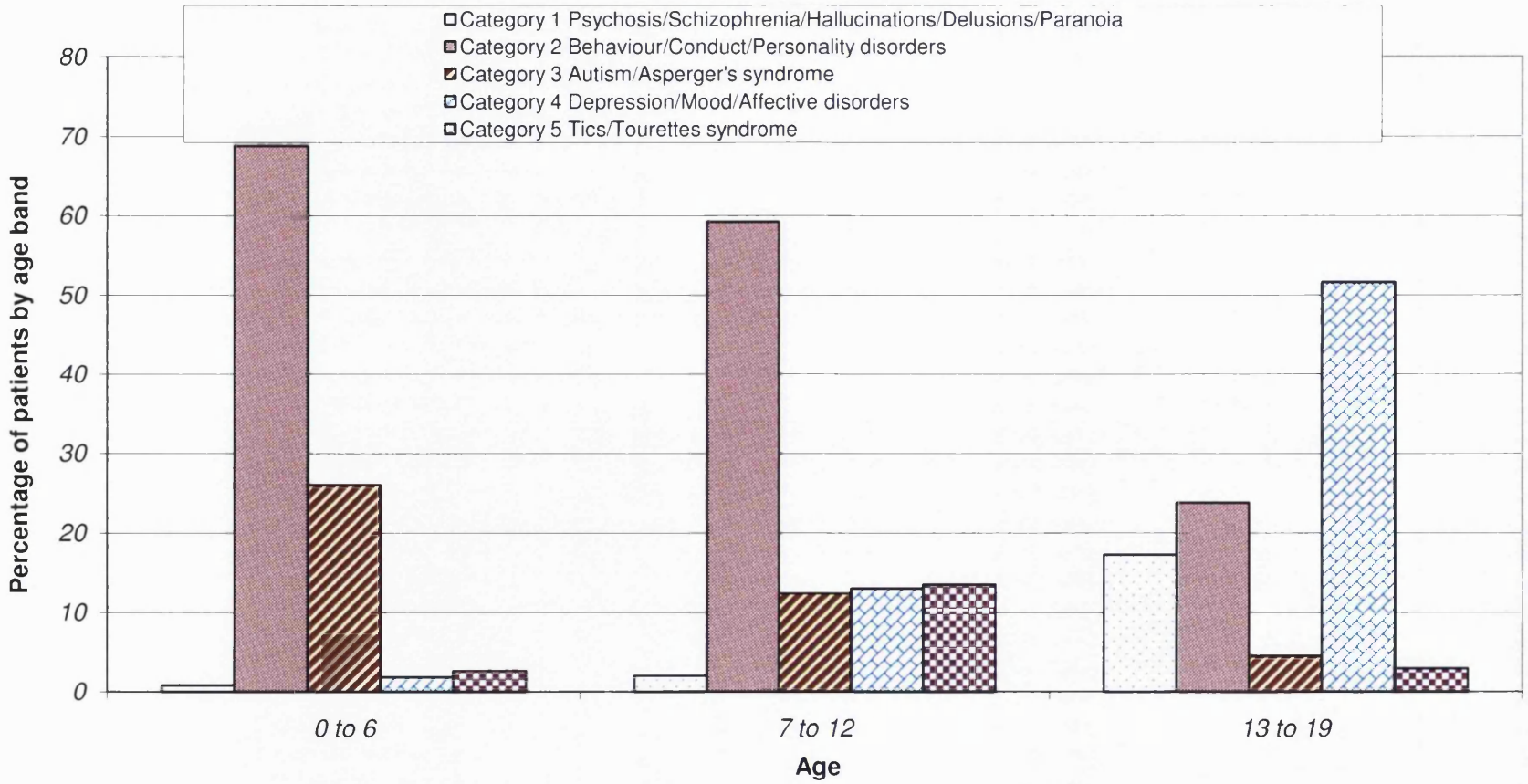


Figure 4.5: GPRD data: Percentage of patients by age group with diagnoses within 6 months of their first prescription



to category 1 compared to 2% of patients in middle childhood and 0.8% of patients in early childhood.

Verification using the IMS database

For verification purposes, the epidemiology of antipsychotic drug prescribing in patients aged 18 years and under was also analysed using the IMS database from 1997 to 2005. The results obtained from the IMS were compared directly to the results from the GPRD for the same study duration (1997 to 2005). The prevalence and incidence rates from the IMS database were very similar at the start and end points of the study period with overlapping confidence intervals. Additionally, both the prevalence and incidence trends mirrored the results obtained from the GPRD where there was a significant increase in the prevalence ($p < 0.01$) of all antipsychotic agents in 1997 (0.45 patients per 1,000 person-years; 95% CI: 0.37 to 0.53 patients per 1,000 person-years) to 2005 (0.78 patients per 1,000 person-years; 95% CI: 0.67 to 0.89 patients per 1,000 person-years) and a stable trend ($p > 0.10$) in the incidence of all antipsychotic agents in 1997 (0.31 patients per 1,000 person-years; 95%CI: 0.24 to 0.38 patients per 1,000 person-years) and 2005 (0.41 patients per 1,000 person-years; 95%CI: 0.33 to 0.49 patients per 1,000 person-years in 2005). Both the prevalence and incidence of atypical and typical antipsychotic drugs using the IMS database also showed similar trends as the GPRD (Figure 4.7).

Figure 4.6: IMS Data: Prevalence of antipsychotic drug prescriptions

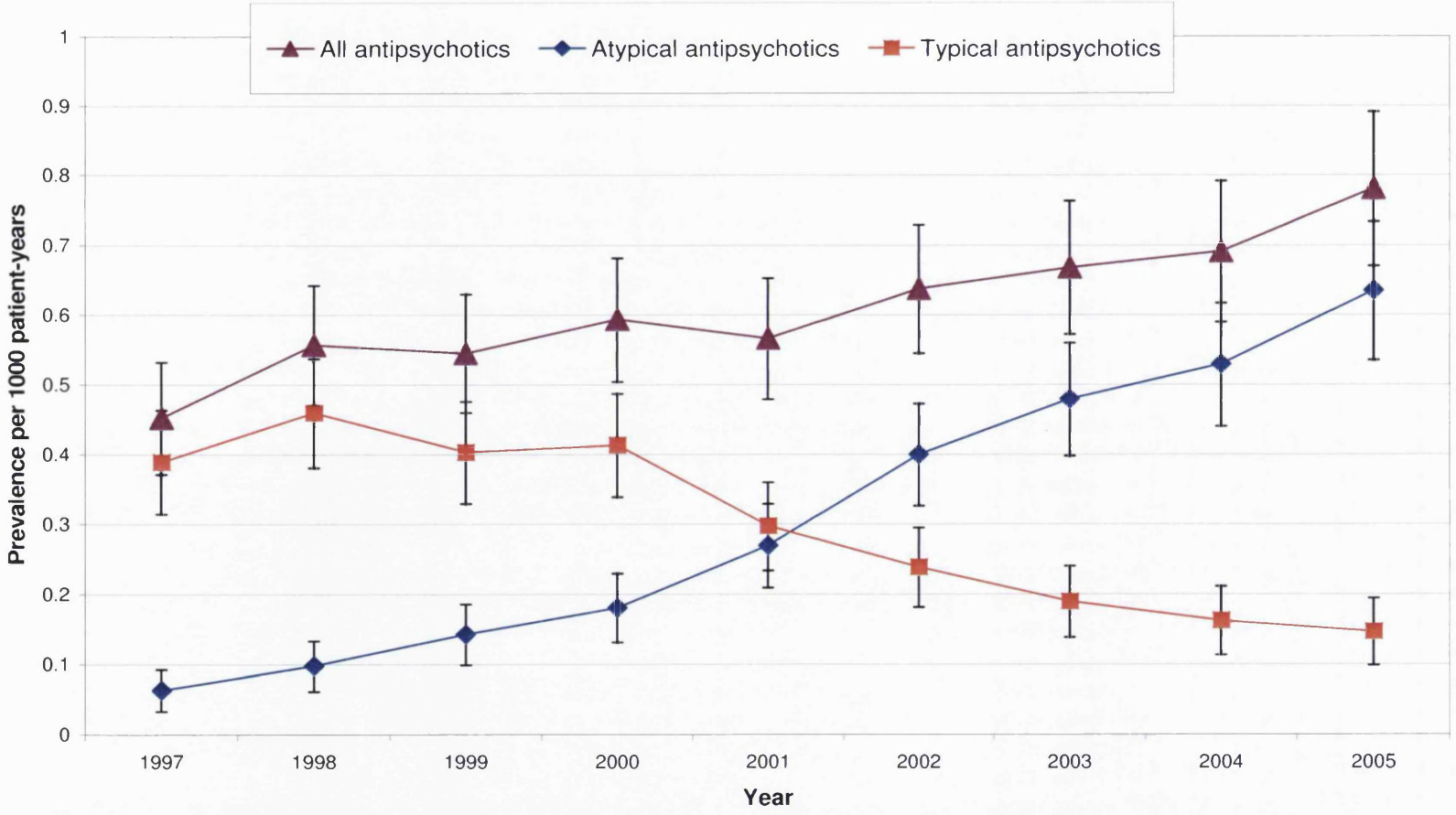
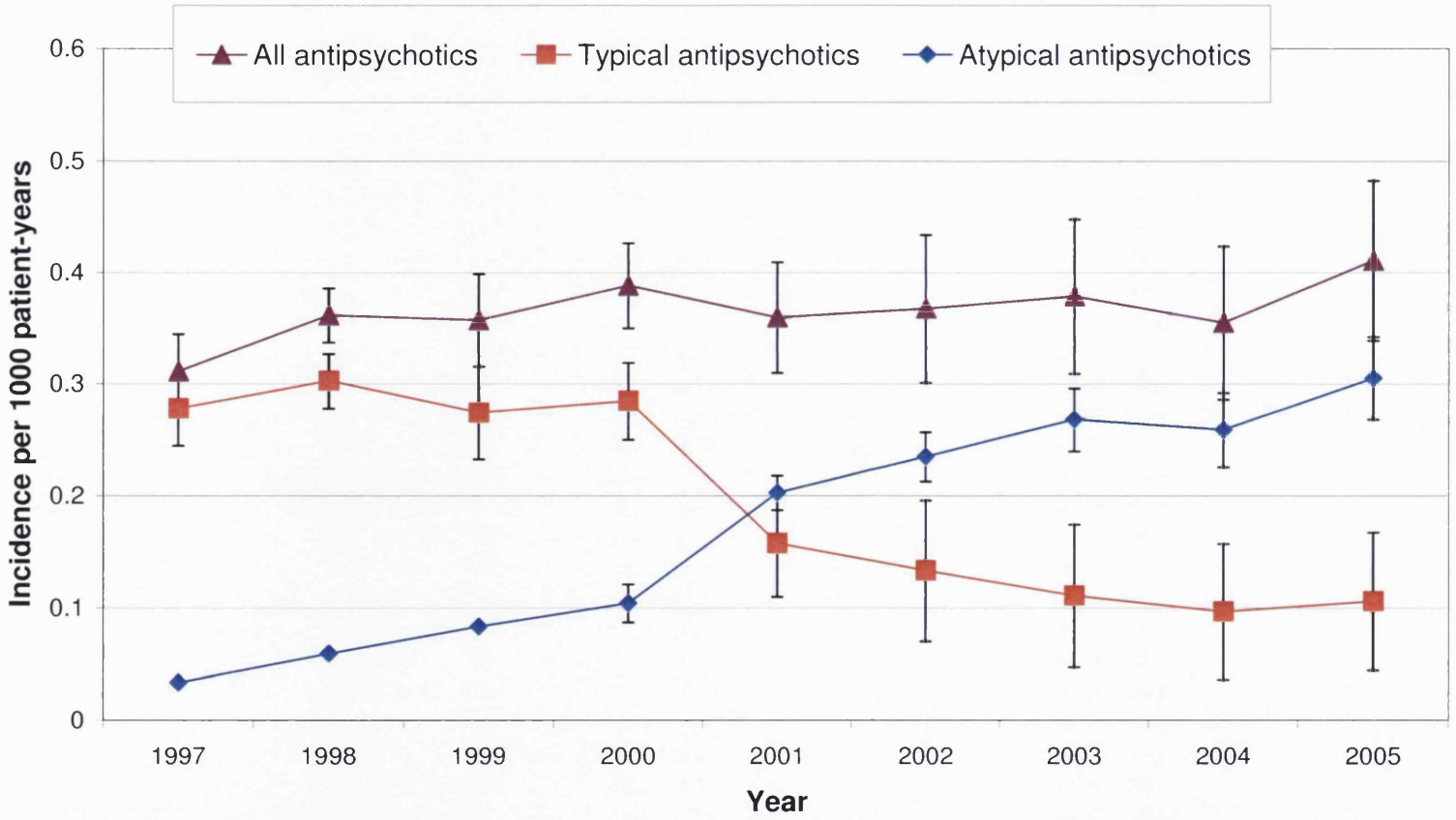


Figure 4.7: IMS Data: Incidence of antipsychotic drug prescriptions



Unlike the GPRD, the IMS database provides data on the associated diagnoses linked to prescriptions issued. Data on diagnoses from the IMS database is illustrated in Figure 4.8. The diagnoses trends of antipsychotic drug prescriptions from the IMS database also mirrored the associated diagnoses from the GPRD where patients in the older age group of 13 to 18 years had a higher proportion of diagnoses related to schizophrenic and depression disorders compared to patients in the younger age group (0 to 6 and 7 to 12 years respectively). Conversely, patients in the younger age groups had a higher proportion of diagnoses related to behavioural disorders compared to patients in the older age group.

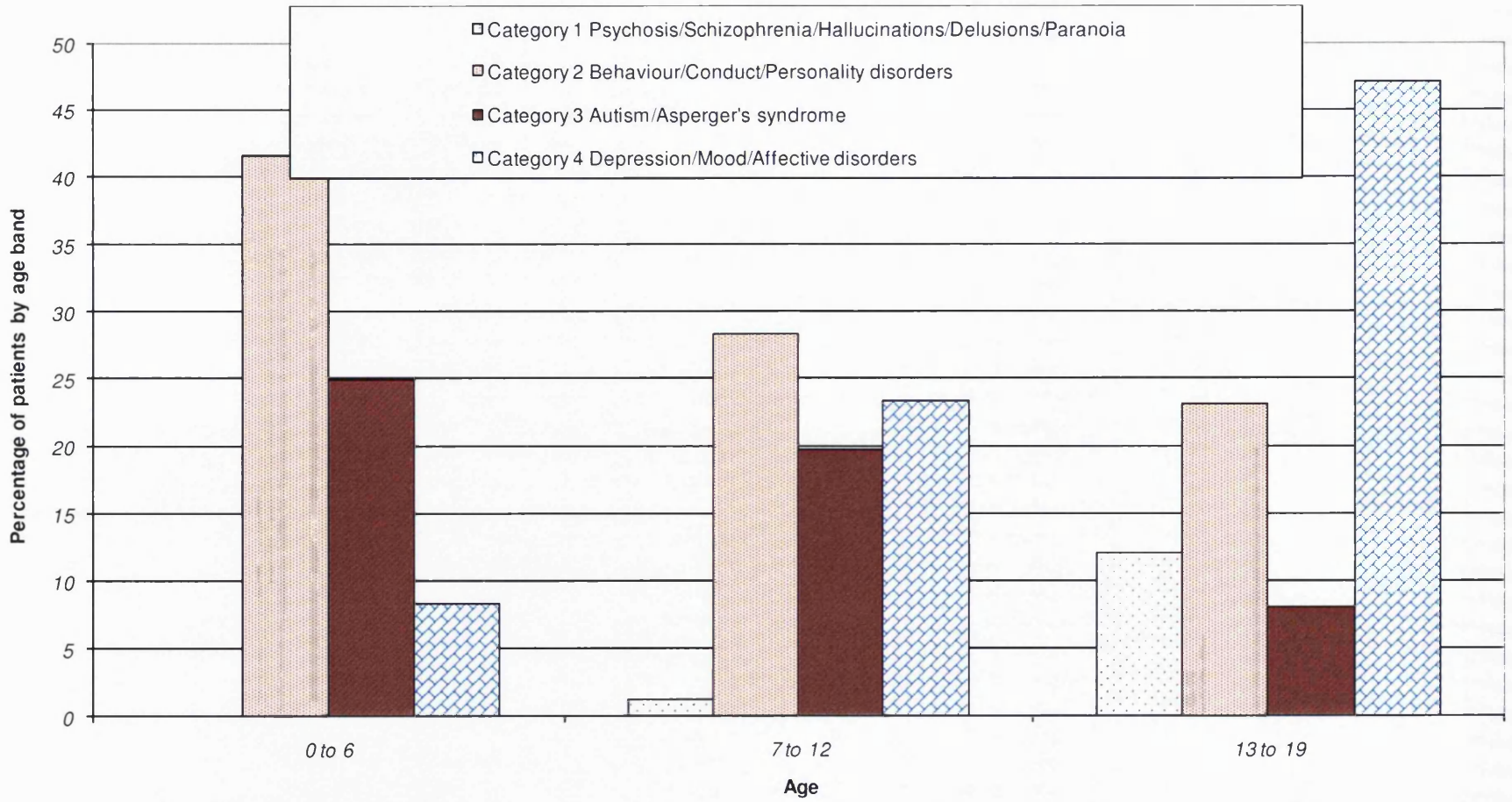
4.4 Discussion

During the past decade, there have been significant changes in the patterns of utilisation and prescribing trends of antipsychotic therapy in children and adolescents (Cooper et al, 2004; Olfson et al, 2006; Kalverdijk et al, 2008). This is the first and largest paediatric cohort study to examine the epidemiology of antipsychotic drug prescribing in the UK. The results presented raise many important issues related to the prescribing of antipsychotic medications in the paediatric population.

Comparison with utilisation studies in other countries

The results obtained present a very different picture from the study by Olfson et al (2006) in the USA which showed a 6-fold increase in antipsychotic treatment between

Figure 4.8: IMS Data: Diagnoses of antipsychotic drug prescriptions



1993 and 2002. During the same period of this study, there was only a 36% increase in the prescribing of antipsychotics.

The difference in prevalence compared to the study in the USA may be due to a number of reasons. Firstly, different methodologies were used. While the Olfson study used outpatient practices similar to this study, the authors reported on office-based visits, where there could be duplication of patients, and hence an overestimation of antipsychotic prescribing prevalence. Their study population also included patients aged 20 years and younger whereas the study population in this study was 18 years and below. Another possible reason for the difference is the variation of prescribing practice between physicians in the USA compared to physicians in the UK. Indirect evidence comes from the prescribing of psychostimulants, where the prevalence of stimulants prescribing in children in the USA is estimated at 1-6% compared to 0.03% in the UK paediatric population (Rey & Sawyer, 2003).

Another important finding is the overall prevalence of antipsychotic drug prescribing almost doubled between 1992 and 2005; however, the overall incidence was relatively stable during the same period. This suggests that patients are being prescribed antipsychotic treatment for longer durations rather than more new patients starting treatment. This is a sharp contrast to the USA data by Cooper et al (2004) who reported the number of new users (aged 2 to 18 years) of antipsychotic medications almost

doubled (23 to 45 per 10,000 children) from 1996 to 2001. The study by Kalverdijk et al (2008) also demonstrated a mild, but statistically significant increase in the incidence of new-onset prescribing of overall antipsychotic agents (1.3 to 1.6 per 1,000 children) from 1998 and 2005. With regards to prevalence of antipsychotic prescribing by age groups, similar trends were demonstrated to the study by Kalverdijk et al (2008) whereby there were significant increases in the prevalence of overall antipsychotic prescribing in the middle childhood and adolescent age groups. Although similar prescribing trends were demonstrated by Kalverdijk et al (2008), the actual prevalence and incidence of that study was higher. This could be because the database used in the Netherlands study comprised of all paediatric patients who receive antipsychotic prescriptions, where as the GPRD only includes prescriptions issued from primary care.

Effect of restricted indications of thioridazine

The most commonly prescribed typical antipsychotic agent in this study was thioridazine, contributing to 27% of all typical antipsychotic prescriptions. In December 2000, the Committee on Safety of Medicines restricted the indications of thioridazine to "the second line treatment of schizophrenia in adults" and also declared that the "balance of risks and benefits is unfavourable for its previous indications (anxiety, agitation and restlessness in the elderly, moderate to severe psychomotor agitation, violent and dangerously impulsive behaviour, mania/hypomania, and behavioural disorders and epilepsy in children)" because of cardiotoxicity associated with its use (Committee on Safety of Medicines,

2000). The effect of this warning is evident when thioridazine prescribing reduced significantly after 2000 and slowed down the increasing trend of overall antipsychotic drug prescribing.

Antipsychotic treatment in early and middle childhood

In the UK, atypical antipsychotic prescribing to patients aged 18 years and under is "off-label" or used outside of the product license; except for amisulpride, risperidone, and clozapine. Amisulpride and risperidone may be prescribed to patients aged 15 years and above with schizophrenia with positive and/or negative symptoms and clozapine may be given to patients 16 years and above with treatment-resistant schizophrenia unresponsive to other antipsychotics. However, there has been an increasing interest in the use of atypical antipsychotic drugs in the treatment of other psychiatric conditions such as bipolar disorder, obsessive compulsive disorder, autism, tic disorder, and Tourette's syndrome in children and adolescents (Coghill, 2003; Dubois, 2005). Analysis by age bands shows the increase in prescribing has been greatest in middle childhood (Figure 4.4). Data on the associated diagnoses from both the GPRD and the IMS database show that adolescent patients in the 13 to 18 year age band have a higher proportion of diagnoses related to schizophrenia and psychosis compared to patients in early and middle childhood (Figures 4.5 and 4.8). This demonstrates that schizophrenia spectrum disorders are less prominent in early and middle childhood compared to adolescence and therefore are unlikely to account for this upward trend in antipsychotic prescribing. This suggests

that these drugs are used for other indications rather than psychotic disorders. Furthermore, the results show that patients in early and middle childhood have a relatively higher proportion of diagnoses related to behaviour disorders and autistic spectrum disorders compared to patients in the 13-18 year age band. This accentuates the need for more rigorous investigations concerning the use of antipsychotic medications for such indications in the young.

Also, a recent study has suggested an increase in the prevalence of autistic spectrum disorders (Baird et al, 2006). Although the reason for this increase is unclear, i.e. whether the increase is due to better ascertainment, broadening diagnostic criteria, or an increased incidence (Baird et al, 2006), such trends may fuel a demand for medications to modify behaviours associated with developmental disorders.

Rising trend of antipsychotic drug prescribing

Results of the study also showed an increase in atypical antipsychotic prescribing and a decline in typical antipsychotic prescribing during the study period (Figures 4.1 and 4.2); this implies that the use of typical antipsychotic drugs in the paediatric population have been largely replaced by the newer atypical antipsychotic agents. Interestingly, a similar trend in antidepressant prescribing to young people was observed between 1992 and 2001, where selective serotonin reuptake inhibitors (SSRIs) gained popularity over tricyclic antidepressants despite a paucity of research into their efficacy and safety (Murray et al,

2004). Subsequently, the UK regulator, Medicines and Healthcare products Regulatory Agency, contraindicated the use of SSRIs other than fluoxetine as new treatment for patients younger than 18 years of age with depressive illness following concerns raised about their safety and the increased risk of suicidal behaviour associated with their use (Committee on Safety of Medicines, 2003). This highlights the availability of sufficient evidence with regards to antipsychotic drug prescribing to children. While scores of clinical trials have been devoted to adults with schizophrenia, relatively few trials of reasonable quality have focused on children with this condition over the past 20 years (Armenteros & Davies, 2006). Many trials involving the younger population were conducted using small sample sizes and short durations of study. Experience from the antidepressant saga raises the question that publication bias may also exist for studies investigating the effects of antipsychotic agents (Whittington et al, 2004).

There have been numerous reports of adverse drug reactions associated with atypical antipsychotic use in children and adolescents such as neuroleptic malignant syndrome, weight gain, metabolic abnormalities, diabetic ketoacidosis, hepatotoxicity, and hyperprolactinaemia (Stigler et al, 2001; Cheng-Shannon et al, 2004; Dubois, 2005). Results on the analysis of treatment exposure on incidence patients (patients who newly start antipsychotic treatment) present steep Kaplan-Meier survival curves for patients on both typical and atypical antipsychotic therapy (Figure 4.1). The steep reduction showed half of the proportion of patients stopping therapy within approximately 2 months with

typical antipsychotic agents and after 6 months with atypical antipsychotic agents. This steep curve and short duration of exposure leads to the possibility that the cessation of therapy in the study cohort is due to the patients experiencing acute adverse effects. This further emphasizes the necessity of long-term safety investigations and ongoing clinical monitoring of atypical antipsychotic therapy in children and adolescents, particularly if the prescribing rate of these medicines continues to grow. It should also be noted that the European Medicines Agency (EMEA) has recognised the lack of adequate investigations concerning these drugs in the paediatric population. Consequently, risperidone was added by the EMEA to a list of drugs known as the priority list (European Medicines Agency, 2008). The priority list is a directory of off-patent medicines for which it is thought studies are required. The specific information needs required for risperidone was described as "Data on efficacy and safety in psychosis in adolescents" as well as "conduct disorder in children (not developmentally delayed)" (European Medicines Agency, 2008).

It has recently been reported that most physicians have financial relationships with the pharmaceutical industry, including receiving drugs samples, payments, or reimbursements for costs associated with professional meetings (Campbell et al, 2007). However, the Medicines Act in the UK prohibits the pharmaceutical industry to promote unlicensed and off label use of medicines. Therefore, it is unlikely that the trends shown by the results are influenced by such relationships as the majority of antipsychotic medications are unlicensed in the study population.

Validation using the IMS database

In addition to the results obtained from the GPRD, additional validation of the results was conducted using the IMS. The validation results from the IMS database showed good correlation with the results from the GPRD. Almost every point prevalence and incidence from both databases also had overlapping confidence intervals, suggesting no differences between the prevalence and incidence of antipsychotic prescribing between 1997 and 2005 of the GPRD and the IMS database. The patterns and trends of diagnoses obtained from the IMS database also mirrored the trend seen from the GPRD where a higher proportion of patients in the 13 to 18 year age-band had diagnoses related to schizophrenic and depressive disorders than patients aged 0 to 6 and 7 to 12.

In summary, data presented from the IMS proved to be very similar with the results obtained from the GPRD and hence demonstrates strong validation. It should also be noted that validation of results using other large health databases is uncommon in published studies, which further highlights the reliability of the results presented.

Another data source which may be considered for future studies investigating prescribing trends is the Prescription Pricing Authority (PPA). All NHS prescriptions issued from primary care are sent to the PPA for reimbursement which allows for analyses on prescribing volume and trends to be conducted. However, a major disadvantage of this

database for paediatric studies is that the database does not record age of patients who receive prescriptions (Wong & Murray, 2005).

Clinical Implications

This study also raises the issue of availability and appropriateness of properly established antipsychotic therapy guidelines in the young population. The current National Institute for Health and Clinical Excellence (NICE) Guidance on Schizophrenia does not cover patients aged below 18 (National Institute for Health and Clinical Excellence, 2002). Findings of a significant increase in the trend of antipsychotic prescribing for paediatric patients underlines the need for improved clinical guidelines in this area. This would be helpful for general practitioners as they are likely to be the first point of contact for the majority of patients and are the ones who continue to prescribe and monitor antipsychotic treatments.

Study limitations

The GPRD does not provide any direct evidence on the pathway into care that children follow; including secondary and tertiary care, which results in prescription of an antipsychotic or the quality of diagnostic decisions which underlie it.

Chapter FOUR: Epidemiology of antipsychotic drug prescribing in UK primary care

The study calculated accurate prevalence and incidence of prescribing in primary care; however, patients who were solely cared for in secondary or tertiary care, or by prison services were unable to be captured. Given that the UK National Health Service is a primary care-driven healthcare system, general practitioners in primary care are the gatekeepers of referral to both secondary and tertiary care. Patients cannot go to secondary or tertiary care without primary care referrals (Bramble, 2003). Furthermore, there has been some evidence to suggest that many children including those with severe forms of mental disorders are not referred for assessment to specialist services and remain in primary care (Montoliu & Crawford, 2002). Additionally, paediatric psychotropic prescription analyses have shown that psychotropic drug prescribing is becoming increasingly common in recent years in general practice (Wong et al, 2004). Therefore the lack of data from secondary and tertiary care is unlikely to have a significant effect on the overall national trend shown by the results.

Finally, not all general practitioners recorded the diagnosis in clinical records; this limits the analysis for diagnostic indications.

Nevertheless, this is the largest UK paediatric cohort study to investigate the trends of antipsychotic drug prescribing and the results are true representative of the trend occurring in UK general practice. The IMS database which was used as verification, confirmed the epidemiological trends of the results obtained from the GPRD.

Chapter FOUR: Epidemiology of antipsychotic drug prescribing in UK primary care

4.5 Conclusions

This study has identified 3 major trends in the prescribing of antipsychotic medications for children and adolescents in the UK. Firstly, the prevalence of antipsychotic prescribing in general practice has almost doubled between 1992 and 2005. Secondly, the greatest increase is affecting children aged 7 to 12 years and thirdly, there is a strong trend for the replacement of typical antipsychotic drugs by atypical antipsychotic agents. This increase in prescribing is predominantly for off-label and unlicensed indications. While this trend is nowhere near the magnitude of such changes in the USA where psychotropic prescriptions for young children are increasingly common, there may be grounds for caution.

As previously shown in Chapter 1, the use of antipsychotic agents is associated with a wide range of side effects, some of which are potentially fatal or may result in long-term morbidity. These adverse effects have been shown to occur in patients from both adult and paediatric populations. As the results from this chapter indicate that the rates of prescribing of antipsychotic agents are clearly rising, this poses a significant safety issue, especially as there is a clear gap in safety investigations of these drugs in the paediatric population. Furthermore, children are likely to be on therapy for longer durations, primarily for unlicensed indications, which in itself leads to an increased risk of possible long-term adverse effects (Chapter 1). Therefore, it is important to monitor the safety of

these medications in children in order to improve the prescribing and therapy of these agents in this special population, and ultimately improve the quality of healthcare in children. Subsequently, the following chapters investigate specific serious adverse events in the cohort of children on antipsychotic therapy identified from this chapter.

5 Chapter FIVE: Mortality in children and adolescents on antipsychotic medication in UK primary care

5.1 Introduction

As demonstrated in Chapter 4, there was an almost 2-fold increase in the prevalence of antipsychotic prescribing from 1992 and 2005 (from 0.39 to 0.77 per 1,000 person-years) (Rani et al, 2008b).

Despite the evident increase in use, the safety profile of antipsychotic medications has not yet been fully established in the young (Chapter 1). The majority of these drugs are used off-label or outside their product license in children and adolescents. More importantly, the connection between the event of unexpected death and antipsychotic medication has long been suspected (Lader, 2006). Sudden death in patients taking antipsychotics is thought to be the result of cardiac complications, more specifically arrhythmias as a result of prolongation of the QT interval which in turn may lead to torsades de pointes and other cardiac arrhythmias (Straus et al, 2004). Deaths in healthy young adults suffering from schizophrenia as a result of myocarditis and cardiomyopathy while exposed to clozapine have also been reported in the literature (Killian et al, 1999; La Grenade et al, 2001). In addition to cardiac effects, other adverse effects that may be potentially fatal or lead to lethal complications include blood disorders such as agranulocytosis associated with

clozapine treatment; metabolic syndrome comprising of weight gain, diabetes mellitus and lipid abnormalities; and neuroleptic malignant syndrome (Lader, 2006).

Therefore the aim of this study was to investigate the mortality in children and adolescents taking antipsychotic medication.

5.2 Methodology

Data source

Data for this study were obtained from the GPRD. The history of the GPRD and validation of its data is described in more detail in Chapter 3.

The study population encompassed all patients in the GPRD aged 0 to 18 years who received at least one prescription for an antipsychotic agent during the defined study period between 1 January 1992 and 31 December 2005 as described in Chapter 3.

Ethics approval was granted by the GPRD's Scientific and Ethical Advisory Group (SEAG) and the Independent Scientific Advisory Committee (ISAC) for Medicines & Healthcare products Regulatory Agency (MHRA) database research (Appendix G).

Data extraction

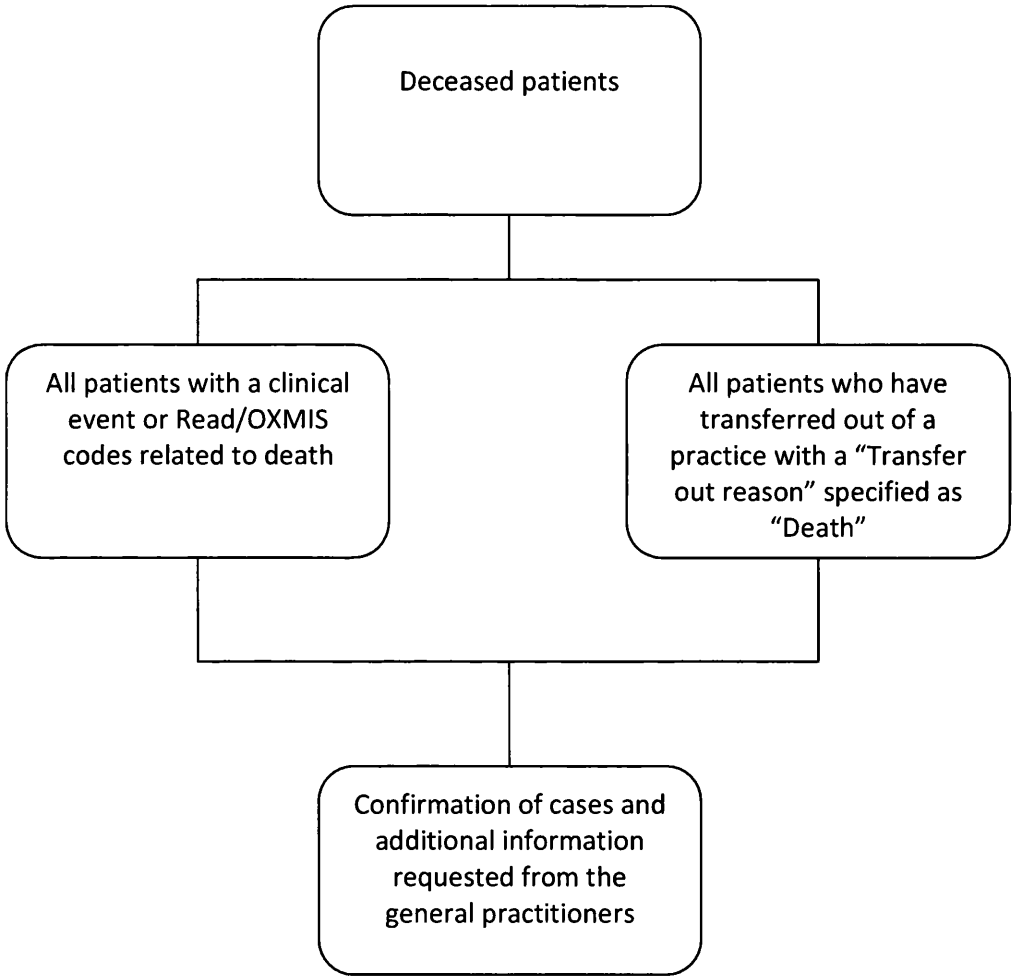
Cases were identified from a cohort of patients previously studied in Chapter 4 (Rani et al, 2008b). Patients in the cohort were followed from the date of the first antipsychotic drug prescribed until the earliest occurrence of a code related to death, age greater than 18 years, or end of the study period. To identify cases of death, an algorithm devised by GPRD was followed. Cases of death were identified by screening patients' medical records for clinical or referral events with a Read/OXMIS code indicating death. Death cases were also identified if a transferred out patient had a "Transfer out reason" specified as "Death".

Confirmation of cases was carried out by examining each individual patient profiles. An example of a patient profile is given in Appendix D. Additional clinical information including cause of death, the presence of co-morbid illnesses, exposure and indication of antipsychotics, as well as concurrent medication was requested from the general practitioners via questionnaires (Appendix H). If required, the death certificates and/or post mortem reports were obtained by the 'Follow-up' and source data verification service the GPRD provide. The verification service allows researchers to obtain additional information to validate death. All patient identifiers were anonymised by the GPRD.

A summary of data extraction and confirmation of deceased patients is illustrated in Figure 5.1.

Chapter FIVE: Mortality in children and adolescents on antipsychotic medication in UK primary care

Figure 5.1: Summary of data extraction and confirmation of deceased patients



Data analysis

Mortality rates

Once cases of death were identified, the mortality rates were calculated as crude mortality rates (CMR) and standardised mortality ratios (SMR). The CMR and SMR were calculated using the method published by Bland (Bland, 1993). Baseline mortality rates were obtained from population data from the Office for National Statistics (ONS). Mortality rates of 1998 (midpoint of the study duration) from the ONS were used as a referral year in the calculation. The CMR was first calculated per 1,000 person-years at risk for an adverse event (all confirmed cases of death that occurred after the first prescription for an antipsychotic, regardless of exposure status).

Following the analysis on exposure status (new cases of death that occurred during treatment exposure plus a latency washout period of 30 days were considered as treatment-emergent) and the causality assessment, the CMR in the study cohort was then calculated per 1,000 treatment-years at risk for an adverse drug reaction. The CMR was calculated using the method shown in Equation 5.1.

Equation 5.1: Calculation of crude mortality rate (CMR)

$$CMR = \frac{Nc}{D} \times 1{,}000$$

Where;

N_c = Number of deaths in the cohort

And D = Total person-years at risk for an adverse event or; total treatment-years at risk for an adverse drug reaction

The SMR and the 95% confidence intervals were then calculated. The SMR is the ratio of deaths observed in the study cohort to the number of deaths that would be expected during the follow-up period if the group in question had experienced the same age and sex specific rates of death as the general population (Bland, 1993). The SMR was calculated using person-years at risk for an adverse event as the denominator (all confirmed cases of death that occurred after the first prescription for an antipsychotic, regardless of exposure status). The expected number of deaths, E was calculated using Equation 5.2.

Equation 5.2: Calculation of the expected number of deaths

$$E = M \times D$$

Where ;

M = Mortality rate of general population

And D = Total person-years at risk for an adverse event

The SMR was calculated using Equation 5.3.

Equation 5.3: Calculation of standardised mortality ratios (SMR)

$$SMR = \frac{Nc}{E}$$

Where;

N_c = Number of deaths in the cohort

And E = Number of deaths that will be expected

Person-years at risk for an adverse event does not take into account the status of drug exposure whereby any event of death that occurs after the first prescription for an antipsychotic agent is included in the analysis, regardless of results from the causality assessment (see below), or whether or not the subject was exposed to antipsychotic therapy at the time of death.

On the other hand, treatment-years only calculate the person-years at which the subject was exposed to antipsychotic therapy. Treatment-years is defined as the date of the first prescription until the earliest occurrence of either the end latency date, date of death, or end of the study period. The end latency date was defined as the end of the prescriptions' duration date plus an additional 30 days. The latency period was added to the episode duration to allow for non-compliance, delay in drug dispensing, as well as half-life drug

kinetics. The equation used to calculate exposure duration is shown in Chapter 4. Both these methods of calculation of person-years and treatment-years at risk are illustrated in detail in Chapter 3.

Causality assessment

Once all cases of death were confirmed, a causality assessment adapted from the WHO-UMC system for standardised case causality assessment method (Uppsala Monitoring Centre) was carried out to determine the likelihood of a relationship between the drug and an event of death. The causality assessment was modified as it is impossible to implement the criteria for re-challenge when investigating mortality. Classification and criteria of the causality assessment is shown in Table 5.1.

Table 5.1: Categories used for the causality assessment for cases of death in the cohort

Causality term	Assessment criteria
Certain	• Event of death with a plausible time relationship to drug intake • Event cannot be explained by other disease or drugs • Event definitive pharmacologically or phenomenologically
Probably / Likely	• Event of death with reasonable time relationship to drug intake • Event unlikely to be attributed to other disease or drugs
Possible	• Event of death with reasonable time relationship to drug intake • Event could be possibly explained by disease or other drugs
Unlikely	• Event of death with a time to drug intake that makes a relationship improbable, but not impossible • Disease or other drugs provide plausible explanations

After conducting the analysis on the causality assessment, it was also assessed independently by Professor Ian Wong[2], a paediatric pharmacoepidemiologist, Dr Noel Cranswick[3], a clinical pharmacologist and Dr Patrick Byrne[4], a consultant child and adolescent psychiatrist. Cases where the antipsychotic therapy were deemed *possibly*, *probably*, and *certainly* associated with the event of death (from the analysis on causality assessments; Table 5.1) were considered as adverse drug reactions.

5.3 Results

A total of 2,767 patients who received at least one antipsychotic prescription contributing 6,007 person-years at risk for an adverse event and 2,041 treatment-years at risk for an adverse drug reaction were previously identified from Chapter 4 (Rani et al, 2008b). From this cohort of patients, a total of 30 deceased patients were identified (Table 5.2).

[2] Professor Ian Chi Kei Wong, Director and Professor of Paediatric Medicines Research,
Centre for Paediatric Pharmacy Research, A collaboration between the School of Pharmacy, Institute of Child Health & Great Ormond Street Hospital for Children
[3] Noel E Cranswick, Director, Clinical Pharmacology, Royal Children's Hospital
Director, APPRU, Murdoch Children's Research Institute & the Royal Children's Hospital
Associate Professor, University of Melbourne
[4] Dr Patrick Byrne MMedSci FRCPsych
Consultant in Adolescent Psychiatry & Hon Research Associate IoP
South London & Maudsley NHS Trust

Table 5.2: Deceased patients

Patient	Age at death	Cause of death	Exposed to antipsychotic
1	12	Anaplastic astrocytoma	Haloperidol
2	9	Acute lymphoblastic leukaemia	Haloperidol
3	13	Neuroblastoma	Methotrimeprazine
4	11	Pneumonia secondary to Hunter's syndrome	Not exposed
5	17	Non Hodgkin's lymphoma	Not exposed
6	6	Nephroblastoma	Methotrimeprazine
7	8	Adrenoleukodystrophy	Thioridazine
8	10	Wilms' tumour	Methotrimeprazine
9	2	Choroid plexus carcinoma	Methotrimeprazine
10	16	Bronchopneumonia Acquired immunodeficiency syndrome	Chlorpromazine
11	9	Brain tumour	Methotrimeprazine
12	18	Drug overdose (MST)	Not exposed
13	6	Undiagnosed progressive neurological condition	Chlorpromazine
14	17	Multiple gliomas, Acute lymphoblastic leukaemia	Haloperidol
15	3	Astrocytoma hypothalamus	Chlorpromazine
16	17	Self harm, multiple injuries	Not exposed
17	14	Sanfilippo syndrome	Not exposed
18	16	Sanfilippo syndrome	Not exposed
19	10	Astrocytoma	Haloperidol
20	15	Pneumonia; Adrenoleukodystrophy	Chlorpromazine
21	13	Epilepsy	Thioridazine
22	18	Malignant lung neoplasm	Haloperidol
23	11	Neuroblastoma	Methotrimeprazine
24	16	Rhabdomyosarcoma	Not exposed
25	13	Medulloblastoma	Methotrimeprazine
26	17	Osteosarcoma	Methotrimeprazine

27	18	Acute peritonitis; Perforation of small bowel by chicken bone; Down's syndrome	Risperidone
28	17	Non-Hodgkin's Lymphoma	Methotrimeprazine
29	3	Pneumonia; Childhood dementing illness with chorea	Haloperidol
30	17	New variant Creutzfeldt-Jakob disease	Not exposed

There was a 97% response rate from the questionnaires sent to the general practitioners. Additional verification was requested for 3 cases of death (Patients 13, 16, and 21) and the death certificates were obtained for 2 of these 3 patients (Patients 16 and 21).

Mortality rates

The CMR was 4.99 cases per 1,000 patients-years at risk for an adverse event (95% CI: 3.21 to 6.78 cases per 1,000 person-years at risk) while the SMR was 20 (95% CI: 13 to 29). After closer investigation of the 30 deceased patients, it was found that the causes of death for the majority of these patients were related to pre-existing medical conditions (Table 5.2). Therefore the results were subject to confounding due to the patients' co-morbid conditions (where the patient suffered from potentially fatal pre-existing medical conditions prior to receiving an antipsychotic medication). Consequently, the analysis of CMR and SMR were then adjusted to exclude these patients.

After exclusion of patients with pre-existing medical conditions

Upon investigating the causes of death in the 30 patients, it was found that 24 of the patients had a cause of death related to neoplasms (N=17), Acquired Immune Deficiency Syndrome (AIDS) (N=1), genetic or inherited disorders (N=5), and childhood dementia (N=1) (Table 5.2). Subsequently, all patients in the cohort who had clinical events related to these conditions prior to their first prescription for an antipsychotic were then excluded in the analysis.

After exclusion, there were 6 cases of death in 5,963 person-years at risk for an adverse event (Patients 12, 13, 16, 21, 27 and 30). There was an equal number of males (N=3) and females (N=3). The median age of death was 17 years (inter quartile range: 14 – 17.75).

Mortality rates after exclusion of patients with pre-existing medical conditions

After adjusting for pre-existing medical conditions, the overall CMR was 1.01 cases per 1,000 person-years at risk for an adverse event (95% CI: 0.20 to 1.81 cases per 1,000 person-years at risk) and the adjusted SMR was 4.03 (95% CI: 1.48 to 8.76).

Causality assessment on the 6 patients

Using the WHO-UMC system for standardised case causality assessment method (Uppsala Monitoring Centre), a causality assessment analysis was conducted on the 6 cases of death. Details of the causality assessment on the 6 subjects are described in Table 5.3.

Table 5.3: Causality assessment on the 6 cases of death

Patient	Gender	Age at death	Cause of death	Antipsychotic agent	Causality assessment	Outcome
12	Female	18	From GP questionnaire: Drug overdose (MST)	Not exposed at the time of death	• Subject was not exposed to antipsychotic therapy when the event occurred, demonstrating a poor time relationship between drug intake and the event • Subject also suffered from depression and suicidal ideation, which provides a more plausible explanation of the circumstances of death	• Antipsychotic drug therefore *unlikely* to have contributed to the cause of death in this case
13	Female	6	From GP questionnaire: Undiagnosed progressive neurological condition	Chlorpromazine	• Subject was exposed to antipsychotic therapy when the event occurred, indicating a reasonable time relationship between drug intake and the event • Subject also suffered from pre-existing dyskinetic cerebral palsy • Subject's cause of death is not	• Antipsychotic drug therefore *unlikely* to have contributed to the cause of death in this case

					phenomenologically or pharmacologically related to antipsychotic medication	
16	Male	17	From GP questionnaire: Unknown; self harm From death certificate: Multiple injuries	Not exposed at the time of death	• Subject was not exposed to antipsychotic therapy when the event occurred, demonstrating a poor time relationship between drug intake and the event • Subject also suffered from depression and was on fluoxetine therapy, which provides a more plausible explanation of the circumstances of death	• Antipsychotic drug therefore *unlikely* to have contributed to the cause of death in this case
21	Male	13	From death certificate: Epilepsy	Thioridazine	• Subject was exposed to antipsychotic therapy when the event occurred, indicating a reasonable time relationship between drug intake and the event • Subject also suffered from seizures, even prior to starting antipsychotic treatment • Thioridazine has been known to	• Antipsychotic drug therefore *possibly* to have contributed to the cause of death in this case

					lower the threshold of seizures	
27	Male	18	From death certificate: 1(a) Acute peritonitis 1(b) Perforation of small bower by chicken bone 2) Downs syndrome	Risperidone	• Subject was exposed to antipsychotic therapy when the event occurred, indicating a reasonable time relationship between drug intake and the event • Subject's cause of death is not phenomenologically or pharmacologically related to antipsychotic medication	• Antipsychotic drug therefore *unlikely* to have contributed to the cause of death in this case
30	Female	17	From GP questionnaire: Creutzfeldt-Jakob disease	Not exposed at the time of death	• Subject was not exposed to antipsychotic therapy when the event occurred, demonstrating a poor time relationship between drug intake and the event • Subject's cause of death is not phenomenologically or pharmacologically related to antipsychotic medication	• Antipsychotic drug therefore *unlikely* to have contributed to the cause of death in this case

Of the 6 cases, 3 patients were exposed to antipsychotic therapy at the time of death (Patients 13, 21 and 27). Patient 13 was exposed to chlorpromazine probably for the management of vomiting while Patients 21 and 27 were on thioridazine and risperidone therapy respectively probably for the management of behaviour disorders.

Only one of the 6 cases of death was *possibly* associated with antipsychotic medication (Patient 21). The cause of death for this patient was listed as epilepsy based on the death certificate obtained. As antipsychotic medications can lower the seizure threshold and modify electroencephalogram (EEG) discharge patterns (Baldessarini & Tarazi, 2001), it was concluded that the antipsychotic medication in question, thioridazine, was *possibly* associated with the event of death in this subject. A more detailed conclusion was not possible as the subject had pre-existing epilepsy and information on drug withdrawal was not sufficiently clear.

The remaining 5 of the 6 identified cases had a cause of death not pharmacologically or phenomenologically relevant to antipsychotic medication, or did not have a plausible time relationship between drug intake and the time of death. Furthermore, the majority of these subjects had underlying chronic medical conditions such depression, degenerative disorders such as Creutzfeldt-Jacob disease, and also cerebral palsy. After conducting the causality assessment, it was concluded that none of the 5 cases of death were likely to be associated with antipsychotic medication.

Therefore results on the causality assessment demonstrated only one patient where the antipsychotic therapy is *possibly* associated with the event of death. Based on this one subject (Patient 21) and after adjusting for person-years of treatment exposure, the CMR was 0.51 cases per 1,000 treatment-years (95%CI: 0.09 to 2.89 cases per 1,000 treatment-years at risk). A summary of the results is illustrated in Figure 5.2.

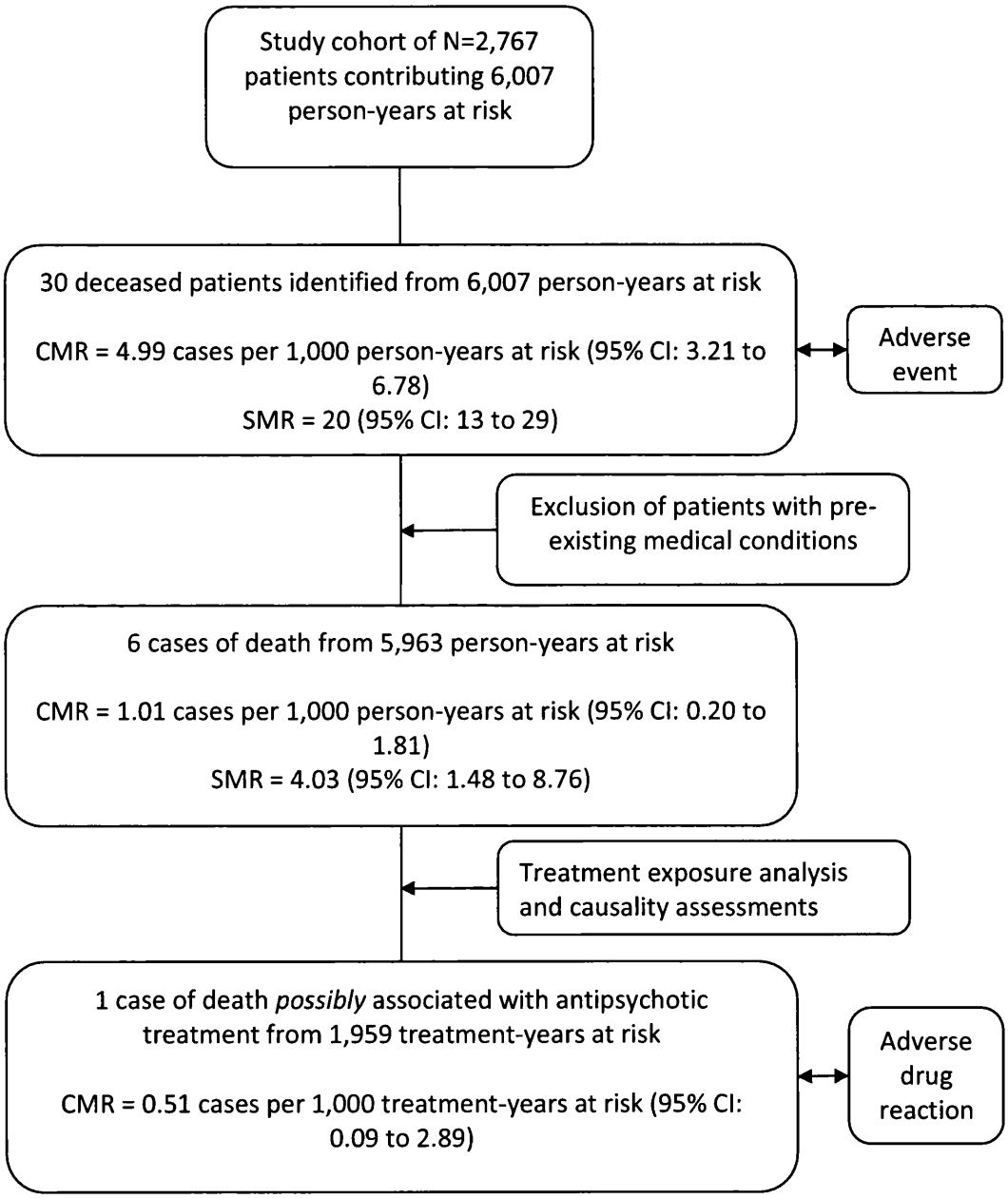
5.4 Discussion

In recent years, much attention has been given to mortality associated with drug treatments including antiepileptics, stimulants, and antibiotics in the paediatric population (Clarkson & Choonara, 2002; Vetter et al, 2008). This is the largest UK paediatric cohort to investigate the mortality related to antipsychotic medication.

Causality assessments

Although the study yielded a relatively high SMR of 4.03 (95% CI: 1.48 to 8.76) based on 6 cases of death in 5,963 person-years at risk for an adverse event, it was *unlikely* that the prescribed antipsychotic drugs were associated with the event of death in the majority of the identified cases. Two of the deceased patients had a cause of death related to suicide (Patients 12 and 16). Both were also suffering from depression. One of the 2 patients (Patient 12) had a cause of death of morphine sulphate overdose which was prescribed to

Figure 5.2: Summary of the results on mortality



her mother. Another patient had a cause of death of acute peritonitis due to the perforation of the small bowel by a chicken bone (Patient 27). This patient was also suffering from Down's syndrome. One patient had a cause of death of undiagnosed progressive neurological condition (Patient 13). Additional information was requested to obtain more detailed information on the cause of death for this patient. Unfortunately the death certificate could not be acquired. While this patient was exposed to antipsychotic therapy at the time of death, the patient was also suffering from dyskinetic cerebral palsy, chronic motor tic disorders and was often referred to both neurologic and paediatric clinics. Therefore it was concluded that the antipsychotic medication was *unlikely* to be associated with the cause of death. The last patient (Patient 30) had a cause of death of variant Creutzfeldt-Jakob disease which is a prion (infectious protein) disease. The disease is thought to be the result of transmission of bovine spongiform encephalopathy from cattle to humans (Variant Creutzfeldt-Jacob disease, 2002). Creutzfeldt-Jacob disease makes up for approximately 85% of cases of prion diseases in humans and the incidence of the disease is reported to be about 1 case per 1,000,000 population with an increasing incidence in the 60 to 74 year old age group (Prusiner, 2001). Clinical manifestations of this condition include dementia, ataxia, insomnia and deviant behaviour (Prusiner, 2001). Nonetheless, the specific indications for antipsychotic therapy in this subject were unclear from the electronic patient profile and the questionnaire completed by the general practitioner for this patient. Creutzfeldt-Jakob disease is reported to be a persistently progressive condition, and often results in death within one year of onset (Prusiner, 2001).

Chapter FIVE: Mortality in children and adolescents on antipsychotic medication in UK primary care

There was only one patient (Patient 21) where the causality assessment concluded that it was *possible* for the antipsychotic medication to be associated with the event of death. This patient was exposed to thioridazine at the time of death, providing a plausible temporal relationship between the drug and the event. The patient was suffering from seizures approximately 2 years prior to receiving his first prescription for thioridazine. The patient died approximately 3 weeks after receiving his last prescription and the cause of death as stated on the coroner's certificate was epilepsy. Antipsychotic medications including thioridazine has been known to lower the seizure threshold and induce EEG discharge patterns which are related to epileptic seizures (Baldessarini & Tarazi, 2001; MHRA Prescribing information for thioridazine). It has also been suggested that children and adolescents exposed to antipsychotic therapy have a significantly higher risk ratio for developing convulsions compared to adult patients (Woods et al, 2002). Patients suffering from epilepsy, including those from the paediatric population, have a higher rate of mortality compared to the general population. This could be due to a complication of the disease itself, or the treatment of epilepsy such as suffocation, aspiration of gastric contents, or as a result of status epilepticus (Appleton, 2003). Additionally, there are a number of deaths in patients with epilepsy which cannot be sufficiently explained. This syndrome is recognised as 'sudden, unexplained death due to epilepsy' or SUDEP (Appleton, 2003). The cause of death for this patient could be explained by the patients' pre-existing seizures or any of the complications of epilepsy previously mentioned;

however, the possibility that the adverse effect of thioridazine contributed to the cause of death cannot be overlooked.

A confounding factor when investigating the association of mortality in patients taking antipsychotic medication is that patients with psychiatric disorders already suffer from an increase in mortality compared to the general population (Allebeck, 1989; Osby et al, 2000). This is true even for patients who are not exposed to antipsychotic medication (Ruschena et al, 1998; Harris & Barraclough, 1998). Additionally, sudden death is a complex condition which may possibly be the result of multiple factors including a pre-existing cardiovascular defect, family history and even depression (Zarate, 2001).

Standardised Mortality Ratios

After the exclusion of patients with pre-existing medical conditions, a total of 6 cases of death in 5,963 person-years at risk for an adverse event were included in the SMR analysis. The SMR was then 4.03 (95%CI: 1.48 to 8.76), suggesting a higher mortality rate in the study cohort of patients who received antipsychotic treatment compared to the general paediatric population.

However, results from the causality assessment demonstrated that antipsychotic therapy was *possibly* associated with the event of death in only one subject (Patient 21), indicating that antipsychotic therapy is not associated with death in the majority of identified cases.

Based on this one case, and after adjusting for the person-years for drug exposure, the new CMR was 0.51 cases per 1,000 treatment-years at risk (95%CI: 0.09 to 2.89).

Limitations

Despite the size of the cohort, it is still relatively small when compared to studies conducted in adults. This is a common problem when conducting safety studies in the paediatric population.

Nevertheless, because the background rate of mortality in the general paediatric population is rare, the study would require an unreasonably large sample size of approximately 49,000 exposed patients and another 49,000 controls to detect a 2-fold increased rate of mortality with 80% power (Appendix I). Unlike clinical trials, sample sizes cannot be increased in pharmacoepidemiological safety studies using databases as there are a finite number of subjects in research databases.

Clinical implications

As previously stated, there has been much attention given to mortality associated with drugs for conditions including epilepsy but few studies have addressed this issue in relation to antipsychotic treatment. It is also known that patients suffering from schizophrenia have higher rates of death as a result of cardiac complications compared to

the general population (Ray & Meador, 2002). Growing reports of serious ventricular arrhythmias and unexplained sudden deaths in patients on antipsychotic medication has gradually shifted the suspicion to the drugs (Ray & Meador, 2002). There is much reason to prioritise research in this area as currently all antipsychotic medication has been reported to prolong the QT interval and can therefore be potentially fatal (Zarate, 2001). Reports of changes in electrocardiograph patterns and myocarditis further accentuate the need to question these potentially fatal effects in children exposed to antipsychotic therapy (McIntyre & Jerrell, 2008). Furthermore, the majority of recent reviews regarding treatment with cardioactive psychotropic drugs are concentrated in adult populations, with very few addressing treatment in children and adolescents (Labellarte et al, 2003). In addition to cardiac arrhythmia, sudden death has also been reported in healthy young adults on clozapine treatment as a result of cardiomyopathy and myocarditis (Killian et al, 1999; La Grenade et al, 2001). As mentioned in Chapter 1, metabolic adverse effects of antipsychotic drugs such as weight gain, increased serum lipid levels and diabetes mellitus may also lead to fatal complications (Lader, 2006). Dyslipidaemia combined with other metabolic effects of antipsychotic therapy in young patients foretells a higher risk for cardiovascular disease, which in turn is the most frequent cause of premature death in patients suffering from psychiatric conditions, including psychotic disorders (McIntyre & Jerrell, 2008).

Additionally, results from Chapter 4 on the utilisation of antipsychotic therapy in children and adolescents indicate that antipsychotic agents are prescribed for a wide range of psychiatric disorders. Therefore it can be said that these patients are usually given a range of psychotropic pharmacotherapy, including antidepressants and stimulants (Bebarta et al, 2005; Rani et al, 2008b). This phenomenon of polypharmacy itself may elevate the risk for cardiovascular events, and indirectly, mortality.

Although the majority of identified cases of death in this study were unlikely to be associated with antipsychotic therapy, the high SMR (SMR of 4.03; based on 6 cases of death in 5,963 person-years at risk for an adverse event) would suggest the possibility of inadequate management or poor control of patients' underlying medical conditions prior to death. This includes the management of diseases such as epilepsy, Creutzfeldt-Jakob disease and depression.

Additionally, the results demonstrate that a number of the study subjects were on antipsychotic therapy for the management of essentially off-label indications other than schizophrenia such as behavioural disorders. As the majority of antipsychotic agents are not licensed in children for many of the indications for which they are commonly used (Chapters 1 and 4), this further emphasizes the lack of sufficient long-term investigations and research in this population.

Chapter FIVE: Mortality in children and adolescents on antipsychotic medication in UK primary care

Despite the unlikelihood for antipsychotic therapy to be associated with the event of death in the majority of identified patients, clinicians would still be advised to use caution when prescribing these drugs to children. Appropriate guidelines regarding the baseline screening of patients, including the presence of any cardiovascular abnormalities including congenital long QT syndrome or history of cardiac illnesses such as arrhythmias should be implemented. As chronic conditions including diabetes mellitus and weight gain may itself increase risk of mortality, parameters of these conditions should also be considered and continuously monitored throughout therapy, especially if the treatment is ongoing for long-term chronic psychiatric conditions.

5.5 Conclusions

Results of the study demonstrated a high mortality rate compared to the general population. However after adjusting for antipsychotic exposure and analysis on causality, it was found that antipsychotic medications were not associated to the cause of death in the majority of these cases. Nevertheless, as antipsychotic therapy is known to potentially cause life-threatening adverse effects, patients exposed to these medications should be monitored carefully. Baseline and periodic parameters such as cardiovascular functions, potentially fatal co-morbidities, and metabolic functions should be observed during antipsychotic therapy. As stated in Chapter 1, children are potentially more at risk to experiencing adverse effects, consequently, the monitoring of these safety parameters are further highlighted.

It is also suggested that further studies with ideally large sample sizes and matched controls are required to further investigate the incidence as well as potential contributing factors of mortality associated with antipsychotic medications in this population.

Chapter SIX: Incidence of liver abnormalities, diabetes mellitus and extrapyramidal symptoms in a cohort of patients on antipsychotic medication

6 Chapter SIX: Incidence of liver abnormalities, diabetes mellitus and extrapyramidal symptoms in a cohort of patients on antipsychotic medication

6.1 Introduction

Results from Chapter 4 have shown a clear increase in the prescribing of antipsychotic medication to the paediatric population. This trend echoes the prescribing patterns seen in the USA and the Netherlands, although not to the same degree (Rani et al, 2008b).

In the face of the obvious increase in prescribing, the safety of these drugs in the paediatric population has not yet been fully established. As stated in Chapter 1, paediatric patients may be more susceptible to adverse effects of antipsychotic medication due to developmental changes during maturation (Lewis, 1998; Gracious & Findling, 2001; Correll & Kane, 2007).

Furthermore, antipsychotic agents have also been reported to cause serious adverse effects which may be potentially fatal, or may have long-term consequences affecting patients' morbidity. Serious adverse effects are not unheard of in both adult and paediatric patients exposed to antipsychotic treatment. There have been a number of case reports and studies describing the occurrence of liver injury and abnormalities (Holtmann et al, 2003a; Holtmann et al, 2003b; Kumra et al, 1997; Malone et al, 1999), diabetes mellitus (Hägg et al, 1998; Koller & Malozowski, 2001; Kornegay et al, 2002;

Chapter SIX: Incidence of liver abnormalities, diabetes mellitus and extrapyramidal symptoms in a cohort of patients on antipsychotic medication

Liebzeit et al, 2001; Mackin et al, 2005) and extrapyramidal symptoms (Sathpathy & Winsberg, 2003) occurring in patients from adult and paediatric populations with psychiatric disorders treated with antipsychotic medication.

Despite these published investigations, the number of patients studied still remains low. This is a common problem in investigative studies in the paediatric population (Greenhill et al, 2003). Results from the study in Chapter 4 identified the largest paediatric cohort exposed to antipsychotic therapy from the UK paediatric population. Therefore, the aim of this chapter was to investigate the incidence of liver abnormalities, diabetes mellitus and extrapyramidal symptoms in this large cohort of children and adolescents exposed to antipsychotic medication.

6.2 Incidence of liver abnormalities

6.2.1 Systematic literature review on liver abnormalities associated with antipsychotic drug therapy in children and adolescents

6.2.1.1 Aim of the literature review

To review published studies which have reported cases or rates of liver abnormalities associated with children and adolescents exposed to antipsychotic therapy.

6.2.1.2 Methodology of the literature review

A Medline (1950 to 31/07/2008) search was conducted using the keywords shown in Table 6.1.

Inclusion criteria

Studies reporting the development of liver abnormalities, or the manifestation of symptoms associated with the liver abnormalities in children and adolescents exposed to antipsychotic therapy were included in the review.

Exclusion criteria

For the purpose of this review, published reviews and editorial opinions, studies that were not in the English language, and studies that did not report on liver abnormalities and/or its associated symptoms associated with antipsychotic drug therapy in children and adolescents were excluded.

6.2.1.3 Results of the literature review

The search resulted in 28 published papers. After removing duplicates and reviewing the titles and abstracts of the articles, a total of 7 papers were deemed relevant (Table 6.2). Two of the 7 publications were open-label studies which reported children who

Chapter SIX: Incidence of liver abnormalities, diabetes mellitus and extrapyramidal symptoms in a cohort of patients on antipsychotic medication

Table 6.1: Keywords used in the literature search for liver abnormalities associated with antipsychotic therapy in children and adolescents

Antipsychotic drug keywords		Population keywords	Diabetes mellitus keywords
atypical	typical	paediatric$	liver damage
antipsychotic$	antipsychotic$	adolescent$	liver toxicity
atypical	typical	adolescence	liver failure
neuroleptic$	neuroleptic$	school child$	steatohepatitis
new$	first generation	juvenile$	hepatitis
antipsychotic$	antipsychotic$	infant$	fatty liver
new$	benperidol	child$	elevated liver enzyme$
neuroleptic$	chlorpromazine	neonate$	raised liver enzyme$
second	chlorprothixene	baby	liver function test$
generation	droperidol	babies	liver$ abnormality
antipsychotic$	flupentixol	pediatric$	hepatotoxicity
amisulpride	flupenthixol	young people	hepatomegaly
amisulpiride	fluphenazine	young person$	hepatic failure
aripiprazole	fluspirilene		jaundice
clozapine	haloperidol		
olanzapine	levomepromazine		
quetiapine	loxapine		
risperidone	methotrimeprazine		
	pericyazine		
	perphenazine		
	pimozide		
	promazine		
	remoxipride		
	sulpiride		
	thioridazine		
	trifluoperazine		
	zuclopenthixol		

experienced asymptomatic changes in liver enzyme levels while being exposed to risperidone (Perry et al, 1997; Erdogan et al, 2008). Two publications were a retrospective chart review (Szigethy et al, 1999) and a retrospective study of patient records (Gonzalez-Heydrich et al, 2003). The retrospective chart review reported one patient who

Table 6.2: Published studies reporting liver abnormalities associated with antipsychotic treatment in paediatric patients

Author	Study Design	Subjects	Result Summary
Aman et al, 2005	A double-blind placebo-controlled trial followed by open-label extensions to investigate acute and long-term safety of risperidone in children and adolescents	• A total of 101 children participated in the placebo-controlled study (Mean age = 8.8 years (±2.7 years); 82 participants were males and the remaining 19 were females). • Thirty-seven subjects in the placebo-group who were not responders subsequently received an 8-week trial of open-label risperidone therapy (Mean age = 8.8 years (±2.6 years); 29 participants were males and the remaining 8 were females). • A total of 63 children participated in the open-label extension (Mean age = 8.6 years (±2.8 years)).	• A statistically significant decrease in AST/SGOT levels was demonstrated in participants exposed to risperidone therapy. • However, this decrease was not clinically significant.
Erdogan et al, 2008	Open-label observational cohort study to investigate changes in liver function tests associated with risperidone therapy in	• 120 child and adolescent patients were started on risperidone therapy after a 2-week period of being drug-free. • Liver function tests and weight of	• The mean dose of risperidone given to the study subjects ranged from 0.25 to 6mg daily. • All but one child experienced an

	children and adolescents	patients were monitored during follow-up visits throughout the study duration.	asymptomatic increase in liver enzymes. • ALT levels increased up to 3-fold and AST levels up to 2-fold. • Change in levels of GGT was significantly related to gender; males experienced a higher change in mean value compared to females (p = 0.022). • Mean body weight increased for the majority of study subjects 57.4% of all study subjects) and extreme weight gain (defined as a weight increase of 7% of more from baseline measurements) was seen in 28.7% of study subjects. However, there was no significant correlation between liver enzyme changes and increase in weight.
Gonzalez-Heydrich et al, 2003	Retrospective study of computerised patient records evaluating liver enzyme evaluations in patients exposed to olanzapine, divalproex (semisodium valproate) or a combination of both agents	• All patients under 18 years of age who were prescribed olanzapine, divalproex between January 1998 and Dcember 1999 with serum levels of ALT, AST, or LDH documented. • A total of 52 children were identified; 17 of these received	• At least one liver enzyme (ALT, AST or LDH) were elevated above the normal range in all of the patients who received olanzapine-divalproex combination therapy, in 59% of patients who received olanzapine therapy alone and in 26% of patients who received divalproex alone. • The mean enzyme level (the average of all

		olanzapine, 12 received a combination of olanzapine and divalproex and 23 received divalproex.	the measured levels for each liver enzyme investigated) was elevated above the normal range in 83% of patients who received the olanzapine-divalproex combination therapy, in 47% of patients who received olanzapine therapy alone and in 17% of patient who received divalproex alone. • One patient (male; 13 years of age) on olanzapine-divalproex combination therapy presented symptoms of abdominal discomfort, nausea, tenderness and vomiting and was diagnosed as to having acute pancreatitis. Both olanzapine and divalproex were discontinued. However, the hepatic enzymes started to rise and peaked at 6 days later. The last laboratory results from the patient were on day 8 where AST and ALT levels decreased moderately. • One patient received divalproex therapy for many years with normal liver function before olanzapine was added. The patient experienced weight gain, elevations in liver enzymes and developed steatohepatitis while on combination therapy. Subsequently, his ALT returned

			to normal range with diet and weight loss and olanzapine was switched to risperidone.
Holtmann et al, 2003a	Case report	• One case. • 17 year old female.	• Patient was first given clozapine for the management of psychosis (300mg daily). • While on clozapine, patient experienced weight gain and mild elevation in liver enzymes. • Patient was then put on risperidone (titrated to 4mg daily) after 4 weeks due to the inconveniences of regular blood cell counts required with clozapine treatment. • While on risperidone, patient's liver enzymes increased further (GGT = 27U/l, AST = 61 U/l, ALT = 108 U/l), as well as triglycerides and LDL-cholesterol. • Dose of risperidone was reduced to 1mg daily but liver enzymes, cholesterol and triglycerides remained moderately elevated. • Antipsychotic therapy was stopped after 12 months due to weight gain,

			amenhorrheoa, and extensive abdominal striae rubrae. • After 10 weeks, patient experienced a relapse of psychosis and at readmission liver enzymes were still moderately elevated and patient presented with fatty infiltration of the liver. • Patient was then started on amisulpride and after 3 months following the withdrawal of risperidone, liver function tests returned to near normal values and body weight also decreased moderately.
Kumra et al, 1997	Case series	• Thirteen children who had been treated with risperidone from December 1993 to April 1996 were included in the case series (10 females and 3 males).	• One child (male, age = 17 years) on a dose of 4mg twice daily of risperidone developed an elevation of aminotrasferace levels suggestive of hepatocellular injury. Findings from an abdominal ultrasound suggested fatty infiltration of the liver. • The subject gained 16.1kg during the 17 months of treatment with risperidone and setraline (BMI at time of liver injury = 33.1kg/m^2). • Patient's medications, including

			risperidone, were tapered off. • One week after risperidone cessation, the patient's liver function test results were still abnormal and a liver biopsy was conducted which showed the presence of mild spotty necrosis and marked fatty change which may have represented early steatohepatitis. • The subject's liver function test results normalised over a period of 3 months; however, his weight did not change. • Another child (male, age = 9 years)on a dose of 6mg daily of risperidone developed significant elevations of liver transaminase levels which were 2 to 3 times above reference values as well as elevated cholesterol and triglyceride values. • An abdominal ultrasound revealed minimal fatty infiltration. • Upon cessation of risperidone, the subject's liver function test values returned to normal over a period of 2

			weeks.
Perry et al, 1997	Open-label pilot trial of risperidone in children and adolescents with pervasive developmental disorder	• A total of 6 patients on risperidone for the treatment of pervasive developmental disorders were included in the study. • Five participants were male and one was female. The mean age of participants was 10.7 years (± 3.3 years).	• Of the 6 participants, one subject (age = 17.5 years) experienced elevations in liver enzymes (SGOT = 43 U/l, SGPT = 87) with a dramatic increase in weight (28 kg) during the first 6 months of risperidone therapy. Risperidone (6mg daily) was withdrawn on the advice of a consultant liver specialist. • Another subject (age = 7 years) experienced moderate elevations in liver enzymes (SGOT = 48 U/l, SGPT = 54) after 14 months of exposure to risperidone.
Szigethy et al, 1999	Retrospective chart review to investigate the rate and clinical factors associated with liver dysfunction in children exposed to risperidone therapy	• A total of 38 children and adolescents (32 males and 6 females; mean age = 10.6 years) were identified.	• The mean dose of risperidone given was 2.5mg daily (range = 0.5 to 10mg) and the mean length of treatment exposure was 15.2 months (range = 1 to 35 months). • Only one patient experienced a slight elevation of ALT outside the reference range (ALT = 46U/l) while exposed to risperidone. This subject also became significantly obese during treatment.

ALT - alanine aminotransferase; AST - aspartate aminotransferase; GGT - gamma glutamyl transferase; SGOT - serum glutamic oxaloacetic transaminase; LDH – lactate dehydrogenase; SGPT - Serum glutamic pyruvic transaminase

experienced a slight elevation in liver enzyme levels (Szigethy et al, 1999) where as the retrospective study on patients' records described the percentage and severity of liver enzyme elevations in children exposed to olanzapine, divalproex (semisodium valproate) or a combination of both agents (Gonzalez-Heydrich et al, 2003). One publication was a double-blind placebo-controlled trial followed by open-label extensions which investigated the safety and tolerability of risperidone therapy in children (Aman et al, 2005). Unlike the results presented from the open-label studies (Perry et al, 1997; Erdogan et al, 2008), the placebo-controlled trial with open-label extensions by Aman et al (2005) demonstrated a decrease in liver enzyme levels in risperidone-exposed patients, which was statistically, though not clinically, significant. Fatty infiltration of the liver, or steatohepatitis, in combination with elevations of liver enzyme levels were presented as a case report and case series in children and adolescents exposed to atypical antipsychotic agents including clozapine and risperidone (Kumra et al, 1997; Holtmann et al, 2003a).

All of the published studies included in the review reported on atypical antipsychotic drugs. The majority of papers reported liver abnormalities associated with risperidone therapy in children and adolescents (Kumra et al, 1997; Perry et al, 1997; Szigethy et al, 1999; Aman et al, 2005, Erdogan et al, 2008). One case report presented steatohepatitis in a child initially given clozapine followed by risperidone (Holtmann et al, 2003a), and one publication investigated liver enzyme levels in children exposed to olanzapine therapy

alone or a combination of olanzapine and divalproex therapy (Gonzalez-Heydrich et al, 2003).

6.2.1.4 Discussion of the literature review

For a number of the published studies included in this review, assessments on causality are limited. This is especially true for studies which reported patients who experienced liver abnormalities while also being exposed to other medications including divalproex (Gonzalez-Heydrich et al, 2003) and carbamazepine (Perry et al, 1997).

It has been stated that steatohepatitis, or fatty liver, is probably due to the excessive weight gain experienced by patients on antipsychotic therapy (Gonzalez-Heydrich et al, 2003). As children have been reported to be more susceptible to the effects on weight by antipsychotic drug therapy (Safer, 2004; Correll, 2008), they too could be more at risk to developing steatohepatitis. However, not all patients on antipsychotic therapy who experienced significant weight gain developed liver abnormalities, as shown in the retrospective chart review by Szigethy et al (1999).

It has also been proposed that gender may have an influence on the development of liver abnormalities antipsychotic-exposed children where male patients are suggested to be more susceptible to this event (Kumra et al, 1997). However, the lack of controls and the

small sample sizes of the published studies limit more meaningful conclusions with regards to possible contributing factors to developing liver injuries.

Results from the published studies also indicate that liver abnormalities including changes in liver enzyme levels or steatohepatitis appear to be reversible with drug cessation and/or weight loss (Kumra et al, 1997; Gonzalez-Heydrich et al, 2003; Holtmann et al, 2003a; Erdogan et al, 2008).

As with other serious albeit relatively rare adverse effects associated with antipsychotic therapy in children such as diabetes mellitus, the majority of published studies are subject to limitations concerning small sample sizes (Kumra et al, 1997; Perry et al, 1997; Aman et al, 2005; Erdogan et al, 2008), short durations of study, and limited analysis with regards to causality (Gonzalez-Heydrich et al, 2003). This is seen to be the case for a number of publications included in this review. These reports on cases of liver abnormalities in children exposed to antipsychotic therapy further intensify the uncertainty about the incidence and clinical relevance of elevations in liver enzymes in this population.

Following that, the aim of this study was to investigate the incidence and nature of liver abnormalities related to antipsychotic therapy, using the large cohort of paediatric patients identified from Chapter 4.

6.2.2 Methodology

Data source

The data for this study were obtained from the GPRD. The history of the GPRD and validation of its data is described in more detail in Chapter 3.

The study population and data extraction methods are described in detail in Chapter 3. Patients who received at least one prescription for an antipsychotic during the defined study period between 1 January 1992 and 31 December 2005 were included in the study.

A similar methodology investigating the risk of acute liver injury with the use of antifungal drugs in adults was adapted (Rodriguez et al, 1999). Patients with a history of cancer, liver disease, cystic fibrosis, gallbladder disease, pancreatic disease, heart failure, HIV infection, rheumatoid arthritis, sarcoidosis, systemic lupus, or inflammatory bowel disease, prior to the first prescription of an antipsychotic were excluded from the study.

Ethics approval was granted by the GPRD's Scientific and Ethical Advisory Group (SEAG) and the Independent Scientific Advisory Committee (ISAC) for Medicines & Healthcare products Regulatory Agency (MHRA) database research (Appendix J).

Chapter SIX: Incidence of liver abnormalities, diabetes mellitus and extrapyramidal symptoms in a cohort of patients on antipsychotic medication

Cases of liver abnormalities

Cases were identified from the cohort described in Chapter 4. The identification of cases was adapted from a similar methodology investigating the risk of acute liver injury with the use of antifungal drugs in adults (Rodriguez et al, 1999). Patients in the cohort were followed from the date of the first antipsychotic drug prescription until the earliest occurrence of a code of liver damage, age greater than 18 years, or end of the study period.

Cases of acute liver injury were identified by screening patients' medical records for clinical or referral events with a Read/OXMIS code indicating an event related to liver abnormalities (Appendix K). Test events such as liver function tests, liver enzyme levels (alanine aminotransferase, alkaline phosphatise, aspartate aminotrasnferase, bilirubin, gamma-glutamyl transerase) were also used to identify subjects with liver abnormalities.

Liver injury was defined following an international consensus meeting on drug-induced liver disorders (Report of an international consensus meeting, 1990). Cases of acute liver injury were defined as patients with symptoms suggestive of liver disorder such as asthenia, abdominal pain, nausea, vomiting, pruritus, jaundice, referrals to specialists or admissions to hospitals, and patients who were free of the exclusion criteria. Additionally, biochemical test results were investigated. Patients with a code related to liver injury and/or biochemical abnormalities in liver function tests were reviewed independently

after removing drug exposure status by Dr Patrick Byrne[5], a consultant child and adolescent psychiatrist. Patients with both a code related to liver injury with an increase over 2 times the upper limit of the reference range in any biochemical parameters related to liver function tests were considered as cases. The patient profile of each identified case was examined. An example of a patient profile is given in Appendix D.

Data analysis

Liver injury is an extremely rare event in the general paediatric population, even in the presence of antipsychotic treatment (Geller & Zuiderwijk, 1998). Therefore a descriptive analysis on the incidence of liver injury was conducted. For case confirmation, a causality assessment adapted from the WHO-UMC system for standardised case causality assessment method (Uppsala Monitoring Centre) was carried out to determine the likelihood of a relationship between the drug and the event of liver abnormality. The use of this system for assessing the relationship between the drug exposure and the adverse event requires knowledge of certain information. Therefore, the patient profiles, clinical records, antipsychotic exposure duration, as well as all therapy records of all cases identified were examined. The criteria used for the causality assessment categories are shown in Table 6.3. After conducting the analysis on the causality assessment, it was also

[5] Dr Patrick Byrne MMedSci FRCPsych
Consultant in Adolescent Psychiatry & Hon Research Associate IoP
South London & Maudsley NHS Trust

assessed independently by Professor Ian Wong[6], a paediatric pharmacoepidemiologist and Dr Patrick Byrne[7], a consultant child and adolescent psychiatrist. Cases where the antipsychotic therapy were deemed *possibly*, *probably*, and *certainly* associated with the event of liver abnormalities were categorised as adverse drug reactions.

Once cases were identified, the incidence of liver adverse events was calculated per 1,000 person-years at risk. Following analysis on exposure status (new cases of adverse events that occurred during the exposure plus a latency washout period of 30 days were considered as treatment-emergent) and causality assessments, the incidence of liver adverse drug reactions in the cohort were calculated per 1,000 treatment-years at risk. Cases where the antipsychotic therapy were classified as *possibly*, *probably*, or *certainly* associated with the liver abnormality (from the analysis on causality assessments, Table 6.3) were deemed as adverse drug reactions.

[6] Professor Ian Chi Kei Wong, Director and Professor of Paediatric Medicines Research,
Centre for Paediatric Pharmacy Research, A collaboration between the School of Pharmacy, Institute of Child Health & Great Ormond Street Hospital for Children

[7] Dr Patrick Byrne MMedSci FRCPsych
Consultant in Adolescent Psychiatry & Hon Research Associate IoP
South London & Maudsley NHS Trust

Table 6.3: Categories used for the causality assessment for cases of liver abnormalities in the study cohort

Causality term	Assessment criteria
Certain	• Event of liver abnormality with a plausible time relationship to drug intake • Event cannot be explained by other disease or drugs • Event definitive pharmacologically or phenomenologically • Rechallenge satisfactory
Probably / Likely	• Event of liver abnormality with reasonable time relationship to drug intake • Event unlikely to be attributed to other disease or drugs • Response to withdrawal clinically reasonable • Rechallenge not required
Possible	• Event of liver abnormality with reasonable time relationship to drug intake • Event could be possibly explained by disease or other drugs • Information on drug withdrawal may be lacking or unclear
Unlikely	• Event of liver abnormality with a time to drug intake that makes a relationship improbable, but not impossible • Disease or other drugs provide plausible explanations

6.2.3 Results

A total of 2,767 children (contributing 6,007 person-years at risk for an adverse event and 2,041 treatment-years at risk for an adverse drug reaction) who received at least one prescription an antipsychotic were previously identified (Rani et al, 2008b). From this cohort, a total of 36 patients had an event related to liver abnormalities after their first prescription for an antipsychotic agent. However, only 6 patients (from 5,924 person-years at risk for an adverse event and 2,019 treatment-years at risk for an adverse drug

reaction) out of the 36 were classified as cases from the inclusion criteria. After excluding patients with a previous history of cancer and/or liver injury (see exclusion criteria) the incidence of liver adverse events in the cohort was 1.01 cases per 1,000 person-years at risk (95% CI: 0.20 to 1.82 cases per 1,000 person-years).

From the analysis on causality assessments (Table 6.4), 5 of the 6 cases did not have a time relationship between the antipsychotic drug intake and the event of liver abnormality. For the one case which had a time relationship (Patient 3), the patient was found to have suffered from a paracetamol overdose which was likely the cause of the liver abnormality. Following the overdose, the patient was continued on the antipsychotic agent and no further liver abnormalities were observed. Therefore results on the causality assessment demonstrated that all of the cases of liver abnormalities were *unlikely* to be associated with antipsychotic therapy. Hence the incidence of liver adverse drug reactions in the study cohort was 0 cases per 1,000 treatment-years at risk (95% CI: 0 to 1.82 cases per 1,000 treatment-years).

A summary of the results including the incidence rates is illustrated in Figure 6.1

Table 6.4: Causality assessment on the 6 cases of liver abnormalities

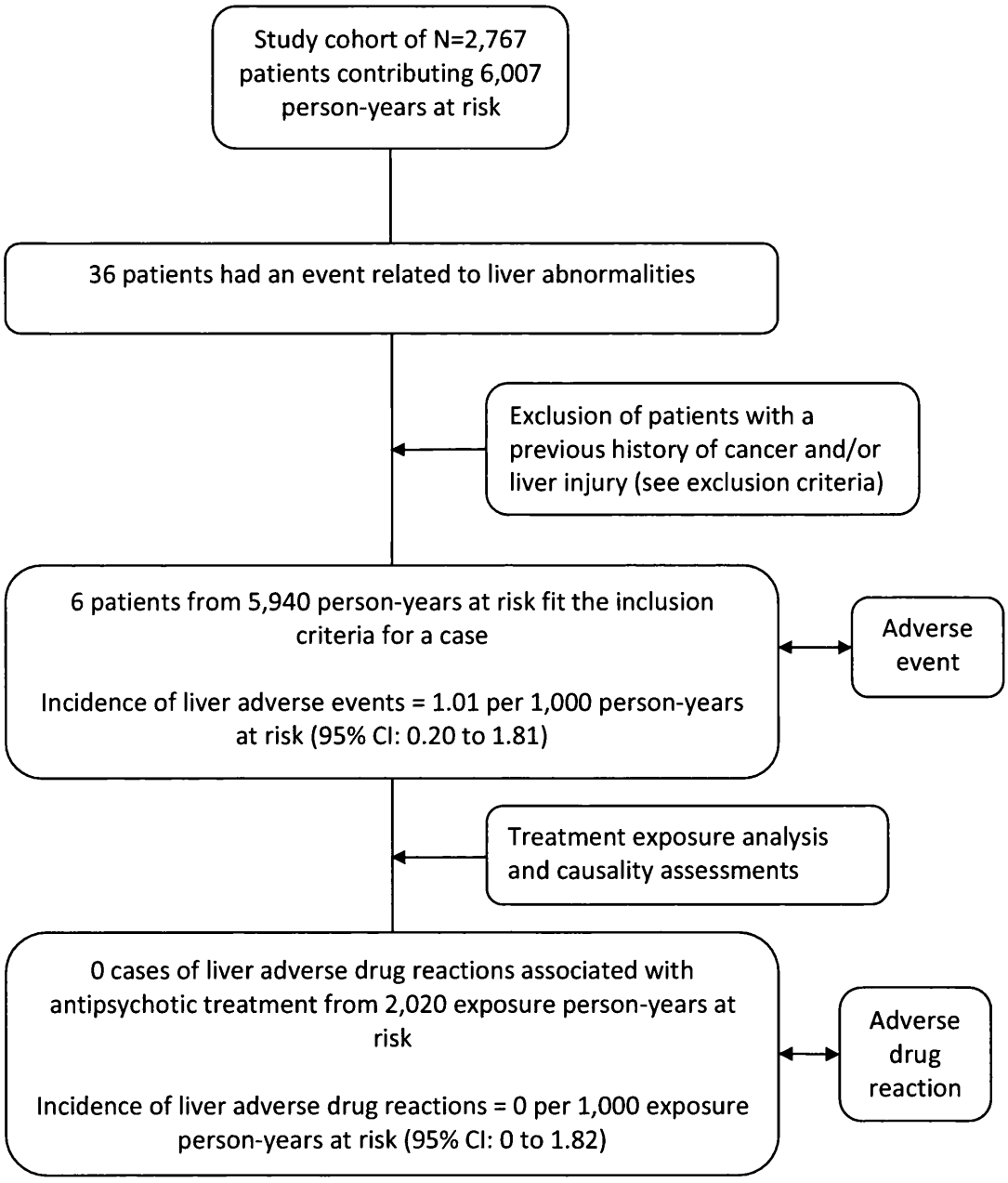
Patient	Gender	Age at event	Liver abnormality	Antipsychotic agent	Causality assessment	Outcome
1	Female	17	i. Liver function test abnormal ii. Abdominal pain	Not exposed at the time of event	• Subject was not exposed to antipsychotic therapy when the event of liver abnormality occurred, demonstrating a poor time relationship between drug intake and the event. • 'Alcohol consumption' was also recorded in the subject's electronic patient profile.	• Antipsychotic drug *unlikely* to be associated with the liver abnormality in this case.
2	Male	16	i. Raised plasma gamma-glutamyl transferase level (>2N) ii. Abdominal pain iii. Nausea iv. Tiredness	Not exposed at the time of event	• Subject was not exposed to antipsychotic therapy when the event of liver abnormality occurred, demonstrating a poor time relationship between drug intake and the event.	• Antipsychotic drug *unlikely* to be associated with the liver abnormality in this case.
3	Female	18	i. Raised ALT blood level (>2N) ii. Abdominal pain	Amisulpride	• Subject developed symptoms of liver abnormalities while exposed to amisulpride therapy, indicating	• Antipsychotic drug *unlikely* to be associated with the

					a reasonable time relationship between drug intake and the event. • However, subject was revealed to have paracetamol poisoning at the time of the event. • Following the event of liver abnormality, amisulpride was continued and no further events related to liver abnormalities were seen.	liver abnormality in this case.
4	Male	17	i. Serum bilirubin raised (>2N) ii. Malaise	Not exposed at the time of event	• Subject was not exposed to antipsychotic therapy when the event of liver abnormality occurred, demonstrating a poor time relationship between drug intake and the event. • 'Sickle cell anaemia' was also recorded in the subject's electronic patient profile, providing a possible explanation for the symptoms of liver abnormality.	• Antipsychotic drug *unlikely* to be associated with the liver abnormality in this case.
5	Female	16, 17, 18	i. Raised ALT level (>2N)	Not exposed at the time of	• Subject was not exposed to	• Antipsychotic drug

			ii. Raised serum alkaline phosphatase level (>2N) iii. Raised ALT/SGPT serum level (>2N) iv. Raised gamma-glutamyl transferase level (>2N)	event	antipsychotic therapy when the event of liver abnormality occurred, demonstrating a poor time relationship between drug intake and the event. • Subject was also taking mesalazine, cyclosporin and suffered from iron deficiency anaemia, which provides possible explanations for the symptoms of liver abnormality.	*unlikely* to be associated with the liver abnormality in this case.
6	Female	15	i. Increased ALT/SGPT serum level (>2N) ii. Jaundice	Not exposed at the time of event	• Subject was not exposed to antipsychotic therapy when the event of liver abnormality occurred, demonstrating a poor time relationship between drug intake and the event. • Subject was also suffering from epilepsy and was taking lamotrigine therapy, which provide possible explanations for the symptoms of liver abnormality.	• Antipsychotic drug *unlikely* to be associated with the liver abnormality in this case.

Chapter SIX: Incidence of liver abnormalities, diabetes mellitus and extrapyramidal symptoms in a cohort of patients on antipsychotic medication

Figure 6.1: Summary of the results on incidence of liver abnormalities



6.2.4 Discussion

Results on the incidence of liver abnormalities show an incidence rate of 1.01 cases per 1,000 person-years at risk for an adverse event (95% CI: 0.20 to 1.81 cases per 1,000 person-years at risk). However, after conducting analysis on exposure status and causality assessments, is was revealed that none of the identified cases were likely to be caused by antipsychotic therapy, bringing the incidence of liver adverse drug reactions to 0 cases per 1,000 treatment-years at risk for an adverse drug reaction (95%CI: 0 to 1.82 cases per 1,000 treatment-years at risk). A low incidence rate is to be expected as liver injury in the paediatric population is a very rare event.

Nonetheless, among over a thousand drugs that are known to induce hepatic side effects, 16% of these are psychotropic agents, including antipsychotic drugs (Llinares Tello et al, 2005). Although antipsychotic-induced liver toxicity is considered a rare event and is more associated with the typical antipsychotic agents from the phenothiazine group such as chlorpromazine, hepatic adverse effects associated with the atypical antipsychotic drugs clozapine, risperidone and olanzapine have also been reported in both adults and children (Fuller et al, 1996; Hummer et al, 1997; Kumra et al, 1997; Cordeiro & Elkis, 2001; Gaertner et al, 2001; Llinares Tello et al, 2005).

As previously discussed in the literature review, changes in liver enzyme levels are considered to be a common effect in patients exposed to typical and atypical

antipsychotic agents (Woods et al, 2002). This increase is thought to be transient and is eventually resolved in the majority of subjects without disruptions in pharmacological management, which suggests that the elevations are more of adaptive changes of liver functions as a result of drug exposure rather than actual liver injuries (Hummer et al, 1997; Gaertner et al, 2001; Erdogan et al, 2004). More importantly, children and adolescents exposed to antipsychotic therapy are reported to have significantly higher risk ratios for developing abnormal liver function test results compared to patients from adult populations (Woods et al, 2002). Although these liver enzyme elevations are assumed not to have clinical significance, there is a lack of data regarding possible long-term clinical effects in patients (Gonzalez-Heydrich et al, 2003).

Although liver function test abnormalities in antipsychotic-exposed children and adolescents are relatively common, serious hepatotoxicity as a result of antipsychotic drug exposure is considered to be extremely rare (Erdogan et al, 2008). In adults however, serious liver injuries including fatal fulminant hepatitis (Macfarlane et al, 1997) and icteric hepatitis (Thatcher et al, 1995; Worrall et al, 1995) have been demonstrated. Another form of liver injury which has been demonstrated in antipsychotic-treated adult subjects is cholestatic hepatitis (Llinares Tello et al, 2005). Cholestatic hepatitis is the result of liver injury and inflammation which leads to significant increases in liver enzyme levels as well as cholestasis (an arrest of the normal flow of bile) (Llinares Tello et al, 2005).

Chapter SIX: Incidence of liver abnormalities, diabetes mellitus and extrapyramidal symptoms in a cohort of patients on antipsychotic medication

Other manifestations of liver injury associated with antipsychotic medication are steatohepatitis, or fatty liver, which has been reported in adolescents treated with risperidone (Kumra et al, 1997; Holtmann et al, 2003a). This condition is a result of the accumulation of fatty acids, chiefly triglycerides and symptoms include transient abdominal pain and hepatomegaly (Baldridge et al, 1995). Proposed contributing factors include obesity, high lipid levels, male gender, and possibly hormonal changes associated with pubertal development (Baldridge et al, 1995; Kumra et al, 1997; Gonzalez-Heydrich et al, 2003; Holtmann et al, 2003a). As antipsychotic medications are commonly associated with weight gain (Casey et al, 2004; Dubois, 2005; Laita et al, 2007), there is an increased risk of obesity which in turn may raise the risk of harmful effects on the liver including steatohepatitis and hepatotoxicity. Nonetheless, as discussed in the literature review, not all patients who experience significant increases in weight develop liver abnormalities (Szigethy et al, 1999). It should also be noted that children diagnosed with steatohepatitis present fatty livers with prominent vesicular changes. Additionally, although fibrosis may not be present in adult cases of non-alcoholic steatohepatitis, portal fibrosis has been demonstrated to be prominent in children presenting with this condition. These fibrotic changes are potentially serious as it may well lead to further hepatic complications such as chronic liver dysfunction and cirrhosis (Baldridge et al, 1995; Erdogan et al, 2004).

Therefore, although increases in liver enzymes is considered a common effect related to antipsychotic therapy, patients who present with these enzyme elevations should also be screened for additional symptoms indicative of more serious liver abnormalities related to hypersensitivity including gastrointestinal complaints, rash, fever, muscle aches, and eosinophilia (Hummer et al, 1997; Erdogan et al, 2004). Rarely, treatment with perphenazine, a typical antipsychotic drug, also causes asymptomatic rises in bilirubin levels (Gaertner et al, 2001).

Following this, it should be highlighted that the low incidence presented in this study does not suggest an absence of risk, but indicates the necessity for more well-monitored trials with ideally larger sample sizes to investigate the occurrence of liver abnormalities as well as the significance of liver enzyme changes in children exposed to antipsychotic medication.

Chapter SIX: Incidence of liver abnormalities, diabetes mellitus and extrapyramidal symptoms in a cohort of patients on antipsychotic medication

6.3 Incidence of diabetes mellitus

6.3.1 Systematic literature review on diabetes mellitus associated with antipsychotic therapy in children and adolescents

6.3.1.1 Aim of the literature review

To review published studies which have reported cases or rates of diabetes mellitus associated with children and adolescents exposed to antipsychotic therapy.

6.3.1.2 Methodology of the literature review

A Medline (1950 to 02/07/2008) search was conducted using the keywords listed in Table 6.5.

Inclusion criteria

Studies reporting the development of diabetes mellitus, or the manifestation of symptoms associated with the condition in children and adolescents exposed to antipsychotic therapy were included in the review.

Exclusion criteria

For the purpose of this review, published reviews and editorial opinions, studies that were not in the English language, and studies that did not report on diabetes mellitus and/or its associated symptoms associated with antipsychotic drug therapy in children and adolescents were excluded.

Table 6.5: Keywords used in the literature search for diabetes mellitus associated with antipsychotic therapy in children and adolescents

Antipsychotic drug keywords		Population keywords	Diabetes mellitus keywords
atypical	typical	paediatric$	diabetes
antipsychotic$	antipsychotic$	adolescent$	diabetes mellitus
atypical	typical	adolescence	hyperglycaemia
neuroleptic$	neuroleptic$	school child$	hyperglycemia
new$	first generation	juvenile$	blood sugar
antipsychotic$	antipsychotic$	infant$	blood glucose
new$	benperidol	child$	diabetic
neuroleptic$	chlorpromazine	neonate$	diabetic ketoacidosis
second	chlorprothixene	baby	
generation	droperidol	babies	
antipsychotic$	flupentixol	pediatric$	
amisulpride	flupenthixol	young people	
amisulpiride	fluphenazine	young person$	
aripiprazole	fluspirilene		
clozapine	haloperidol		
olanzapine	levomepromazine		
quetiapine	loxapine		
risperidone	methotrimeprazine		
	pericyazine		
	perphenazine		
	pimozide		
	promazine		
	remoxipride		
	sulpiride		

thioridazine trifluoperazine zuclopenthixol		

6.3.1.3 Results of the literature review

The search resulted in 51 published papers. After removing duplicates and reviewing the titles and abstracts of the articles, a total of 10 papers were deemed relevant. From these 10 publications, 4 were case reports (Domon & Webber, 2001; Selva & Scott, 2001; Courvoisie et al, 2004; Logue et al, 2007), 2 were case series (Saito & Kafantaris, 2002; Bloch et al, 2003), 2 were reports of spontaneous adverse events using the Food and Drug Administration's MedWatch Drug Surveillance System in the USA (Koller & Malozowski, 2001; Koller et al, 2004) and 2 were cohort studies (Harrison-Woolrych et al, 2007; Jerrell & McIntyre, 2008).

The majority of published studies included in the review reported on atypical antipsychotic drugs. Only one paper included typical antipsychotic agents as part of the retrospective cohort study (Jerell & McIntyre, 2008). The atypical antipsychotic olanzapine was the most commonly reported antipsychotic agent to be associated with diabetes mellitus among the published case reports and case series (Domon & Webber, 2001; Selva & Scott, 2001; Bloch et al, 2003; Courvoisie et al, 2004). Other atypical antipsychotic agents reported in the published case reports and case series include risperidone in 2

adolescents (Saito & Kafantaris, 2002) as well as quetiapine and aripiprazole in an adolescent patient and one child respectively (Saito & Kafantaris, 2002; Logue et al, 2007).

The 2 published reports on spontaneous adverse drug events presented paediatric patients with diabetes mellitus who were exposed to risperidone (Koller et al, 2004), olanzapine and clozapine (Koller & Malozowski, 2001). A more detailed description of the published papers included in the review is shown in Table 6.6.

Table 6.6: Published studies reporting diabetes mellitus associated with antipsychotic treatment in paediatric patients

Author	Study Design	Subjects	Result Summary
Bloch et al, 2003	Case series.	• Five cases. • Ages 14 to 17 years. • Three females and 2 males.	• All case reports involved paediatric patients exposed to olanzapine. • All cases developed hyperglycaemia (fasting blood glucose levels 148 – 402 mg/dL; 36 – 120 days after starting olanzapine therapy). • All patients were extremely obese. • Only one patient had a family history of diabetes mellitus. • Diabetes mellitus was resolved in 3 of the five patients; where as the remaining 2 patients eventually developed diabetes mellitus.
Courvoisie et al, 2004	Case report.	• One case. • 7 year old male.	• Patient on olanzapine with a dose of 2.5mg every night. • Patient had hyperglycaemia (serum glucose level reported was 302 mg/dL) and trace amounts of urine ketones were reported.

			• Insulin was administered to stabilise the patient's blood sugar level. • Insulin was discontinued after one week from hospital discharge. • Patient had strong family history of diabetes and had gained considerable weight during olanzapine therapy. • Following the cessation of olanzapine, the patient's weight decreased and need for insulin was reversed. • Two years after initial presentation, the patient was diagnosed with diabetes mellitus.
Domon & Webber, 2001	Case report.	• One case. • 15 year old male.	• Patient exposed to olanzapine. • Patient had a strong family history for type II diabetes mellitus. • Patient was obese at initial stages of olanzapine treatment and gained weight when examined 4 months after presentation (BMI = 34.1 kg/m^2). • Three months later, patient experienced significant weight loss and symptoms consistent with diabetes mellitus including polyuria and

			polydipsia. • Olanzapine was then discontinued. • No pharmacological or dietary management was given. • Blood glucose levels normalised after 8 weeks.
Harrison-Woolrych et al, 2007	Observational cohort study.	• A total of 420 children aged 2 to 15 years (contributing to 641.2 patient-years of exposure) were identified. • Cohort was identified from the Intensive Medicines Monitoring Program databases in New Zealand. • All children aged 15 years and below who were prescribed atypical antipsychotic agents between April and July 2003 were included in the cohort.	• A total of 2 reports of diabetes mellitus was identified from the study cohort. • Both reports were male patients exposed to risperidone. • One patient (13 years of age) developed new-onset diabetes and the remaining patient (9 years of age) experienced a worsening of pre-existing diabetes mellitus which resulted in severe diabetic ketoacidosis and encephalopathy. • The estimated incidence of new-onset diabetes or exacerbation of pre-existing diabetes mellitus in the study population was 4 cases per 1,000 patient-years (95% CI: 0.5 to 15).
Jerrell & McIntyre, 2008	Retrospective cohort study.	• A total of 4140 children exposed to antipsychotic therapy were identified.	• A regression analysis was conducted to determine the likelihood of patients exposed to antipsychotic therapy to develop diabetes

		• Average age of patients in the cohort exposed to antipsychotic therapy was 10.4 years (SD = 3.6 years). • Cohort was identified from the Medicaid database in the USA, and included all patients aged 17 years and under from 1996 to 2005.	mellitus. • The odds ratio of developing metabolic conditions of type II diabetes and dyslipidaemia was shown to be higher for females (odds ratio = 2.04; 95%CI: 1.59 to 2.63; $p < 0.0001$), those exposed to multiple antipsychotic therapy (odds ratio = 2.65; 95%CI: 1.47-4.74; $p = 0.001$), and patients aged 13 years and older (odds ratio = 1.80; 95%CI: 1.39 to 2.33; $p < 0.0001$).
Koller & Malozowski, 2001	Report of spontaneous adverse events.	• Data source was the Food and Drug Administration's MedWatch Drug Surveillance system of the USA (January 1993 to May 2001). • All cases reporting olanzapine- and clozapine-associated diabetes mellitus in patients aged below 19 years were reported. • Nine reports of hyperglycaemia associated with olanzapine treatment in patients aged 13 to 18 years were identified. Five of these were females and the	• Among the reports of olanzapine-associated diabetes mellitus, 7 of these presented with new-onset hyperglycaemia, and the remaining 2 experienced a worsening of pre-existing diabetes mellitus. • The dosing range for olanzapine in these patients were 10 to 20mg daily. • Two patients presented with hyperglycaemia within one week of starting olanzapine, and 6 patients presented with hyperglycaemia within 6 weeks of drug initiation. • Glucose levels in 4 patients normalised after cessation of or a reduction in dosage of olanzapine treatment.

		remaining 4 were males. • Eleven reports of hyperglycaemia associated with clozapine treatment in patients aged 13 to 18 years were identified. Four of these were females and the remaining 7 were males.	• Hyperglycaemia recurred in one patient after 6 months of stopping olanzapine treatment • Among the reports of clozapine-associated diabetes mellitus, 8 of these presented with new-onset hyperglycaemia, 2 experienced a worsening of pre-existing diabetes mellitus, and the status of one subject was not provided. • The dosing range for clozapine in these patients were 100 to 1000mg daily. • Presentation of hyperglycaemia was 6 weeks from drug commencement in 6 subjects, and within 6 months for the remaining 5 patients • Clozapine treatment was stopped, or the dose decreased in 6 patients. Glucose normalisation was achieved in 3 of these subjects.
Koller et al, 2004	Report of spontaneous adverse events.	• Data source was the Food and Drug Administration's MedWatch Drug Surveillance system of the USA (January 1993 to February 2002) • Twelve children were identified among over 100 risperidone-associated	• All patients were exposed to risperidone, with a dosing range of 1 to 10 mg daily. • Among the cases which presented with new-onset diabetes mellitus, 7 subjects developed the condition within 6 months of starting risperidone therapy. • Two patients had ketoacidosis.

		diabetic adverse-event reports. • Mean age of children was 13.5 years (SD = 3 years). • Seven children were male and the remaining 5 were female.	• Hyperglycaemia normalised after risperidone was discontinued in 3 patients, including in one subject who was also given dietary management.
Logue et al, 2007	Case report.	• One case. • 7 year old male.	• Patient was exposed to aripiprazole with a dose of 2.5mg daily. • Patient was overweight, with a BMI of 21kg/m^2 (98^{th} percentile). • Patient had a positive family history of type II diabetes mellitus. • Within 4 weeks of aripiprazole (no other treatment), the patient developed symptoms consistent with new-onset diabetes including hyperglycaemia (659mg/dL), mild ketonuria, polyuria, polyphagia and polydipsia. • Aripiprazole was discontinued and patient was given NPH (Neutral Protamine Hagedorn, an intermediate acting insulin) and Humalin insulin. • After 4 weeks of subcutaneous insulin treatment,

			the patient's blood sugar levels normalised. • Seven months after the patient's initial presentation, he developed insulin-dependent diabetes mellitus.
Saito & Kafantaris, 2002	Case series.	• Three cases. • Ages 13 to 17 years. • One female and 2 males.	• Two patients were exposed to risperidone and one patient to quetiapine. • All patients were obese (BMI ranging from 35 to 43 kg/m^2). • All patients presented symptoms consistent with diabetes mellitus including polydipsia, trace ketones and hyperglycaemia (fasting blood glucose ranging from 155 to 1,292 mg/dL). • For the management of diabetes mellitus, 2 patients were given insulin (one eventually switched to metformin) and one patient was given dietary management.
Selva & Scott, 2001	Case report.	• One case. • 16 year old female.	• Patient was exposed to olanzapine with a dose of 10mg daily, which was increased to 15mg daily. • Patient had a strong family history for type II diabetes mellitus. • Patient gained 30 pounds in weight since

			olanzapine was initiated. • The patient presented symptoms including significant glucosuria, ketonuria and was reported to have a serum glucose level of 669 mg/dL. • Olanzapine was discontinued and the patient was given insulin therapy. • After 17 days, insulin was discontinued and the patient's blood glucose levels normalised. • After 6 months from initial presentation, the patient was diagnosed to have type II diabetes mellitus.

6.3.1.4 Discussion of the literature review

Despite a clear increase in the utilisation of antipsychotic drug therapy in children and adolescents in many countries (Chapter 4), there is still a lack of published safety data for these drugs in the young (Malone et al, 1999; Armenteros & Davies, 2006). Additionally, results from this literature review confirm earlier findings which indicate a gap in the literature and quantity of studies investigating diabetes mellitus in children and adolescents exposed to antipsychotic therapy (Cohen & Huinink, 2007). The majority of the publications identified in this review were case reports (Domon & Webber, 2001; Selva & Scott, 2001; Courvoisie et al, 2004; Logue et al, 2007) and case series (Saito & Kafantaris, 2002; Bloch et al, 2003) and only 2 publications were cohort studies which reported either an estimated incidence (Harrison-Woolrych et al, 2007), or an odds ratio (Jerrell & McIntyre, 2008) of developing diabetes mellitus. Of the 2 cohort studies, only the study conducted by Jerrell & McIntyre (2008) included children on typical antipsychotic agents. However, the results in the form of odds ratios which were presented in this study were not exclusive to diabetes mellitus, but were the odds ratio of developing metabolic conditions of type II diabetes mellitus as well as dyslipidaemia (Jerrell & McIntyre, 2008). The remaining cohort study (Harrison-Woolrych et al, 2007) as well as the case reports (Domon & Webber, 2001; Selva & Scott, 2001; Courvoisie et al, 2004; Logue et al, 2007), case series (Saito & Kafantaris, 2002; Bloch et al, 2003) and

reports on spontaneous adverse drug events (Koller et al, 2001; Koller et al, 2004) only reported diabetes mellitus associated with atypical antipsychotic drugs.

Five of the publications identified in this review reported diabetes mellitus associated with the atypical antipsychotic agent olanzapine (Domon & Webber, 2001; Koller et al, 2001; Selva & Scott, 2001; Bloch et al, 2003; Couvoisie et al, 2004) which incidentally, is also proposed to have one of the highest rates of weight gain in exposed children (Saito & Kafantaris, 2002).

Among the proposed factors which may contribute to the development of diabetes mellitus in paediatric patients exposed to antipsychotic therapy include a positive family history of diabetes mellitus and obesity (Cohen & Huinink, 2007). All the paediatric patients who developed diabetes mellitus in the identified published case reports and case series were overweight and/or suffered from obesity (Domon & Webber, 2001; Selva & Scott, 2001; Saito & Kafantaris, 2002; Bloch et al, 2003; Courvoisie et al, 2004; Logue et al, 2007); and the majority of these patients had a positive family history of diabetes mellitus, except for 4 patients in the case series reported by Bloch et al (2003). Although a family history of diabetes mellitus is considered a higher risk factor for patients to increase in weight and develop insulin resistance and glucose dysregulation, not all reported patients have this element (Bloch et al, 2003; Newcomer et al, 2002).

Chapter SIX: Incidence of liver abnormalities, diabetes mellitus and extrapyramidal symptoms in a cohort of patients on antipsychotic medication

It has been reported that hyperglycaemia and diabetes mellitus appears to be reversible upon cessation of the offending antipsychotic agent; and reappears when the drug is reintroduced (Rigalleau et al, 2000). Diabetes mellitus was shown to resolve upon discontinuation of the suspected antipsychotic agent in all the case reports (Domon & Webber, 2001; Selva & Scott, 2001; Courvoisie et al, 2004; Logue et al, 2007); however, 3 of these patients eventually developed diabetes mellitus between 6 months to 2 years after their initial presentation, even after the period of glucose normalisation following cessation of antipsychotic treatment (Selva & Scott, 2001; Courvoisie et al, 2004; Logue et al, 2007). This phenomenon was also presented in patients from the case series reported by Bloch et al (2003) where 2 of the 5 patients reported eventually developed diabetes mellitus even after a drug-free period. It has been proposed that the recurrence of full-blown diabetes mellitus in these patients is a reflection of the underlying predisposition of these subjects to the condition; which was unmasked with antipsychotic drug treatment (Courvoisie et al, 2004). Furthermore, cessation of the antipsychotic agent may not always result in a favourable outcome or resolved diabetes mellitus. This has been shown in published case series whereby cessation of olanzapine therapy in a patient who developed diabetes mellitus achieved only partial remission, suggesting that the condition could potentially be an irreversible side effect (Bloch et al, 2003).

Results from the spontaneous adverse events reports have also suggested the possibility of antipsychotic agents, specifically the atypical antipsychotics risperidone (Koller et al,

2004), olanzapine and clozapine (Koller et al, 2001) having the potential to further exacerbate or worsen pre-existing diabetes mellitus in exposed children.

Major limitations for the majority of these publications (case reports, case series and reports on spontaneous adverse events) include small number of study subjects, lack of control groups, confounding by concurrent medications or illnesses, as well as the incapability of conducting causality assessments to determine the likelihood of an association between the antipsychotic agent and the event of diabetes mellitus. This is especially true for the reports on spontaneous adverse drug events (Koller et al, 2001; Koller et al, 2004). It has been proposed that despite the low number of contribution of reports and allowing for reporting and publishing bias, the severity of diabetes mellitus in children exposed to antipsychotic medication remains high (Cohen & Huinink, 2007). This further highlights the need for more rigorous investigations on antipsychotic-induced diabetes mellitus in children and adolescents with ideally large sample sizes and longer study durations.

Consequently, the aim of this study was to investigate the incidence of diabetes mellitus related to antipsychotic drug therapy, using the large cohort of paediatric patients exposed to antipsychotic agents around the UK identified from Chapter 4, and compare this with the rates found in the general paediatric population.

6.3.2 Methodology

Data source

The data for this study were obtained from the GPRD. The history of the GPRD and validation of its data is described in more detail in Chapter 3.

The study population and data extraction methods are described in detail in Chapter 3. Patients who received at least one prescription for an antipsychotic during the defined study period between 1 January 1992 and 31 December 2005 were included in the study.

Patients with a history of diabetes prior to the first prescription of an antipsychotic were excluded from the study. Additionally, patients with a medical condition that may increase the likelihood of detection of diabetes mellitus such as pregnancy were excluded. Patients who are diagnosed with hyperglycaemia but without subsequent diagnoses or treatments for diabetes mellitus were also excluded.

Ethics approval was granted by the GPRD's Scientific and Ethical Advisory Group (SEAG) and the Independent Scientific Advisory Committee (ISAC) for Medicines & Healthcare products Regulatory Agency (MHRA) database research (Appendix J).

Chapter SIX: Incidence of liver abnormalities, diabetes mellitus and extrapyramidal symptoms in a cohort of patients on antipsychotic medication

Cases of diabetes

Cases were identified from the cohort described in Chapter 4. Patients in the cohort were followed from the date of the first prescription until the earliest occurrence of a clinical event related to diabetes mellitus (Appendix L), age greater than 18 years, or the end of the study period.

Cases were defined based on similar methodologies investigating the incidence of diabetes mellitus associated with antipsychotic drug use in adults (Kornegay et al, 2002; Carslon et al, 2006). Cases were defined as patients with symptoms consistent with a diagnosis of diabetes mellitus including prescriptions for oral hypoglycaemic agents, insulin, or referrals to diabetic clinics. Potential cases were confirmed by evaluating the individual patient profiles, therefore the patient profile of each identified case was examined. An example of a patient profile is given in Appendix D. The earlier date of either the first diagnosis for diabetes mellitus or the date when the hypoglycaemic agent was first prescribed was regarded as the date for a new case of diabetes mellitus.

Data analysis

Once cases of diabetes mellitus were identified from the study cohort, the incidence of diabetes mellitus adverse events per 1,000 person-years at risk was calculated with 95% confidence intervals. Following that, exposure analysis as well as a causality assessment

adapted from the WHO-UMC system for standardised causality assessment method (Uppsala Monitoring Centre) was conducted to investigate the likelihood of a relationship between the antipsychotic and the event of diabetes mellitus. The criteria and categories used for the assessment is shown in Table 6.7. After conducting the analysis on the causality assessment, it was also assessed independently by Professor Ian Wong[8], a paediatric pharmacoepidemiologist and Dr Patrick Byrne[9], a consultant child and adolescent psychiatrist. Cases where the antipsychotic agent was classified as *possibly*, *probably*, or *certainly* associated with diabetes mellitus were considered as adverse drug reactions. Subsequently, the incidence of diabetes mellitus adverse drug reactions was calculated per 1,000 treatment-years at risk with 95% confidence intervals.

Table 6.7: Categories used for the causality assessment for cases of diabetes mellitus in the study cohort

Causality term	Assessment criteria
Certain	• Event of diabetes mellitus with a plausible time relationship to drug intake • Event cannot be explained by other disease or drugs • Event definitive pharmacologically or phenomenologically • Rechallenge satisfactory
Probably / Likely	• Event of diabetes mellitus with reasonable time relationship to drug intake

[8] Professor Ian Chi Kei Wong, Director and Professor of Paediatric Medicines Research,
Centre for Paediatric Pharmacy Research, A collaboration between the School of Pharmacy, Institute of Child Health & Great Ormond Street Hospital for Children

[9] Dr Patrick Byrne MMedSci FRCPsych
Consultant in Adolescent Psychiatry & Hon Research Associate IoP
South London & Maudsley NHS Trust

	• Event unlikely to be attributed to other disease or drugs • Response to withdrawal clinically reasonable • Rechallenge not required
Possible	• Event of diabetes mellitus with reasonable time relationship to drug intake • Event could be possibly explained by disease or other drugs • Information on drug withdrawal may be lacking or unclear
Unlikely	• Event of diabetes mellitus with a time to drug intake that makes a relationship improbable, but not impossible • Disease or other drugs provide plausible explanations

The standardised incidence ratio (SIR) is the ratio of the observed number of cases in the study cohort to the expected number of cases that would be expected during the follow-period in the total population (Webb et al, 2005). For this purpose, the incidence of diabetes mellitus in the total GPRD population in patients aged 18 years and younger was first determined. The incidence of diabetes mellitus, I^d, in the total GPRD population was identified using diabetic medical codes (Appendix L) and product codes related to anti-diabetic therapy agents (Appendix M) and was calculated using the method shown in Equation 6.1.

Equation 6.1: Calculation of incidence of diabetes mellitus in the GPRD general paediatric population

$$I^d = \frac{N^{Id}}{K} \times 1{,}000$$

Where I^d = Incidence of diabetes mellitus in the total GPRD cohort for patients 18 years and younger

N^{Id} = Number of patients with either a new medical code related to diabetes mellitus or a new prescription for an anti-diabetic agent in a particular year

And K = Total number of person-years in the GPRD population aged 18 years and younger in a particular year

The incidence of diabetes mellitus in the total GPRD population was stratified into 4 age bands (0 to 1, 2 to 5, 6 to 11, and 12 to 18 years). The expected number of incidence cases of diabetes mellitus, E_d, was then calculated using Equation 6.2 shown below:

Equation 6.2: Calculation of the expected number of incidence cases of diabetes mellitus

$$E_d = I^d \times D$$

Where E_d = Expected number of incident cases of diabetes mellitus in the population

I^d = Incident rate of diabetes mellitus seen in the total GPRD population;

And D = Total person-years at risk for an adverse event

The SIR with 95% confidence intervals was then calculated using the Equation 6.3 shown below:

Equation 6.3: Calculation of standardised incidence ratios (SIR) of diabetes mellitus

$$SIR = \frac{Nc}{E_d}$$

Where N_c = Number of cases of diabetes mellitus identified in the cohort

And E_d = Number of cases of diabetes mellitus that will be expected

6.3.3 Results

A total of 2,767 children (contributing 6,007 person-years) who received at least one prescription an antipsychotic were previously identified (Rani et al, 2008b). From this cohort, a total of 3 patients were identified having a clinical event or a therapy event related to diabetes mellitus. However, one patient was excluded because the subject had received a single use insulin syringe but did not have any further events related to diabetes mellitus or anti-diabetic therapy. Consequently, there were a total of 2 cases of diabetes mellitus in 5,934 person-years at risk for an adverse event. The incidence of diabetes mellitus adverse events was 0.34 cases per 1,000 person-years at risk (95% CI: 0.09 to 1.23 cases per 1,000 person-years at risk). The SIR for diabetes mellitus was 1.61 (95% CI: 0.20 to 5.81).

Following analysis on drug exposure and causality assessments, only one (Patient 1) of the 2 patients was a current user at the time of the first event of diabetes mellitus i.e. exposed to antipsychotic therapy at the time of the event. For the causality assessment, it was

concluded that there was a *possible* association between antipsychotic therapy and diabetes mellitus for this subject. However, there was no further information on drug withdrawal or re-challenge to the antipsychotic agent as the patient was continued on sulpiride treatment after the first occurrence of diabetes mellitus. For the remaining patient (Patient 2), it was *unlikely* that antipsychotic therapy was associated with the event of diabetes mellitus as there was a poor time relationship between drug exposure and the first event of diabetes mellitus. Results from the causality assessment are shown in Table 6.8.

The cohort contributed to 2,016 treatment-years. Therefore the incidence of diabetes mellitus adverse drug reactions (based on the one case) was 0.50 cases per 1,000 treatment-years at risk (95% CI: 0.09 to 2.80 cases per 1,000 treatment-years at risk).

Table 6.8: Causality assessment on the 2 cases of diabetes mellitus

Patient	Gender	Age at event	Diabetes mellitus event	Antipsychotic agent	Causality assessment	Outcome
1	Male	16	i. Blood sugar method ii. Mixtard 30 Penfill 100iu/ml (Human Insulin) iii. Metformin	Sulpiride	• Subject developed diabetes mellitus while exposed to sulpiride therapy, indicating a reasonable time relationship between drug intake and the event. • Subject was continued on sulpiride while Mixtard and metformin were continuously given as well. Therefore, information on drug withdrawal is lacking in this subject.	• Antipsychotic drug *possibly* to be associated with diabetes mellitus in this case.
2	Female	18	i. Diabetes Mellitus	Not exposed at the time of event	• Subject was not exposed to antipsychotic therapy when the event of diabetes mellitus occurred (time from prescription to first diabetes event > 1500 days), demonstrating a poor time relationship between drug intake and the event. • Subject was also taking Depo-provera.	• Antipsychotic drug *unlikely* to be associated with diabetes mellitus in this case.

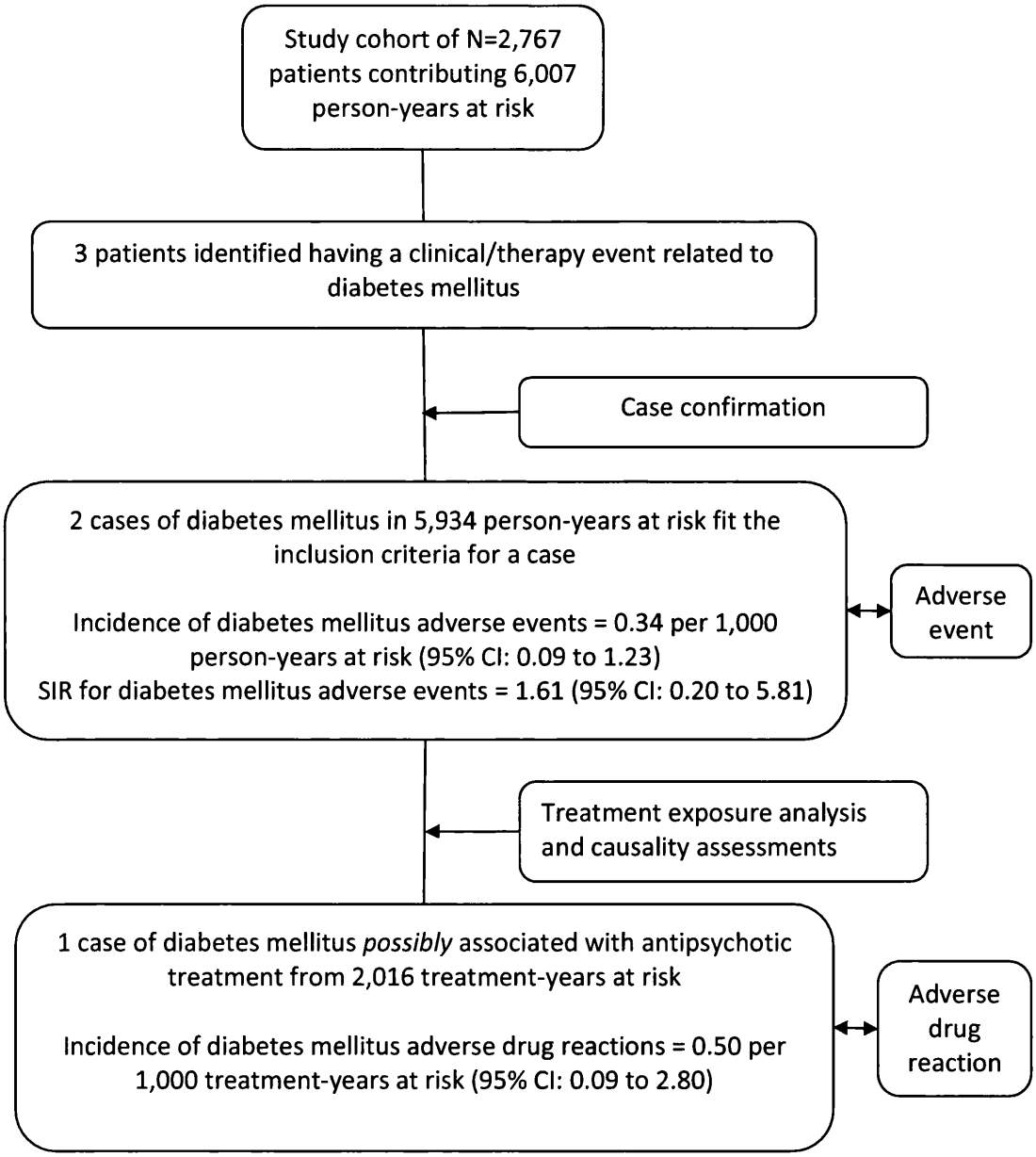
A summary of the results is illustrated in Figure 6.2.

6.3.4 Discussion

Diabetes mellitus has been reported in adult and paediatric patients exposed to both typical and atypical antipsychotic therapy (Hägg et al, 1998; Wirshing et al, 1998; Koller & Malozowski, 2001; Mackin et al, 2005).

There are a number of possible mechanisms leading to hyperglycaemia and diabetic ketoacidosis that have been proposed. This includes primary damage to the pancreatic islet cells with or without a combination of dysregulation of the sympathetic nervous system. Secondary mechanisms of hyperglycaemia include the co-morbid effects related to weight gain leading to insulin resistance (Ragucci & Wells, 2001; Bloch et al, 2003). This phenomenon has been implied in a number of case reports and case series whereby a majority of antipsychotic-exposed subjects who developed diabetes mellitus-associated symptoms were also overweight or suffered from obesity (Domon & Webber, 2001; Selva & Scott, 2001; Saito & Kafantaris, 2002; Bloch et al, 2003; Courvoisie et al, 2004; Logue et al, 2007). Besides obesity, other proposed factors which may contribute to the development of diabetes mellitus in paediatric patients exposed to antipsychotic therapy include a positive family history of diabetes mellitus and ethnicity (Cohen & Huinink, 2007).

Figure 6.2: Summary of the results on incidence of diabetes mellitus



Chapter SIX: Incidence of liver abnormalities, diabetes mellitus and extrapyramidal symptoms in a cohort of patients on antipsychotic medication

Unfortunately, as there is a recognised relationship between glucose intolerance and mental illness, it remains difficult to assess causality between antipsychotic treatment and the occurrence of this condition (Liebzeit et al, 2001; Dubois, 2005; Mackin et al, 2005). The results presented in this study demonstrated only one case whereby antipsychotic therapy was *possibly* associated with the event of diabetes mellitus (Patient 1). This subject did not have a record for obesity or for being overweight and a family history of diabetes mellitus was also absent from the electronic patient profile records. These elements however should not be overlooked as this information might have been omitted by the general practitioner. As for ethnicity, the GPRD does not divulge this data.

Although the association between diabetes mellitus and typical antipsychotic therapy has not been thoroughly established, data on the link between hyperglycaemia and glucose dysregulation and atypical antipsychotic agents have been increasing (Saito & Kafantaris, 2002). It has also been reported that as the use of atypical antipsychotic drugs have been increasing, so has the number of reports on the incidence or worsening of diabetes mellitus, as well as ketoacidosis associated with their use, in both the adult and paediatric populations (Liebzeit et al, 2001; Cohen & Huinink, 2007). Although diabetes mellitus is a serious condition associated with high morbidity and mortality, literature and published studies investigating this condition in children and adolescents exposed to antipsychotic therapy remains sparse (Cohen & Huinink, 2007). Results from the literature review earlier in this section demonstrated that paediatric patients on antipsychotic therapy possibly

have an increased risk of developing metabolic disorders including type II diabetes mellitus (Jerrell & McIntyre, 2008). However, the majority of published studies identified in the review were case reports and case series, therefore highlighting paucity in large-scale studies investigating antipsychotic-induced diabetes mellitus in the paediatric population.

As discussed following the literature review on diabetes mellitus and antipsychotic agents, it has been reported that hyperglycaemia and diabetes mellitus appears to be reversible upon cessation of the offending antipsychotic agent in some patients; and reappears when the drug is reintroduced (Rigalleau et al, 2000). Upon cessation of the offending drug, glucose homeostasis is probably achieved by a reduction of weight which leads to a decreased insulin resistance, sufficiently allowing for the patients' endogenous insulin production to maintain normal carbohydrate management (Courvoisie et al, 2004). This was not the case for Patient 1 whereby sulpiride therapy was ongoing, and was not discontinued after the subject developed type I diabetes mellitus; therefore restraining analysis on causality with regards to re-challenging.

It has also been demonstrated that even among patients' whose diabetes mellitus is resolved upon cessation of the suspected antipsychotic agent, there are those who still eventually develop the condition after the initial presentation (Saito & Kafantaris, 2002). In these patients, it is argued that this recurrence of diabetes mellitus is a reflection of the

underlying predisposition of the patient to the condition, which was unmasked with antipsychotic drug treatment (Courvoisie et al, 2004). Nevertheless, cessation of the suspected drug may not always result in a favourable outcome or resolved diabetes mellitus, highlighting the possibility that glucose dysregulation could potentially be an irreversible side effect of antipsychotic therapy (Bloch et al, 2003). Conversely, the development of diabetes mellitus could also just be a coincidental phenomenon which occurred during antipsychotic therapy.

An observational cohort study using paediatric populations from New Zealand presented an incidence of 4 cases of new-onset diabetes mellitus or a worsening diabetes mellitus per 1,000 person-years (95% CI: 0.5 to 15 cases per 1,000 person-years) from 489 person-years of atypical antipsychotic treatment (Harrison-Woolrych et al, 2007). The results presented using the GPRD demonstrated an incidence of 0.50 cases of new-onset diabetes mellitus adverse drug reactions per 1,000 treatment-years (95% CI: 0.09 to 2.80 cases per 1,000 treatment-years). The overlapping confidence intervals of these values suggest that there is no significant statistical difference of the reported incidence rates between the 2 studies. Nevertheless, there are a number of differences with regards to the methodology used by Harrison-Woolrych et al (2007) and this study using the GPRD. Firstly, the GPRD study cohort included all paediatric patients aged 18 years and younger who were exposed to both typical and atypical antipsychotic drugs, while the study by Harrison-Woolrych et al included children aged 15 years and below who were only exposed to

atypical antipsychotic agents. Secondly, the data source used by Harrison-Woolrych and colleagues were obtained by questionnaires sent to each paediatric patients' psychiatrist or general practitioner where as the data source used in this study was relatively more indirect, being obtained solely from automated general practice-based database. Therefore, it could be more likely that clinicians from the New Zealand study were more vigilant in reporting adverse reactions, or better well-trained in recognising such events in patients exposed to atypical antipsychotic treatment compared to general practitioners who contribute to the GPRD. Thirdly, this study only included new-onset diabetes mellitus and cases of pre-existing diabetes mellitus were subsequently excluded from analysis. Consequently, this may underestimate the actual risk of antipsychotic agents' effect on glucose regulation in the GPRD study cohort. Finally, the size of the study cohorts from the 2 studies was also very different, where the cohort of paediatric patients identified from the GPRD being much larger.

The calculated SIR when compared to the incidence of diabetes mellitus in the general paediatric population from the GPRD was 1.61 (95% CI: 0.20 to 5.81). This ratio however, was not significant as the confidence interval includes 1. The calculated SIR also presented with wide confidence intervals, therefore limiting more meaningful interpretations to be made. Furthermore, diabetes mellitus was *possibly* associated with antipsychotic therapy in only one subject (Patient 1). This subject was likely to have insulin-dependent diabetes mellitus, which, although not unheard of (Goldstein et al, 1999), is less commonly

reported than type II diabetes mellitus in patients exposed to antipsychotic treatment (Hägg et al, 1998; Kornegay et al, 2002).

It should also be reminded that a common adverse effect of antipsychotic medication is weight gain (Casey et al, 2004; Dubois, 2005; Laita et al, 2007). Most cases which report patients who develop diabetes mellitus while exposed to atypical antipsychotic agents involve clozapine and olanzapine, which incidentally are also proposed to have the highest rates of weight gain (Saito & Kafantaris, 2002). Results from the literature review in on diabetes mellitus in this section also indicate that the atypical antipsychotics risperidone (Koller et al, 2004), olanzapine and clozapine (Koller & Malozowski, 2001) having the potential to further exacerbate or worsen pre-existing diabetes mellitus in exposed children. A study by Meyer (2002) suggested that olanzapine is also associated with greater increases in fasting glucose and lipid levels compared to risperidone; and these changes may be independent of increases in weight (Meyer, 2002; Saito & Kafantaris, 2002). It should be noted that risperidone and olanzapine are the highest and second highest prescribed atypical antipsychotic agents in respectively in the UK paediatric population from the results presented in Chapter 4. Additionally, antipsychotic therapy may also cause changes in serum lipid levels (Casey et al, 2004; Laita et al, 2007). When these effects are combined with the potential for these drugs to cause hyperglycaemia and diabetes mellitus, the increased risk for metabolic syndrome and mortality is elevated (Casey et al, 2004). This further accentuates the need for more research to investigate

treatment-emergent diabetes in children exposed to antipsychotic medication, as well as continuous monitoring of glucose tolerance throughout exposure to these agents.

6.4 Incidence of extrapyramidal symptoms

Unlike liver abnormalities and diabetes mellitus, extrapyramidal symptoms are a more frequent side effect associated with antipsychotic therapy. Although the newer atypical antipsychotic agents are considered to be safer, extrapyramidal symptoms have been reported in children taking both typical and atypical antipsychotic therapy (Armenteros & Davies, 2006; Correll, 2008).

Available published studies reporting the occurrence and rate of this adverse effect in adult and paediatric patients are primarily derived from clinical trials (Casey, 1999; Correll & Kane, 2007). Furthermore, the majority of these studies consist of relatively small sample sizes and short durations of study (Pool et al, 1976; Armenteros et al, 1997; Findling et al, 2003; King et al, 2003; Laita et al, 2007; Gencer et al, 2008; Findling et al, 2008). Additionally, there is a wide range of variance among the reported rates from these published studies. For example, King et al (2003) reported 8% of study subjects (4/50 children) developed extrapyramidal symptoms while treated with risperidone, while Findling et al (2008) reported up to 22% of study subjects (22/102 children) developed extrapyramidal side effects while on aripiprazole treatment. Even with haloperidol, a long-

established typical antipsychotic agent, there is a wide variance in the published rates of extrapyramidal side effect in exposed children. Pool et al (1976) reported 76% of study subjects (18/25) experienced extrapyramidal symptoms while a study by Gencer et al (2008) reported only 20% of the study subjects (3/15 children) developed this adverse effect during the study period. Other published studies include case reports and case series reporting children or adolescents who experienced extrapyramidal symptoms while exposed to antipsychotic treatment (Ahmed et al, 1998; Sathpathy & Winsberg, 2003).

Consequently, this section investigates the incidence of extrapyramidal symptoms in the large cohort of children and adolescents exposed to antipsychotic drug therapy identified in Chapter 4.

6.4.1 Methodology

Data source

The data for this study were obtained from the GPRD. The history of the GPRD and validation of its data is described in more detail in Chapter 3.

The study population and data extraction methods are described in detail in Chapter 3. Patients who received at least one prescription for an antipsychotic during the defined study period between 1 January 1993 and 31 December 2005 were included in the study.

Chapter SIX: Incidence of liver abnormalities, diabetes mellitus and extrapyramidal symptoms in a cohort of patients on antipsychotic medication

Patients with a history of extrapyramidal symptoms prior to the first prescription of an antipsychotic were excluded from the study.

Cases of extrapyramidal symptoms

Cases were identified from the antipsychotic cohort described in Chapter 4, except the study duration was modified to 01 January 1993 until 31 December 2005 to match the comparator cohort used. The additional comparator cohort was identified from another study using the GPRD, which comprised of paediatric patients who received prescriptions for antiepileptic medications from 1993 to 2005 (Ackers et al, 2007). Incident patients in both the cohorts were followed from the date of the first prescription of an antipsychotic or an antiepileptic agent until the earliest occurrence of a clinical event related to extrapyramidal symptoms (Appendix N), age greater than 18 years, end of the exposure duration of the drug, or the end of the study period. Cases were defined as patients who experience clinical events consistent with extrapyramidal symptoms while being exposed to antipsychotic or antiepileptic therapy. Case confirmation was evaluated by Professor Ian Wong[10], a paediatric pharmacoepidemiologist and Dr Patrick Byrne[11], a consultant child and adolescent psychiatrist.

[10] Professor Ian Chi Kei Wong, Director and Professor of Paediatric Medicines Research,
Centre for Paediatric Pharmacy Research, A collaboration between the School of Pharmacy, Institute of Child Health & Great Ormond Street Hospital for Children

[11] Dr Patrick Byrne MMedSci FRCPsych

Chapter SIX: Incidence of liver abnormalities, diabetes mellitus and extrapyramidal symptoms in a cohort of patients on antipsychotic medication

Data analysis

Incidence of extrapyramidal adverse events: exposed versus unexposed to antipsychotic therapy

Extrapyramidal symptoms are a common adverse effect associated with antipsychotic therapy (Electronic Medicines Compendium; Casey, 1999). To investigate the occurrence of this adverse event, the incidence of extrapyramidal symptoms in the cohort of patients exposed to antipsychotic treatment was compared to the incidence of extrapyramidal symptoms in the comparator cohort of patients not exposed to antipsychotic treatment.

An available cohort of patients from the GPRD who were identified for a different study investigating the pharmacoepidemiology of antiepileptic drugs was used as the comparator cohort (Ackers et al, 2007). The index dates for these 2 cohorts were the date of the first prescription for either an antipsychotic medication or an antiepileptic medication. Durations of drug exposure, whether to antipsychotic medication or antiepileptic medication, were calculated using Equation 6.4.

Patients in the cohort were followed from the date of the first prescription until the earliest occurrence of a clinical event related to extrapyramidal symptoms (Appendix N), age greater than 18 years, end of the drug exposure duration, or end of the study period.

Equation 6.4: Calculation of duration of drug exposure

Duration of drug exposure = E^{rx} - S^{rx} + L
Where E^{rx} = End date of the treatment duration of the last antipsychotic or antiepileptic prescription
And S^{rx} = Start date; which is the first prescription for an antipsychotic or antiepileptic agent (First prescription date)
And L = Latency period of 30 days

Once cases of patients who experienced extrapyramidal symptoms were identified, a logistic regression was conducted to investigate odds ratios of experiencing an extrapyramidal symptom. The model was adjusted for gender, age at first prescription, and duration of drug exposure in treatment-years.

Causality assessments in antipsychotic-exposed cohort

Following the analysis on logistic regression, a causality assessment was conducted to determine the likelihood of an association between the event of extrapyramidal symptoms and antipsychotic therapy in the cohort of subjects exposed to antipsychotic medications. The causality assessment was adapted from the WHO-UMC system for

standardised causality assessment method (Uppsala Monitoring Centre). The criteria and categories used for the assessment are shown in Table 6.9. After conducting the analysis on the causality assessment, it was also assessed independently by Professor Ian Wong[12], a paediatric pharmacoepidemiologist. Cases where the antipsychotic agent was classified as *possibly*, *probably*, or *certainly* associated with extrapyramidal symptoms were considered as adverse drug reactions. The incidence of extrapyramidal adverse drug reactions in subjects exposed to antipsychotic therapy was then calculated per 1,000 treatment-years at risk with 95% confidence intervals.

Table 6.9: Categories used for the causality assessment for cases of extrapyramidal events in the study cohort exposed to antipsychotic therapy

Causality term	Assessment criteria
Certain	• Event of extrapyramidal symptom with a plausible time relationship to drug intake • Event cannot be explained by other disease or drugs • Event definitive pharmacologically or phenomenologically • Rechallenge satisfactory
Probably / Likely	• Event of extrapyramidal symptom with reasonable time relationship to drug intake • Event unlikely to be attributed to other disease or drugs • Response to withdrawal clinically reasonable • Rechallenge not required
Possible	• Event of extrapyramidal symptom with reasonable time relationship to drug intake • Event could be possibly explained by disease or other drugs

[12] Professor Ian Chi Kei Wong, Director and Professor of Paediatric Medicines Research, Centre for Paediatric Pharmacy Research, A collaboration between the School of Pharmacy, Institute of Child Health & Great Ormond Street Hospital for Children

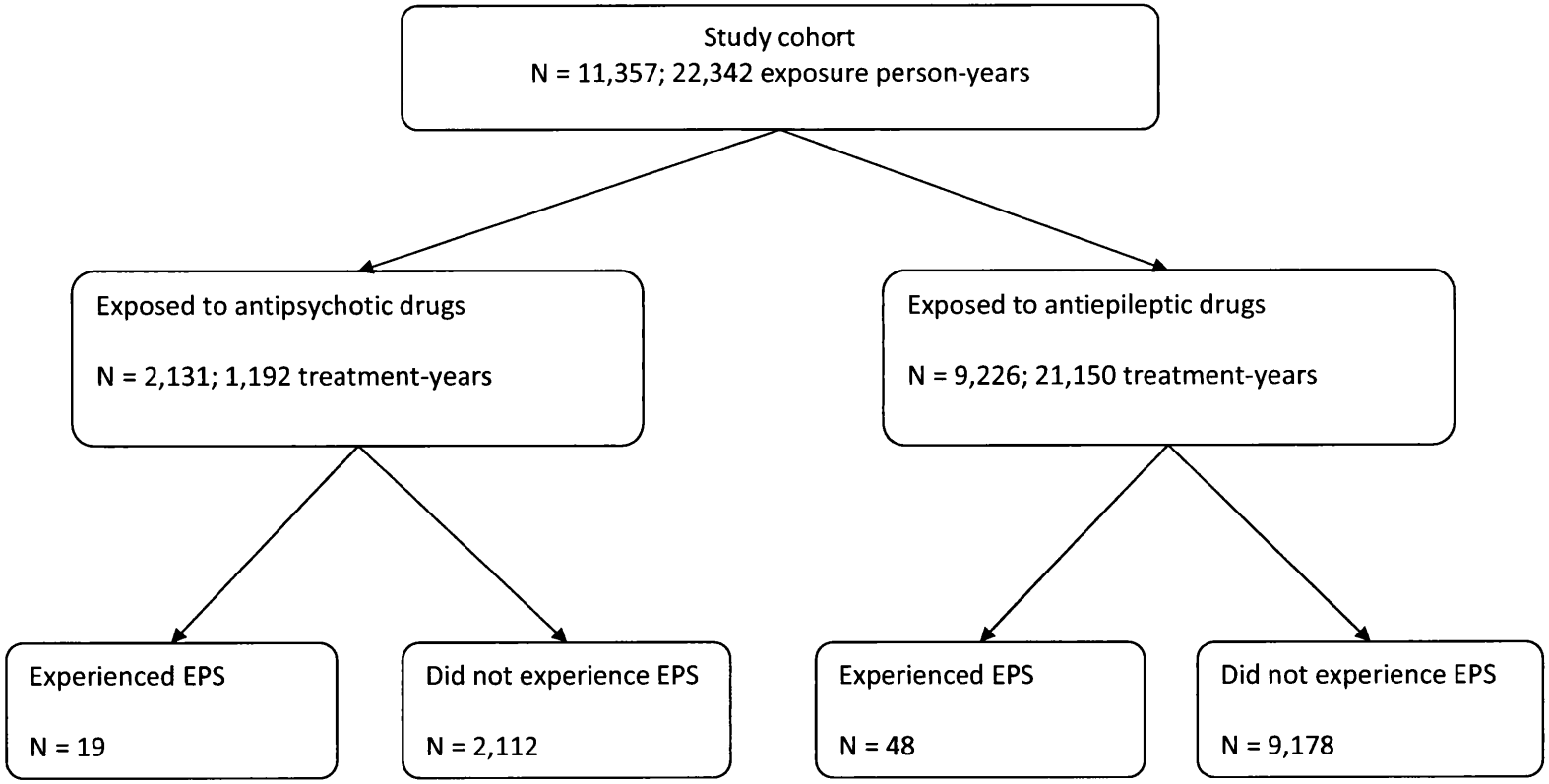
	• Information on drug withdrawal may be lacking or unclear
Unlikely	• Event of extrapyramidal symptom with a time to drug intake that makes a relationship improbable, but not impossible • Disease or other drugs provide plausible explanations

6.4.2 Results

A total of 11,357 incidence patients contributing 22,342 treatment-years were identified in this study. Out of the 11,357 patients, 2,131 subjects received antipsychotic medication contributing to 1,192 treatment-years; and 9,226 subjects were exposed to antiepileptic medication contributing to 21,150 treatment-years. There were 19 and 48 subjects who experienced an event related to extrapyramidal symptoms while being exposed to antipsychotic treatment and antiepileptic treatment respectively (Figure 6.3).

The incidence of extrapyramidal adverse events was 15.93 cases per 1,000 treatment-years at risk (95% CI: 9.62 to 24.78 cases per 1,000 treatment-years at risk) in the cohort of patients exposed to antipsychotic medication; and 2.27 cases per 1,000 treatment-years at risk (95% CI: 1.63 to 2.91 cases per 1,000 treatment-years) in the cohort of patients exposed to antiepileptic drugs.

Figure 6.3: Study cohort investigating extrapyramidal symptoms



The odds ratios from the logistic regression analysis demonstrate that patients exposed to antipsychotic treatment have a higher likelihood of experiencing an extrapyramidal symptom compared to patients in the comparator cohort (OR: 1.88; 95% CI: 1.03 to 3.45; p = 0.04) as shown in Table 6.10.

Table 6.10: Odds ratios from logistic regression analysis

Variable	Odds ratio (95% CI); p value
Exposure to antipsychotic	1.88 (1.01 to 3.45); p = 0.040
Duration of exposure	1.00 (0.99 to 1.00); p = 0.936
Gender (Male as reference)	1.17 (0.72 to 1.92); p = 0.518
Age at first prescription	0.98 (0.94 to 1.03); p = 0.415

Durations of exposure, whether to antipsychotic or antiepileptic therapy, patient gender and age at first prescription for an antipsychotic or antiepileptic medication was found to have no significant impact on the odds ratio of developing extrapyramidal symptoms.

From the 2,131 subjects contributing to 1,192 treatment-years on antipsychotic therapy, a causality assessment was conducted on the 19 subjects who experienced events related to extrapyramidal symptoms. Details of the 19 subjects and the results of the causality assessments are shown in Table 6.11.

Table 6.11: Causality assessment on the 19 cases of extrapyramidal symptoms

Patient	Gender	Age at event	Extrapyramidal symptom	Antipsychotic agent	Causality assessment	Outcome
1	Male	13	Dystonia	Haloperidol	• Subject developed dystonia only after haloperidol was prescribed (only 1 prescription for haloperidol was given), indicating a plausible time relationship between drug and the event. • Subject did not have any other drug or disease which could have caused dystonia. • Haloperidol was discontinued and no other extrapyramidal symptoms were seen, therefore demonstrating a reasonable response to haloperidol withdrawal. • Dystonia is a pharmacologically definitive side effect of haloperidol. • However, there was no information on rechallenge.	• Antipsychotic drug was *probably* associated with the event of extrapyramidal symptom in this case.
2	Male	18	Muscle rigidity	Sulpiride	• Prior to starting sulpiride, subject was on pimozide monotherapy 11 months, and no event related to	• Antipsychotic drug was *probably* associated with the event of

					extrapyramidal symptoms was seen during this period. • Subject developed muscle rigidity only after pimozide therapy was switched to sulpiride (only 1 prescription of sulpiride was given), indicating a plausible time relationship between drug intake and the event. • Subject did not have any other drug or disease which could have caused muscle rigidity. • Sulpiride was discontinued and the subject was switched to risperidone therapy in combination with pimozide and procyclidine. Following that, no other extrapyramidal symptoms was seen, therefore demonstrating a reasonable response to sulpiride withdrawal. • Muscle rigidity is a pharmacologically definitive side effect of sulpiride. • However, there was no information on rechallenge.	extrapyramidal symptom in this case.
3	Male	17	Dystonia	Chlorpromazine	• Subject developed dystonia only after	• Antipsychotic drug was

					the first prescription of chlorpromazine was given, indicating a plausible time relationship between drug intake and the event. • The subject was also on fluoxetine and paroxetine prior to chlorpromazine therapy; transient abnormal movements are uncommon (but not impossible) with fluoxetine and paroxetine. • Additionally, chlorpromazine was not discontinued following the event of dystonia, and procyclidine was also prescribed in combination with chlorpromazine. Therefore, information on drug withdrawal is lacking in this subject.	*possibly* associated with the event of extrapyramidal symptom in this case.
4	Male	18	Cogwheel rigidity	Chlorpromazine	• Subject developed cogwheel rigidity only after chlorpromazine was prescribed (only 1 prescription of chlorpromazine was given), indicating a plausible time relationship between drug intake and the event. • Subject did not have any other drug or disease which could have caused	• Antipsychotic drug was *probably* associated with the event of extrapyramidal symptom in this case.

					muscle rigidity. • Chlorpromazine was discontinued and no other extrapyramidal symptoms were seen, therefore demonstrating a reasonable response to chlorpromazine withdrawal. • Rigidity is a pharmacologically definitive side effect of chlorpromazine. • However, there was no information on rechallenge.	
5	Female	17	Tremor	Chlorpromazine	• Subject developed tremor while on chlorpromazine therapy, indicating a plausible time relationship between drug intake and the event. • The subject was also on cabarmazepine prior to chlorpromazine therapy; Abnormal involuntary movements are uncommon (but not impossible) with cabarmazepine. • Additionally, chlorpromazine was not discontinued following the event of tremor, and procyclidine was also	• Antipsychotic drug was *possibly* associated with the event of extrapyramidal symptom in this case.

					prescribed in combination with chlorpromazine. Therefore, information on drug withdrawal is lacking in this subject.	
6	Male	14	Dystonia	Trifluoperazine	• Subject developed dystonia only after trifluoperazine was prescribed (only 1 prescription of trifluoperazine was given), indicating a plausible time relationship between drug intake and the event. • Subject did not have any other drug or disease which could have caused dystonia. • Trifluoperazine was discontinued and no other extrapyramidal symptoms were seen, therefore demonstrating a reasonable response to chlorpromazine withdrawal. • Dystonia is a pharmacologically definitive side effect of trifluoperazine. • However, there was no information on rechallenge.	• Antipsychotic drug was *probably* associated with the event of extrapyramidal symptom in this case.
7	Female	17	Torticollis	Pericyazine	• Subject developed torticollis (which is	• Antipsychotic drug was

					a symptom of dystonia) after the first prescription for pericyazine, indicating a plausible time relationship between drug intake and the event. • There were no other events specific to extrapyramidal effects following torticollis, suggesting that torticollis was possibly idiosyncratic and not drug related. • Additionally, pericyazine was not discontinued following the event of torticollis. Therefore, information on drug withdrawal is lacking in this subject.	*possibly* associated with the event of extrapyramidal symptom in this case.
8	Male	17	Cogwheel rigidity	Zuclopenthixol	• Subject developed cogwheel rigidity after the first prescription for zuclopenthixol, indicating a plausible time relationship between drug intake and the event. • Zuclopenthixol was not discontinued following the event of tremor, and procyclidine was also prescribed in combination with zuclopenthixol. Therefore, information on drug withdrawal is lacking in this subject.	• Antipsychotic drug was *possibly* associated with the event of extrapyramidal symptom in this case.

9	Male	15	Tremor	Chlorpromazine	• Subject developed cogwheel rigidity after the first prescription for chlorpromazine, indicating a plausible time relationship between drug intake and the event. • Chlorpromazine was not discontinued following the event of tremor. Therefore, information on drug withdrawal is lacking in this subject.	• Antipsychotic drug was *possibly* associated with the event of extrapyramidal symptom in this case.
10	Male	5	Tremor	Haloperidol	• Subject developed tremor only after haloperidol was prescribed (only 1 prescription of haloperidol was given), indicating a plausible time relationship between drug intake and the event. • Subject had also been on salbutamol aerosol inhaler therapy since March 1994; however tremor only occurred in July 1996 after being prescribed haloperidol. Therefore it is unlikely that tremor was attributed to salbutamol therapy. • Haloperidol was discontinued and no other extrapyramidal symptoms were seen, therefore demonstrating a reasonable response to haloperidol	• Antipsychotic drug was *probably* associated with the event of extrapyramidal symptom in this case.

					withdrawal. • Tremor is a pharmacologically definitive side effect of haloperidol. • However, there was no information on rechallenge.	
11	Male	18	Tremor	Sulpiride	• Subject developed tremor while on sulpiride therapy, indicating a plausible time relationship between drug intake and the event. • Subject did not have any other drug or disease which could have caused dystonia. • Sulpiride was discontinued and no other extrapyramidal symptoms were seen, therefore demonstrating a reasonable response to sulpiride withdrawal. • Tremor is a pharmacologically definitive side effect of sulpiride. • However, there was no information on rechallenge.	• Antipsychotic drug was *probably* associated with the event of extrapyramidal symptom in this case.
12	Male	10	Tardive dyskinesia	Risperidone	• Subject developed tardive dyskinesia after approximately 7 months of risperidone therapy, indicating a	• Antipsychotic drug was *possibly* associated with the event of

					plausible time relationship between drug intake and the event. • Risperidone was not discontinued following the event of tardive dyskinesia. Therefore, information on drug withdrawal is lacking in this subject.	extrapyramidal symptom in this case.
13	Male	12	Tardive dyskinesia	Haloperidol	• Subject developed tardive dyskinesia after approximately 8 months of haloperidol therapy, indicating a plausible time relationship between drug intake and the event. • Subject did not have any other drug or disease which could have caused tardive dyskinesia. • Haloperidol was discontinued and no other extrapyramidal symptoms were seen, therefore demonstrating a reasonable response to sulpiride withdrawal. • Tardive dyskinesia is a pharmacologically definitive side effect of haloperidol. • However, there was no information on	• Antipsychotic drug was *probably* associated with the event of extrapyramidal symptom in this case.

					rechallenge.	
14	Male	17	Tardive dyskinesia	Risperidone	• Subject developed tardive dyskinesia after approximately 4 months of risperidone therapy, indicating a plausible time relationship between drug intake and the event. • Subject did not have any other drug or disease which could have caused tardive dyskinesia. • Risperidone was stopped and no other extrapyramidal symptoms were seen, therefore demonstrating a reasonable response to risperidone withdrawal. • Risperidone was restarted approximately 2 months after the event of tardive dyskinesia in combination with procyclidine. However, the subject developed drug-induced parkinsonism symptoms approximately 3 months after restarting treatment therefore providing data on rechallenge. • Tardive dyskinesia and parkinsonism symptoms are pharmacologically definitive side effects of risperidone.	• Antipsychotic drug was *certainly* associated with the event of extrapyramidal symptoms in this case.

15	Female	12	Dystonia	Haloperidol	• Subject developed dystonia only after haloperidol was first prescribed, indicating a plausible time relationship between drug intake and the event. • Prior to haloperidol treatment, subject was on pimozide for approximately 44 months without experiencing any events related to extrapyramidal symptoms. • Haloperidol was not discontinued following the event of dystonia. Therefore, information on drug withdrawal is lacking in this subject.	• Antipsychotic drug was *possibly* associated with the event of extrapyramidal symptom in this case.
16	Male	17	Dystonia	Haloperidol	• Subject developed dystonia only after haloperidol was prescribed (only 1 prescription of haloperidol was given), indicating a plausible time relationship between drug intake and the event. • Subject did not have any other drug or disease which could have caused dystonia. • Haloperidol was discontinued and no other extrapyramidal symptoms were seen, therefore demonstrating a	• Antipsychotic drug was *probably* associated with the event of extrapyramidal symptom in this case.

					reasonable response to haloperidol withdrawal. • Dystonia is a pharmacologically definitive side effect of haloperidol. • However, there was no information on rechallenge.	
17	Male	15	Dystonia	Risperidone	• Subject developed dystonia while exposed to risperidone therapy, indicating a plausible time relationship between drug intake and the event. • Subject did not have any other drug or disease which could have caused dystonia. • Risperidone was discontinued and no other extrapyramidal symptoms were seen, therefore demonstrating a reasonable response to risperidone withdrawal. • Dystonia is a pharmacologically definitive side effect of risperidone. • However, there was no information on rechallenge.	• Antipsychotic drug was *probably* associated with the event of extrapyramidal symptom in this case.
18	Male	17	Cogwheel rigidity	Risperidone	• Subject developed dystonia only after the first prescription for risperidone	• Antipsychotic drug was *possibly* associated with

					was given, indicating a plausible time relationship between drug intake and the event. • Prior to risperidone treatment, subject was on flupenthixol and thioridazine in combination with procyclidine for approximately 8 months without experiencing any events related to extrapyramidal symptoms. • Risperidone was not discontinued following the event of tremor, and procyclidine was also then prescribed in combination with risperidone. Therefore, information on drug withdrawal is lacking in this subject.	the event of extrapyramidal symptom in this case.
19	Female	17	Extrapyramidal movements	Risperidone	• Subject developed extrapyramidal movements while being exposed to risperidone, indicating a plausible time relationship between drug intake and the event. • Subject was also on citalopram therapy. Tremor is a frequent side effect related to citalopram. • Risperidone was not discontinued following the event, and was	• Antipsychotic drug was *possibly* associated with the event of extrapyramidal symptom in this case.

					continued in combination with citalopram. Therefore, information on drug withdrawal is lacking in this subject.	

Of the 19 cases identified, there was 1 case where the antipsychotic agent in question was *certainly* associated with antipsychotic therapy (Patient 14), 9 cases of extrapyramidal symptoms were deemed *probably* associated with antipsychotic therapy (Patients 1, 2, 4, 6, 10, 11, 13, 16 and 17) and 9 cases of extrapyramidal symptoms were deemed *possibly* associated with antipsychotic therapy (Patients 3, 5, 7, 8, 9, 12, 15, 18 and 19). Therefore all 19 cases were considered adverse drug reactions. As a result, the incidence of extrapyramidal adverse reactions in the cohort of subjects exposed to antipsychotic treatment remained the same, which was 15.93 cases per 1,000 treatment-years at risk (95% CI: 9.62 to 24.78 cases per 1,000 treatment-years at risk).

6.4.3 Discussion

The incidence of patients exposed to antipsychotic medication in the cohort who experienced extrapyramidal symptoms was 15.39 cases per 1,000 treatment-years (95% CI: 8.52 to 22.25 cases per 1,000 treatment-years). This rate is relatively low compared to rates of extrapyramidal symptoms reported in published studies and clinical trials (Pool et al, 1976; King et al, 2003; Armenteros & Davies, 2006). Nonetheless, the sample size used for this study was much larger than the samples used in the published clinical trials. It is also possible that not all general practitioners who contributed data to the GPRD were vigilant or sufficiently trained in diagnosing and identifying all types of extrapyramidal

symptoms such as tremor. Ultimately though, this should not affect the derived odds ratios as the comparator cohort was derived from the same population.

The results show that patients exposed to antipsychotic medication have a higher likelihood of experiencing an event related to extrapyramidal symptoms compared to patients exposed to antiepileptic drugs. It must be noted however that these results are confounded by the comparator cohort as a number of antiepileptic medication including carbamazepine and lamotrigine may, albeit rarely, also cause movement disorders or worsen parkinsonian symptoms (Electronic Medicines Compendium). Even so, this confounder would in fact underestimate the odds ratio of antipsychotic medication to cause extrapyramidal symptoms in the results.

A recent randomised trial investigating extrapyramidal side effects of antipsychotic therapy in adults revealed that risperidone had higher rates of concomitant antiparkinsonism therapy compared to subjects taking quetiapine and ziprasidone (an atypical antipsychotic agent marketed in the USA) (Miller et al, 2008). As risperidone was revealed to be the most commonly prescribed atypical antipsychotic agent in Chapter 4, this is a cause for concern. Furthermore, drug interactions with neurodevelopmental processes of children, combined with the relatively permeable blood-brain barrier in younger patients could potentially contribute to the higher risk of children to develop

neurological adverse effects including extrapyramidal effects related to antipsychotic therapy (Woods et al, 2003).

Although relatively common, extrapyramidal side effects associated with antipsychotic drug therapy and its impact in young patients should not be disregarded. As mentioned in Chapter 1, extrapyramidal symptoms can manifest throughout the course of antipsychotic treatment, from the initial few weeks, or even much later (Gracious & Findling, 2001). There is also evidence to suggest that patients presenting with extrapyramidal symptoms during the initial stages of treatment are more likely to develop tardive dyskinesia (Jibson & Tandon, 1998). Additionally, extrapyramidal side effects are associated with cognitive dysfunction in patients suffering from psychotic disorders (Bilder, 1997); and the manifestation of these symptoms play an important role in patients' compliance and adherence to therapy, and may have a negative impact on their social functioning (Jibson & Tandon, 1998). Therefore, early management of extrapyramidal side effects, either by controlling the symptoms or modification of drug therapy may have a positive impact on patients or improve the overall clinical care and management.

The analysis on the causality assessment in the antipsychotic-treated cohort deemed that all 19 subjects who experienced extrapyramidal adverse events to be either *certainly, probably or possibly* associated with antipsychotic therapy. The process for determining causality was facilitated as a number of extrapyramidal symptoms which occurred,

including tardive dyskinesia and dystonia, are definitive of antipsychotic therapy. However, the strict criteria of rechallenging were implemented for a case to be considered as *certain*. Consequently, only one case of extrapyramidal symptoms was deemed *certainly* associated with antipsychotic therapy (Patient 14) where rechallenging was evident. This subject experienced tardive dyskinesia while exposed to risperidone. Following drug withdrawal, there were no further events related to extrapyramidal symptoms. Interestingly, the subject was restarted on risperidone in combination with procyclidine 2 months after the initial presentation of tardive dyskinesia. Following this, the subject developed drug-induced parkinsonism symptoms 3 months after restarting treatment, despite concomitant procyclidine therapy. Nonetheless, it should be noted that all data obtained for this study were from general practitioner records, and the actual filling or dispensing of prescribed medicines, as well as the patients' compliance could not be determined.

Further scrutiny on the 19 cases revealed that the majority of these subjects were given antipsychotic therapy for what were probably essentially non-psychotic indications including behaviour, autistic and affective disorders and Tourette's syndrome. As the majority of these psychiatric conditions are off-label indications of antipsychotic therapy, this further accentuates the lack of sufficient long-term investigations and research in the paediatric population.

Chapter SIX: Incidence of liver abnormalities, diabetes mellitus and extrapyramidal symptoms in a cohort of patients on antipsychotic medication

6.5 Overall discussion on the incidence of liver abnormalities, diabetes mellitus and extrapyramidal symptoms in the study cohort

The study investigating antipsychotic prescribing to children and adolescents in Chapter 4 demonstrated an increase in prevalence of antipsychotic prescribing with a stable prescribing incidence during the study period of 1992 to 2005; suggesting that patients are on antipsychotic treatment for longer periods of time rather than more new patients starting antipsychotic treatment (Rani et al, 2008b). This would be a cause for concern as it has been shown that adverse effects including extrapyramidal symptoms, endocrine disorders, and diabetic side effects are more common in patients exposed to long-term treatment than patients with short-term exposure treatment (Kornegay et al, 2002; Laita et al, 2007).

Causality assessments

The causality assessments used in this chapter allowed for a systematic analysis to determine the likelihood of an association between antipsychotic drug intake and the events of interest. Important elements in the criterion for causality include whether or not the event of interest was pharmacologically or phenomenologically definitive of antipsychotic therapy, the presence or absence of a plausible response to drug withdrawal, and a rechallenge to the drug following cessation. The causality assessments demonstrated that antipsychotic therapy was *unlikely* to be associated with any of the

indentified cases of liver abnormalities and was *possibly* associated with one of the 2 cases of diabetes mellitus. For this one case of diabetes mellitus, data on drug withdrawal and drug rechallenge was absent, thus limiting the measure of causality. On the other hand, all 19 identified cases of extrapyramidal symptoms were at least *possibly* associated with antipsychotic therapy. There was also one case whereby the antipsychotic agent was rechallenged following cessation of therapy after the subject developed tardive dyskinesia. This subject subsequently developed extrapyramidal symptoms, resulting in the antipsychotic agent being *certainly* associated with the event.

Clinical implications

This study also raises the issue of availability and appropriateness of properly established antipsychotic therapy guidelines in the young population. As obesity is a known risk factor for developing insulin resistance and diabetes mellitus, as well as liver abnormalities including steatohepatitis, transient weight gain caused by antipsychotic therapy further accentuates the need for caution in children and adolescents exposed to these agents (Cohen & Huinink, 2007; Gonzalez-Heydrich et al, 2003). Furthermore, children on antipsychotic therapy often suffer from a wide range of psychiatric disorders, and are therefore more likely to be the subject of polypharmacy. Pharmacotherapy combinations itself may increase the risk of adverse effects in paediatric patients. For example, cases of acute pancreatitis, steatohepatitis, and elevations in hepatic enzymes have been reported

in both children and adults exposed to a combination of semisodium valproate and olanzapine (Ragucci & Wells, 2001; Gonzalez-Heydrich et al, 2003). It is recommended for clinicians to monitor patients under their care for parameters including baseline weight measurements, liver function tests and glucose levels as well as periodic monitoring of these functions.

Limitations

For the incidence of diabetes mellitus, co-morbid conditions including obesity and ethnicity which may contribute to the incidence of the condition were not explored in the analysis as this data is not systematically recorded for patients in the database.

Secondly, paediatric patients who experience the serious adverse effects of interest that require specialist treatment or occur during hospitalisation would not appear directly in the GPRD. This includes serious adverse drug reactions as a result from paediatric patients receiving therapy solely from specialist child and adolescent mental health clinics or tertiary children's hospitals. Nevertheless, as patients ultimately return to primary care under their general practitioners, it is unlikely that the general practitioners do not document such important events into their records.

Chapter SIX: Incidence of liver abnormalities, diabetes mellitus and extrapyramidal symptoms in a cohort of patients on antipsychotic medication

As recommended for the detection of serious adverse events (Greenhill et al, 2003), a large paediatric cohort exposed to antipsychotic therapy contributing to approximately 6,000 person-years was used as the data source. Nevertheless, when investigating incidence rates of rare events, the results were still limited by the sample size. Consequently, the number of patients in the study cohort was still relatively low to be able to draw more meaningful conclusions from the results obtained. This is an acknowledged problem of investigative studies in the paediatric population where sample sizes often limit the interpretation of results (Greenhill et al, 2003). As the background rate of these investigated adverse events (especially liver abnormalities and diabetes mellitus) in the general paediatric population is rare, a very large sample size is required to detect a difference in the study cohort. Unlike clinical trials, sample size cannot be increased in pharmacoepidemiological studies using automated databases as the sample is limited by the size of the database. When comparing incidence rates between antipsychotic-exposed paediatric patients and controls, a study cohort of approximately 47,000 antipsychotic-exposed patients and controls would be required to detect a 2-fold increased odds ratio for liver abnormalities with 80% power (based on a hypothetical rate of 1 case per 1,000 in the general population) [13] (Appendix O); and for the incidence of diabetes mellitus, a study population of about 262,000 exposed subjects and controls is needed to detect a 2-fold increase in odds ratio with 80% power[14] (Appendix P).

[13] Based on a 1 to 1 ratio of exposed to unexposed
[14] Based on a 1 to 1 ratio of exposed to unexposed

Consequently, for a study to detect significant odds ratios of experiencing adverse events in antipsychotic-exposed patients compared to controls, larger sample sizes are required. For this purpose, it is suggested that large pharmacoepidemiological databases be combined to increase the overall size of study subjects. For example, a recent database, named The Health Improvement Network (THIN) database, which, like the GPRD contains patient information and clinical records of general practices in the UK (Lewis et al, 2007). Although there are some practices which are overlapped by the 2 databases, there are over 100 practices which are non-GPRD contributors in the THIN database (Lewis et al, 2007). By combining these 2 databases, sample sizes of future studies involving paediatric subjects could potentially be increased.

Alternatively, a different pharmacoepidemiological approach can be taken whereby each patient (or case) contributes two forms of denominator durations; a duration unexposed person-years and treatment-years. The total incidence of adverse events of interest that occur during non-exposed person-years can then be compared to the total incidence which occurred during treatment-years. For example, in Figure 3.4 (Chapter 3, p 88), the time in database not contributing to person-years at risk for an adverse event will be the cumulative duration of unexposed person-years of the 5 patients, which in this case is approximately 19 person-years. The incidence of adverse events of interest which occur during this time-period can then be compared to the incidence of adverse events that

occur during the duration of person-years of drug exposure (treatment-years). This is also known as a case-crossover design study (Hernández-Díaz et al, 2003). As the identified cohort used in this study contributes to a total of approximately 4,000 person-years and 2,041 treatment-years, this method should be considered for future investigations.

Additionally, in future studies, patients presenting with pre-existing medical conditions such as diabetes mellitus or liver abnormalities prior to receiving antipsychotic therapy could be identified and excluded before identification of the study cohort. In this study, the antipsychotic-exposed cohort was identified from the GPRD prior to case exclusion. Ultimately though, this did not affect the overall findings presented.

Although the results from this chapter revealed a low incidence rate of liver abnormalities and diabetes mellitus in the study cohort, whereby there were no cases of liver adverse drug reactions (incidence of 0 cases per 1,000 treatment-years at risk; 95% CI: 0 to 1.82 cases per 1,000 treatment-years), and the SIR of diabetes mellitus demonstrated an SIR of 1.61 (95% CI: 0.20 to 5.81) (which indicate that subjects who received antipsychotic therapy are not at a higher risk for developing diabetes mellitus, as the SIR presents wide confidence intervals and includes 1), the worst case scenario based on the incidences of these rates could be projected. Based on the upper limits of the 95% confidence intervals, the worst case scenario of liver adverse drug reactions in antipsychotic-exposed children is 1.82 cases per 1,000 treatment-years and the worst case scenario for children on

antipsychotic therapy to develop diabetes mellitus compared to the general paediatric population is 5.81. Thus, these results should not be taken as definitive, but should be considered to reduce the uncertainty of the research question posed and contribute to the body of knowledge in this important area.

Nevertheless, although there have been many case reports and case series published reporting subjects who experience liver abnormalities and diabetes mellitus-associated symptoms associated with antipsychotic therapy, this study presents incidence rates and/or odds ratios of experiencing liver abnormalities, diabetes mellitus and extrapyramidal symptoms from what was the largest cohort of antipsychotic-exposed children from the general paediatric population in the UK.

6.6 Conclusions

Results of this study present the incidence rates of liver abnormalities, diabetes mellitus and extrapyramidal symptoms in a large cohort of antipsychotic-treated paediatric patients. The results demonstrate a relatively low incidence of these adverse reactions in the study cohort. Additional analysis on the SIR of developing diabetes mellitus compared to the general paediatric population revealed that children on antipsychotic drug treatment have no significant increase in risk for developing diabetes mellitus. Analysis on the odds ratio of developing extrapyramidal effects however indicate that paediatric

patients exposed to antipsychotic therapy are at higher risk for developing these symptoms compared to children treated with antiepileptic agents.

Nevertheless, the results of the study is limited by the power and sample size of patients investigated. As the cohort of patients studied in this chapter is currently the largest paediatric cohort from the UK paediatric population, alternative methods for evaluating the safety of these psychotropic agents in children should be explored. It is recommended that other research methodologies should be considered to explore this important research area, including the investigation of the occurrence, pathology and impact of serious adverse events associated with antipsychotic therapy in children and adolescents and to ultimately improve the healthcare of paediatric patients.

Chapter SEVEN: Paediatric Atypical antipsychotic Monitoring Safety study (PAMS)

7 CHAPTER SEVEN: Paediatric Atypical antipsychotic Monitoring Safety study (PAMS)

7.1 Introduction

In previous chapters, the incidence of serious adverse drug reactions of mortality (Chapter 5), diabetes mellitus, liver abnormalities, as well as extrapyramidal symptoms (Chapter 6), was investigated based on a study population derived from a primary care-based data source, the GPRD. The GPRD allowed for a high level of data quality from what was the largest paediatric cohort exposed to antipsychotic therapy from the UK population. Despite this, the investigations on rare, serious adverse effects of antipsychotic agents in the identified cohort were still limited by the sample size and power of the study population (Chapters 5 and 6).

Consequently, it was recommended that other research methodologies should be explored to evaluate the safety of antipsychotic medication in children and adolescents (Chapter 6). As previously stated in Chapter 1, the severity of adverse effects of antipsychotic therapy in adults emphasizes the importance of investigating the potential adverse effects of these drugs in the paediatric population (Laita et al, 2007). More importantly, it has been reported that adverse effects associated with moderate doses of antipsychotic therapy in children are more prevalent and severe compared to the effects reported in adult patients (Sikich et al, 2004). In general, it is unwise to extrapolate safety data from studies in adults to children as there are significant variations due to age and

development in both drug pharmacokinetics and pharmacodynamics, which may lead to increased bioavailability of antipsychotic drugs in younger patients, potentially resulting in increased therapeutic and adverse effects (Piscitelli et al, 1994; Vitiello et al, 2003; DuBois, 2005). Furthermore, the long-term effects of early treatment with psychotropic drugs have also not been fully studied (Vitiello et al, 2003). Although cases of serious adverse drug reactions such as neuroleptic malignant syndrome (Hanft et al, 2004) and liver abnormalities (Kumra et al, 1997) have been reported, there have been few well designed clinical studies in children to systematically evaluate adverse drug reactions associated with atypical antipsychotic drug use in this target population. Furthermore, since their introduction, the use of these newer generation antipsychotic drugs, the atypical antipsychotic agents, have been rising and largely replacing the older typical antipsychotic drugs in children and adolescents (Chapter 4; Rani et al, 2008b; Martin & Leslie, 2003; Kalverdijk et al, 2008). Despite this, the availability of evidence for the safety and efficacy of these drugs in the paediatric population is limited, whereby the majority of available studies are the direct or indirect result of open-label trials, reviews, and case reports (Chapter 1; Malone et al, 1999; Bhana et al, 2001; Bryden et al, 2001; Laita et al, 2007).

In the past, the safety of medicines was mainly monitored by spontaneous reporting schemes, such as the Yellow Card reporting system run by the UK MHRA. However, under-reporting is a recognised problem with this method; particularly with off-label and unlicensed use of medicines in children (Royal College of Paediatrics and Child Health,

2004). Due to the above reason, a Royal College of Paediatric and Child Health (RCPCH) report recommended the use of targeted pharmacovigilance to monitor drug safety in children (Royal College of Paediatrics and Child Health, 2004). Targeted pharmacovigilance is focused on monitoring the safety profiles of specific groups of drugs in relation to specific adverse drug reactions. This method has led to the development of evidence based guidelines to reduce drug toxicity with regards to particular groups of drugs (Royal College of Paediatrics and Child Health, 2004; Choonara, 2006). For that reason, targeted pharmacovigilance should be essential when investigating the safety of atypical antipsychotic treatment in paediatric patients.

Consequently, this chapter aims to conduct a pilot prospective targeted pharmacovigilance study in children and adolescents seen in secondary and tertiary care to monitor adverse drug reactions associated with atypical antipsychotic medications; as well as to explore the feasibility of conducting a targeted pharmacovigilance study on atypical antipsychotic therapy in children seen in secondary and tertiary care.

7.2 Methodology

Setting

Secondary and tertiary paediatric/adolescent mental health inpatient and outpatient units.

Chapter SEVEN: Paediatric Atypical antipsychotic Monitoring Safety study (PAMS)

Participants

Collaborators identified from the UK Paediatric Psychopharmacology Groups (PPGs) in London and the West Midlands. The members of the PPGs include consultant paediatricians, consultant child and adolescent psychiatrists, and paediatric pharmacists.

Inclusion criteria

Clinical practitioners within the PPG who initiated new treatments of children and adolescents (defined as patients aged 18 years or younger) with atypical antipsychotic medication.

Exclusion criteria

Clinicians who do not prescribe atypical antipsychotics regularly (i.e. at least 1 prescription every 2 months).

Reporting criteria

The participants reported the number of patients on atypical antipsychotic treatment under their care. This included the baseline number of patients when the study began,

and the number of patients starting and the number of patients stopping atypical antipsychotic treatment throughout the duration of the study.

Secondly, the participants reported all children and adolescents who fulfilled the above criteria who developed reportable adverse drug reactions. An adverse drug reaction was considered reportable if it fulfilled one of the following criteria:

- Required termination of treatment of the atypical antipsychotic agent and/or a required treatment of the suspected adverse drug reaction.
- Was an adverse drug reaction which was previously unknown, in the reporting clinician's opinion.
- Was considered 'serious' as defined in the ICH Guideline for Clinical Safety Data Management (ICH Harmonised Tripartite Guideline, 1994) which any was untoward medical occurrence that at any dose:-
    - Results in death
    - Is life-threatening
    - Requires inpatient hospitalisation or prolongation of existing hospitalisation
    - Results in persistent or significant disability or incapacity
    - Is a congenital anomaly or birth defect

Each ADR report contributed by a participating clinician may include more than 1 event. For example, a clinician may encounter a patient who experienced extrapyramidal

symptoms, as well as weight gain and thus enter this data into 1 report. Hence, each ADR report may include more than 1 ADR.

Participants were also asked to provide the following information when reporting an adverse drug reaction:

- Patient demographic details – Month and year of birth, gender.
- Atypical antipsychotic details – Name of atypical antipsychotic, dose, duration of treatment, indications.
- Details of the reaction being reported – Symptom, outcome, and actions required in the management of the adverse drug reaction.
- Additional details – Concurrent medication, additional information.

Confidence intervals for the rate of adverse drug reactions reported by type of drug were calculated using Stata SE 9.1 (Stata Corp, College Station, TX).

Data collection

Participants contributed data via a password protected online data collection form (Appendix Q). Data from one participant from a specialist tertiary hospital was collected by hand. All recorded data were then collated into a database. Data collection was conducted for one year, from September 2005 to September 2006. (Website address for online data collection form: https://www.hsytu.york.ac.uk/pams/login.aspx)

Chapter SEVEN: Paediatric Atypical antipsychotic Monitoring Safety study (PAMS)

Ethical approval was granted by a UK Multicentre Research Ethics Committee (Appendix R). Additionally, 14 Research and Development approvals to conduct the study were granted from 16 NHS trusts within London and the West Midlands. The time to obtain Research and Development approval took up to 8 months.

7.3 Results

A total of 35 clinicians consented to participate in the study. Data from 22 of the participating clinicians were excluded due to incomplete reporting. Data from the remaining 13 (37%) participating clinicians were eligible for the final analysis. The 13 participants reported baseline and follow-up number of patients on atypical antipsychotic treatment, and at least one adverse drug reaction report during the duration of the study. Characteristics of the participants are shown in Table 7.1.

There were a total of 280 patients who received atypical antipsychotic treatment under the care of the 13 participating clinicians. From these 280 patients, there were 40 adverse drug reaction reports (0.14 reports per patient; 95% CI: 0.10 to 0.19 reports per patient) from 37 patients. Of the 37 patients, 13 experienced more than 1 adverse drug reaction, bringing the total number of adverse reactions to 56 adverse drug reactions (0.20 adverse drug reactions per patient; 95% CI: 0.15 - 0.25 adverse reactions per patient). The median

age of patients who experienced adverse reactions was 15 years (inter quartile range 10 to 17 years).

Table 7.1: Participant characteristics

	All Participants	Participants with eligible data
Clinician Type		
Child / Adolescent Psychiatrists or Neuropsychiatrists	27	9
Paediatricians	8	4
Total	**35**	**13**
Practice Type		
Inpatient Units	3	1
Outpatient Units	30	11
Inpatient and Day Care Units	1	1
Inpatient, Outpatient and Day Care Units	1	0
Total	**35**	**13**

Although the highest number of reports was related to risperidone use, risperidone was also the most common type of atypical antipsychotic prescribed and in fact had the lowest rate of adverse drug reactions. Because of the relatively small sample size, the rates of adverse reactions by type of atypical antipsychotic agent demonstrate wide confidence intervals as shown in Table 7.2.

Table 7.2: Number of Adverse Drug Reactions (ADRs) reported by category

Category	Number of ADRs						
	Risperidone	Aripiprazole	Olanzapine	Clozapine	Quetiapine	Amisulpride	Total
Category 1: General Disorders							
Flu-like symptoms		1					1
Encopresis	1						1
Raised creatinine kinase	1						1
Fever		1		1			2
Neuroleptic malignant syndrome			1				1
Total	**2**	**2**	**1**	**1**			**6**
Category 2: Endocrine and Metabolic Disorders							
Raised triglycerides				1			1
Hyperprolactinaemia	3	1				3	7
Weight gain	11	1	2		3		17
Total	**14**	**2**	**2**	**1**	**3**	**3**	**25**
Category 3: Psychiatric Disorders							
Behaviour disorders		1			1		2
Total		**1**			**1**		**2**
Category 4: Nervous System Disorders							
Headaches		1					1
Sedation			1				1
Extrapyramidal symptoms	2	4	2			1	9
Total	**2**	**5**	**3**			**1**	**11**
Category 5: Cardiac, Blood and Vascular Disorders	2			1			3

Tachycardia			1	1	1		3
Hypotension				2			2
Neutropaenia	**2**		**1**	**4**	**1**		**8**
Total							
Category 6: Gastrointestinal Disorders							
Abdominal pains	1						1
Nausea	1						1
Total	**2**						**2**
Category 7: Renal and Urinary Disorders							
Enuresis	1	1					2
Total	**1**	**1**					**2**
Total	**23**	**11**	**7**	**6**	**5**	**4**	**56**
Number of patients on treatment	**156**	**56**	**38**	**8**	**16**	**7**	**281**
Rate of ADR (95% Confidence Interval)	**0.15 (0.09-0.21)**	**0.20 (0.10-0.32)**	**0.18 (0.08-0.34)**	**0.75 (0.35-0.97)**	**0.31 (0.11-0.59)**	**0.57 (0.18-0.90)**	**0.20 (0.15-0.25)**

The commonest atypical antipsychotic prescribed was risperidone (55.7% of patients), followed by aripiprazole (20.0%), olanzapine (11.1%), quetiapine (5.7%), clozapine (2.9%) and amisulpride (2.5%). The most reported adverse drug reactions according to type of antipsychotic drug correlated with the number of patients on treatment for risperidone, aripiprazole, olanzapine and amisulpride. The number and types of adverse reactions reported were grouped into 7 different categories (Table 7.2).

The durations of atypical antipsychotic drug exposure was recorded for 54 out of the 56 adverse reactions reported. The median duration of exposure was 42 days (inter quartile range 23.25 to 90 days of drug exposure).

In terms of actions required for the management of adverse drug reactions, the most common action was drug withdrawal. The suspected atypical antipsychotic drug was withdrawn in 36 out of the 56 adverse reactions reported (64% of total adverse drug reactions reported). Dose reduction of the offending drug was done in 9 of the adverse reaction reports (16%) and no action was taken in 5 of the reports (9%). Other actions for the management of adverse drug reactions include additional treatment, dietary advice, and continuous monitoring of the adverse reaction.

7.4 Discussion

As there has been substantial public interest on drug safety in children; combined with the potential effects of psychotropic medications on physical and brain development,

it is important to identify and develop valid methods for detecting possible drug-induced adverse effects seen associated with drug exposure (Greenhill et al, 2003).

This is the first target pharmacovigilance study to monitor adverse drug reactions associated with atypical antipsychotic medication in children and adolescents in UK secondary and tertiary settings. The results of this pilot study raise many key methodological issues related to conducting such a study nationally (Rani et al, 2008a).

Methodology of PAMS

The data source used for this study was clinicians from various PPGs, mainly the London PPG and the West Midlands PPG. Each PPG consists of approximately 50 members from secondary- and tertiary-care hospitals or clinics. PPG clinicians consist of mainly consultant child or adolescent psychiatrists and consultant community paediatricians. Regular meetings within the PPGs are held every 3 to 4 months where members discuss complicated cases of child psychiatric patients seen in practice, as well as updates on current research and safety issues seen in child psychiatry.

By using clinicians as the study data source, in depth data was obtained in relation to the adverse reactions reported. The reports provided useful qualitative data such as patient demographics, dose and duration of drug exposure, symptoms of the reported reactions, management and outcomes, and other important details such as concurrent medication. Furthermore, as the participating clinicians were volunteers, the study cost was minimised.

Nevertheless, because the study was clinician-based, the majority of participants were subject to time constraints which limited the amount of data contributed, specifically data on the number of patients exposed to treatment. Without this, analysis on the rate of adverse reactions was limited due to an absence of accurate information on the real-life total clinical populations including the true frequency of prescriptions to provide a denominator.

Moreover, the level of data required for this study called for a high amount of commitment from the participating clinicians. As the participants were a volunteer force, there were no specific incentives for them to contribute to this study. This might have lead to skewed results whereby only the more committed participants were the source of data. Conceivably these clinicians may represent the most enthusiastic practitioners who were more likely to prescribe for novel indications or at British National Formulary limits rather than the 'average' clinician. The final analysis would then not portray the real life scenario of typical psychopharmacotherapy practitioners.

To extend the PAMS study nationally, certain methodological issues should be addressed. The participants for this pilot period were given initial training in the way of brief instruction during PPG meetings and electronically via e-mail. A comprehensive training programme for future participants by means of one-to-one training sessions may help improve the reporting rate of participating clinicians, specifically the reporting of number of patients on treatment. As well as training, clearer agreed

definitions of what an adverse drug reaction is, the need to report and whether treatment was stopped as a result of the adverse reaction is needed. For example, serious weight gain can be defined as an increase in body weight by 20% from baseline body weight at the start of treatment. Only if a patient experiences this increase should it then be reported. These definitions can be agreed upon using a consensus panel consisting of paediatric psychopharmacologists.

With the appropriate funding, incentive payments can also be provided for participating clinicians who contribute data. An example would be the Child and Adolescent Psychiatry Trials Network (CAPTN) which currently has over 200 practicing child and adolescent psychiatrists in the USA and Canada (Child and Adolescent Psychiatry Trials Network). CAPTN sets up contracts for clinicians upon participation and provides incentives which include research costs at an hourly rate. This network provides the opportunity for members to interact and share knowledge, participate and contribute to various research projects, and ultimately improve the care of paediatric patients. Alternatively a wider reporting scheme such as that used by the British Paediatric Surveillance Unit (BPSU) which is funded by the Department of Health should also be considered. The BPSU enables paediatricians to participate in the surveillance and study of rare disorders affecting children. A constraint to this method is the lack of accurate baseline data. The PAMS study allowed for data on number of patients on treatment to be collected which can then be used to calculate a proxy of the incidence of adverse reactions from the proportion of adverse reactions to the number of new starters per month and involved both child psychiatrists as well as

paediatricians as data sources. Consequently, data obtained from a future study design complementing the current BPSU surveillance project will be particularly valuable as a BPSU or psychiatry surveillance system of atypical antipsychotics in children is currently unavailable.

The majority of participating clinicians found it difficult to report the number of patients (including baseline and follow-up number of patients) on treatment, which in turn limited the analysis of rate of adverse reactions reported. This can be overcome in the future by limiting the study to new patients where participants only report the number of patients newly starting atypical antipsychotic treatment. Alternatively, with the appropriate funding, research assistants could be employed to collect this information from different practices. This would also reduce the possibility of duplicate reporting, especially in practices where potential patients might be seen by more than one participating clinician.

Additionally, the database resulting from the future study could also be accessed by participating clinicians. This would offer a detailed, organised method of storing relevant clinical information concerning patients under their care including therapy details, any adverse reactions experienced by these patients, as well as treatment outcomes. This then may help improve clinical practice for participating clinicians.

In summary, the availability of PPGs around the UK provides a potentially useful research network which is currently underused. Research networks consisting of

practicing clinicians could potentially provide a wide range of benefits, from data for efficacy and safety research, as well as an available network for interaction and sharing of specialist knowledge. In addition, the involvement of experienced, prominent clinicians in the PPGs provides expert input into prospective future studies. A surveillance, or targeted pharmacovigilance system conducted in such a practice-based network would also allow for a large sample of study subjects and good representation of real-world clinical paediatric patients.

Adverse drug reactions reported

Despite the relatively small number of patients under the care of the participants, the study managed to capture uncommon and rare adverse reactions such as enuresis and neuroleptic malignant syndrome (NMS). NMS is considered a very rare (< 0.01% with olanzapine) and potentially fatal adverse effect associated with the use of neuroleptic medications (Electronic Medicines Compendium). The clinical symptoms of this condition include muscle rigidity, pyrexia, and increased creatine kinase levels (Burns, 2001; Hanft, et al, 2004). Additionally, there was also one case of diabetes mellitus reported in a 12 year old child who developed diabetic ketoacidosis as a result of risperidone overdose. However this data was not included in the analysis as the reporting clinician did not report the number of patients on atypical antipsychotic treatment seen in her practice. Adverse reactions that were reported but not included in the final analysis are shown in Table 7.3 (all were associated with risperidone therapy).

Table 7.3: Reported adverse drug reactions which not included in final analysis

Reported adverse drug reaction (N)	Management of adverse reaction
Tardive dyskinesia (1)	Additional treatment given
Behavioural problems: agitation (1)	Medication withdrawn
Psychiatric problems: nightmares, insomnia, hallucinations (1)	Medication withdrawn
Weight gain (2)	No action
Diabetes mellitus-associated symptoms: increased urinary frequency and thirst, ketoacidosis (1)	Dose of risperidone reduced and additional treatment and monitoring was given

The rate of adverse drug reactions reported was also extremely high with every one in 5 patients experiencing a reaction. This again may be because the data were a result from more enthusiastic or committed participating clinicians who were vigilant in detecting and reporting these events. This could also be possibly due to the sample of patients themselves, whereby patients seen by the participating clinicians are more serious cases compared to those seen in general practice. Nevertheless, a study by Harrison-Woolrych et al (2007) presented a total of 257 adverse event reports from 131 paediatric patients (31% of the identified study cohort aged 2 to 15 years) exposed to antipsychotic therapy. Weight gain was the most reported adverse event in the cohort (Harrison-Woolrych et al, 2007), which is in line with the results demonstrated from the PAMS study. The study also managed to capture 2 reports of diabetes

mellitus (Harrison-Woolrych et al, 2007). Additionally, results from another large retrospective safety study investigating children exposed to antipsychotic therapy reported that a quarter of the study sample experienced between 1 to 3 co morbid metabolic and cardiovascular conditions including obesity, diabetes mellitus and hypertension by the end of the study duration (McIntyre & Jerrell, 2008). Consequently, the possibility of a high rate of adverse drug reactions, and the presence of rare or serious events in children who are treated with atypical antipsychotic drugs should not be ignored.

The majority of reported adverse drug reactions of weight gain in the PAMS study were managed by withdrawing the atypical antipsychotic agent. As a point of interest, in recent years, other possible management strategies for weight gain have been investigated such as pharmacological approaches with orlistat (Green et al, 2000), amantadine (Stigler et al, 2004) and metformin (Klein et al, 2006). Metformin has been studied for the management of weight gain as an adjunct to atypical antipsychotic therapy in a randomised controlled trial in children (Klein et al, 2006). The study reported that metformin was well tolerated and effective in reducing the effect of weight gain associated with atypical antipsychotic treatment, as well as producing a facilitating effect in reducing impaired glucose tolerance and decreased insulin sensitivity in the study subjects (Klein et al, 2006).

Although the atypical antipsychotic agents have slight differences in their respective pharmacology, the potential adverse effects of these medications are thought to be

comparatively similar due to the similar pharmacological action (Burns, 2001). This presents a prescribing problem to practitioners treating patients with neuropsychiatric conditions from the paediatric population as the choice of medications available for children and adolescents is relatively limited. As most of these drugs are used outside their licensed indications in patients less than 18 years of age, there is also a lack of dosing guidelines available for clinicians. Furthermore, although the PAMS study demonstrated good qualitative data, there was not enough power to compare the rate of reported adverse reactions by the different types of atypical antipsychotic agents due to the relatively small sample size of the study. As a result of this, wide confidence intervals for the rates of adverse reactions are demonstrated. Additionally, as the data collection period was conducted for only one year, adverse effects that may emerge slowly and subtly may have escaped detection (Greenhill et al, 2003). Nevertheless, as this project was a pilot study, these issues are expected.

7.5 Conclusions

This study demonstrated that a clinician-based targeted pharmacovigilance study on atypical antipsychotic therapy in children provides useful qualitative data. For future studies, it is recommended that a more improved research design is needed to ensure rigorous and accurate data collection. Appropriate research funding and research support is required to recruit and maintain pharmacovigilance in a wider sample of clinical practices by providing for costs of management and high quality on-site data collection. Furthermore, the study yielded a very high rate of adverse reactions, including rare conditions. As utilisation studies including the pharmacoepidemiological

study in Chapter 5 have demonstrated a rising trend of atypical antipsychotic prescribing to the paediatric population, this indicates an urgent need for improved pharmacovigilance studies to evaluate the safety of these drugs in children.

8 Chapter EIGHT: Overall conclusions

Antipsychotic treatment is an important component of pharmacological management in paediatric psychiatry practice for wide variety of severe mental and behavioural disorders. However, the majority of these agents are used in an off-label manner, or outside their product license. Furthermore, these agents are being increasingly used for off-label indications despite a lack in properly established safety guidelines and paucity in tolerability studies in the paediatric population. Little controlled evidence has been fully established with regards to the safety of antipsychotic therapy in children. Results from the pharmacoepidemiological analyses of antipsychotic prescribing also indicate the prescribing trend for these drugs seem to be continuously rising, with a prevalence which almost doubled from 1992 to 2005. The greatest increase was revealed to occur in children in the 7 to 12 year age band for what were probably non-licensed indications. The newer atypical antipsychotic agents were shown to be replacing the older typical antipsychotic drugs throughout the study duration.

There are a number of challenging issues in conducting safety studies in children and adolescents, including small samples of study subjects as well as a lack of a properly validated method of collecting side effect data (Greenhill et al, 2003). Using the GPRD, the largest antipsychotic-treated paediatric cohort in the UK was identified. From this cohort, it was demonstrated that the antipsychotic drugs do not cause frequent serious adverse drug reactions. While the mortality study indicated a high mortality rate in antipsychotic-treated children compared to the general population, it was

revealed that antipsychotic therapy was not associated with the cause of death in the majority of the identified subjects. This however, highlighted a possibly inadequacy in the management of certain medical conditions including epilepsy, Creutzfeldt-Jakob disease and depression. Results from the safety studies indicated a low incidence and risk of liver abnormalities and diabetes mellitus in the study cohort. It was also demonstrated that there was no increase in risk for antipsychotic-exposed paediatric patients to develop diabetes mellitus compared to the general paediatric population.

However, these studies lacked the power to study rare events that occur at a rate less than 0.1%. Chapter 6 further discusses additional methods which could be adopted for future studies, including combining large databases and using a case-crossover design.

The PAMS study in Chapter 7 provided an alternative method for investigating the safety of antipsychotic agents in children. The results from Chapter 7 demonstrated that targeted pharmacovigilance is a valuable method for investigating antipsychotic drug safety, particularly for the increasingly used atypical antipsychotic agents. The study established that data obtained from secondary and tertiary care clinicians provided useful figures and demonstrated various adverse drug reactions associated with these drugs. Furthermore, the PAMS study demonstrated a very high rate of adverse reactions, and interestingly, a number of rare conditions were also reported. It is recommended that a nationwide targeted pharmacovigilance study on atypical antipsychotic therapy in children should be prioritised. It is also suggested that this method of investigation should be further explored to better understand and quantify

adverse drug reactions associated with these agents in the paediatric population, and ultimately improve the quality of healthcare in children with psychiatric conditions.

Taken as a whole, it is hoped that the overall results and interpretations of the studies conducted contribute to the growing body of knowledge in this area, and ultimately help clinicians avoid potential harm and improve the overall care and management of paediatric patients exposed to antipsychotic therapy.

References

Ackers R, Murray ML, Besag FMC, Wong ICK (2007), Prioritizing children's medicines for research: a pharmacoepidemiological study of antiepileptic drugs. *British Journal of Clinical Pharmacology*, 63(6): 689-697.

Adams CE, Rathbone J, Thornley B, Clarke M, Borrill J, Wahlbeck K, Awad AG (2005), Chlorpromazine for schizophrenia: a Cochrane systematic review of 50 years of randomized controlled trials. *BMC Medicine*, http://www.biomedcentral.com/1741-7015/3/15, Accessed on 20 June 2006.

Ad-dab'bagh Y, Greenfield B, Milne-Smith J, Freedman H (2000), Inpatient treatment of severe disruptive behaviour disorders with risperidone and milieu therapy. *Canadian Journal of Psychiatry*, 45: 376-382.

Ahmed S, Chengappa R, Naidu VR, Baker RW, Parepally H, Schooler NR (1998), Clozapine withdrawal-emergent dystonias and dyskinesias: a case series. *Journal of Clinical Psychiatry*, 59: 472-477.

Alacqua M, Trifiro G, Arcoraci V, Germano E, Magazu A, Valarase T, Di Vita G, Gagliano C, Spina E (2008), Use and tolerability of newer antipsychotics and antidepressants: a chart review in a paediatric setting. *Pharmacy World & Science*, 30(1): 44-50.

References

Allebeck P (1989), Schizophrenia: A life-shortening disease. *Schizophrenia Bulletin*, 15(1): 81-89.

Aman MG, Arnold LE, McDougle CJ, Vitiello B, Scahill L, Davies M, McCracken JT, Tierney E, Nash PL, Posey DJ, Chuang S, Martin A, Shah B, Gonzalez NM, Swiezy NB, Ritz L, Koenig K, McGough J, Ghuman JK, Lindsay RL (2005), Acute and long-term safety and tolerability of risperidone in children with autism. *Journal of Child and Adolescent Psychopharmacology*, 15(6): 869-884.

Aparasu RR & Bhatara V (2005), Antipsychotic prescribing trends among youths, 1997-2002. *Psychiatric Services*, 56(8):904.

Aparasu RR & Bhatara V (2007), Patterns and determinants of antipsychotic prescribing in children and adolescents, 2003-2004. *Current Medical Research & Opinion*, 23(1): 49-56.

Appleton RE (2003), Mortality in paediatric epilepsy. *Archives of Disease in Childhood*, 88(12): 1091-1094.

Armenteros JL & Davies M (2006), Antipsychotics in early onset schizophrenia. *European Child and Adolescent Psychiatry*, 15: 141-148.

References

Armenteros JL, Whitaker AH, Welikson M, Stedge DJ, Gorman J (1997), Risperidone in adolescents with schizophrenia: an open pilot study. *Journal of the American Academy of Child and Adolescent Psychiatry*, 36(5): 694-700.

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

Baldessarini RJ & Tarazi FI (2001), . Hardman JG, Limbird LE (Ed) (2001), *Goodman & Gilman's The Pharmacological basis of therapeutics 10th edition*. McGraw-Hill Companies, USA; pp 492.

Baldridge AD, Perez-Atayde AR, Graeme-Cook F, Higgins L, Lavine LE (1995), Idiopathic steatohepatitis in childhood: a multicentre retrospective study. *Journal of Pediatrics*, 127(5): 700-704.

Bebarta VS, Kostic MA, Gonzalez MG (2005), Managing adverse reactions to psychotropic medications. *Pediatric Annals*, 34(12): 947-954.

Berry N, Pradhan S, Sagar R, Gupta SK (2003), Neuroleptic malignant syndrome in an adolescent receiving olanzapine-lithium combination therapy. *Pharmacotherapy*, 23(2): 255-259.

References

Bhana N, Foster RH, Olney R, Plosker GL (2001), Olanzapine: An updated review of its use in the management of schizophrenia. *Drugs*, 61(1): 111-161.

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

Biswas PN, Wilton LW, Pearce GL, Freemantle S, Shakir SAW (2001), The pharmacovigilance of olanzapine: results of a post-marketing surveillance study on 8858 patients in England. *Journal of Psychopharmacology*, 15(4): 265-271.

Bitter I (2006), Pharmacological treatment of schizophrenia. *European Neurological Disease*; pp 93-94. http://www.touchbriefings.com/pdf/1981/bitter.pdf. Accessed 18 July 2006.

Bland M (1993), *An Introduction to Medical Statistics.* Oxford University Press, UK; pp 299-302.

Bloch Y, Vardi O, Mendlovic S, Levkovitz Y, Gothelf D, Ratzoni G (2003), Hyperglycemia from olanzapine treatment in adolescents. *Journal of Child and Adolescent Psychopharmacology*, 13(1): 97-102.

Borison R (1997), Recent Advances in the Pharmacotherapy of Schizophrenia. *Harvard Review of Psychiatry*, 4: 255-271.

References

Bramble D (2003), Annotation: The use of psychotropic medications in children: a British view. *Journal of Child Psychology and Psychiatry*, 44(2): 169-179.

British National Formulary (2008). http://www.bnf.org. Accessed 15 August 2008.

Brown CS, Farmer RG, Soberman JE, Eichner SF (2004), Pharmacokinetic factors in the adverse cardiovascular effects of antipsychotic drugs. *Clinical Pharmacokinetics*, 43(1): 33-56.

Brown TM (1999), Clozapine, Neuroleptic malignant syndrome, and pancerebellar syndrome. *Psychosomatics*, 40(6): 518-520.

Bryden KE, Carrey NJ, Kutcher SP (2001), Update and recommendations for the use of antipsychotics in early-onset psychoses. *Journal of Child and Adolescent Psychopharmacology*, 11(2): 113-130.

Burns MJ (2001), The pharmacology and toxicology of atypical antipsychotic agents. *Clinical Toxicology*, 39(1): 1-14.

Bymaster FP, Calligaro DO, Falcone JF, March RD, Moore NA, Tye NC, Seeman P, Wong DT (1996), Radioreceptor binding profile of the antipsychotic olanzapine. *Neuropsychopharmacology*, 14(2): 87-96.

References

Campbell EG, Russell LG, Mountford J, Miller LG, Cleary PD, Blumenthal D. A national survey of physician-industry relationships (2007), *New England Journal of Medicine*, 356: 1742-1750.

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

Campbell M, Rapoport JL, Simpson GM (1999), Antipsychotics in children and adolescents. *Journal of the American Academy of Child and Adolescent Psychiatry*, 38(5): 537-545.

Cannon TD, Huttunen MO, Dahlström M, Larmo I, Räsänen P, Juriloo A (2002), Antipsychotic drug treatment in the prodromal phase of schizophrenia. *American Journal of Psychiatry*, 159(7): 1230-1232.

Carlson C, Hornbuckle K, DeLisle F, Kryzhanovskaya L, Breir A, Cavazzoni P (2006), Diabetes Mellitus and antipsychotic treatment in the United Kingdom. *European Neuropsychopharmacology*, 16(5): 366-375.

Casaer P, Croonenberghs JAN, Lagae L, Deboutte D (2002), Risperidone in the treatment of childhood autistic disorder: an open pilot study. *Acta Neuropsychiatrica*, 14: 242-249.

References

Casey DE (1999), Tardive dyskinesia and atypical antipsychotic drugs. *Schizophrenia Research,* 35: S61-S66.

Casey DE, Haupt DW, Newcomer JW, Henderson DC, Sernyak J, Davidson M, Lindenmayer J, Manoukian SV, Banerji MA, Lebovitz HE, Hennekens CH (2004), Antipsychotic-induced weight gain and metabolic abnormalities: implications for increased mortality in patients with schizophrenia. *Journal of Clinical Psychiatry,* 65(Suppl 7): 4-18.

Cheer SM & Wagstaff AJ (2004), Quetiapine: A review of its use in the management of schizophrenia. *CNS Drugs*, 18(3): 173-199.

Cheng-Shannon J, McGough JJ, Pataki C, McCracken JT (2004), Second-generation antipsychotic medications in children and adolescents. *Journal of Child and Adolescent Psychopharmacology*, 14(3): 372-394.

Child and Adolescent Psychiatry Trials Network. http://www.captn.org. Accessed 22 January 2008.

Choonara I (2006), Paediatric pharmacovigilance. *Paediatric and Perinatal Drug Therapy*, 7(2): 50-53.

Clark A (2001), Proposed treatment for adolescent psychosis. 2: Bipolar illness. *Advances in Psychiatric Treatment,* 7: 143-149.

References

Clark AF (2004), Incidences of new prescribing by British child and adolescent psychiatrists: a prospective study over 12 months. *Journal of Psychopharmacology*, 18(1): 115-120.

Clark TG, Bradburn MJ, Love SB, Altman DG (2003), Survival analysis part I: basic concepts and first analysis. *British Journal of Cancer*, 89: 232-238.

Clarkson A & Choonara I (2002), Surveillance for fatal suspected adverse drug reactions in the UK. *Archives of Disease in Childhood*, 87: 462-467.

Coghill D (2003), Current issues in child and adolescent psychopharmacology. Part 2: Anxiety and obsessive-compulsive disorders, autism, Tourette's and schizophrenia. *Advances in Psychiatric Treatment,* 9: 289-299.

Cohen D & Huinink S (2007), Atypical antipsychotic-induced diabetes mellitus in child and adolescent psychiatry. *CNS Drugs,* 21(12): 1035-1038.

Committee on Safety of Medicines (2000), Thioridazine: restricted indications and new warnings on cardiotoxicity.
http://www.info.doh.gov.uk/doh/embroadcast.nsf/f011981a95f31f4180256c07003d34a0/fc5d1f63a16da86b80256dad00480816?OpenDocument. Accessed 13 June 2006.

References

Committee on Safety of Medicines (2003), Selective serotonin reuptake inhibitors – Use in children and adolescents with major depressive disorder. http://www.info.doh.gov.uk/doh/embroadcast.nsf/0/183a970c6d74afad80256df800338c99/$FILE/CEM2003-20.doc. Accessed 22 June 2006.

Conroy S, McIntyre J, Choonara I, Stephenson T (2000), Drug trials in children: problems and the way forward. *British Journal of Clinical Pharmacology*, 49: 93-97.

Cooper WO, Hickson GB, Fuchs C, Arbogast PG, Ray WA (2004), New users of antipsychotic medications among children enrolled in TennCare. *Archives of Pediatrics and Adolescent Medicine*, 158: 753 -759.

Cordeiro Jr Q & Elkis H (2001), Pancreatitis and cholestatic hepatitis induced by risperidone. *Journal of Clinical Psychopharmacology*, 21(5): 529-530.

Correll CU (2007), Weight gain and metabolic effects of mood stabilizers and antipsychotics in pediatric bipolar disorder: a systematic review and pooled analysis of short-term trials. *Journal of the American Academy of Child and Adolescent Psychiatry*, 46(6): 267-700.

Correll CU (2008), Antipsychotic use in children and adolescents: minimizing adverse effects to maximize outcomes. *Journal of the American Academy of Child and Adolescent Psychiatry*, 47(1): 9-20.

References

Correll CU & Kane JM (2007), One-year incidence rates of tardive dyskinesia in children and adolescents treated with second-generation antipsychotics: a systematic review. *Journal of Child and Adolescent Psychopharmacology*, 17(5): 647-655.

Correll CU, Leucht S, Kane JM (2004), Lower risk for tardive dyskinesia associated with second-generation antipsychotics: a systematic review of 1-year studies. *American Journal of Psychiatry*, 161: 414-425.

Courvoisie HE, Cooke DW, Riddle MA (2004), Olanzapine-induced diabetes in a seven-year-old boy. *Journal of Child and Adolescent Psychopharmacology*, 14(4): 612-616.

Croonenberghs J, Fegert JM, Findling RL, De Smedt G, Van Dongen S, Risperidone Disruptive Behavior Study Group (2005), Risperidone in children with disruptive behavior disorders and subaverage intelligence: a 1-year, open-label study of 504 patients. *Journal of the American Academy of Child and Adolescent Psychiatry*, 44(1): 64-72.

Davis JM, Chen N, Glick ID (2003), A meta-analysis of the efficacy of second-generation antipsychotics. *Archives of General Psychiatry*, 60: 553-564.

Dean AJ, McDermott BM, Marshall RT (2006), Psychotropic medication utilization in a child and adolescent mental health service. *Journal of Child and Adolescent Psychopharmacology*, 16(3): 273-285.

References

DelBello MP, Schwiers ML, Rosenberg HL, Strakowski SM (2002), A double-blind, randomized, placebo-controlled study of quetiapine as adjunctive treatment for adolescent mania. *Journal of the American Academy of Child and Adolescent Psychiatry*, 41(10): 1216-1223.

Diler RS, Firat S, Avci A (2002), An open-label trial of risperidone in children with autism. *Current Therapeutic Research*, 63(1): 91-102.

Doey T, Handelman K, Seabrook JA, Steele M (2007), Survey of atypical antipsychotic prescribing by Canadian child psychiatrists and developmental pediatricians for patients aged under 18 years. *Canadian Journal of Psychiatry*, 52(6): 363-368.

Domon SE & Webber JC (2001), Hyperglycemia and hypertriglyceridemia secondary to olanzapine. *Journal of Child and Adolescent Psychopharmacology*, 11(3): 285-288.

DuBois D (2005), Toxicology and overdose of atypical antipsychotic medications in children: does newer necessarily mean safer? *Current Opinion in Pediatrics,* 17: 227-233.

Earls F & Mezzacappa E (2002), Conduct and Oppositional Disorders, in Rutter M & Taylor E (ed.). *Child and Adolescent Psychiatry 4th edition*. Blackwell Publishing Company, UK; pp. 419.

Efron D, Hiscock H, Sewell JR, Cranswick NE, Vance AL, Tyl Y, Luk ES (2003), Prescribing of psychotropic medications for children by Australian pediatricians and child psychiatrists. *Pediatrics*, 111(2): 372-375.

Electronic Medicines Compendium. http://emc.medicines.org.uk. Accessed 14 July 2008.

Ercan ES, Kutlu A, Çıkoğlu S, Veznedaroğlu B, Erermis S, Varan A (2003), Risperidone in children and adolescents with conduct disorder. *Current Therapeutic Research*, 64(1): 55-64.

Erdogan A, Atasoy N, Akkurt H, Ozturk D, Karaahmet E, Yalug I, Yalug K, Ankarali H, Balsioglu I (2008), Risperidone and liver function tests in children and adolescents: a short-term prospective study. *Progress in Neuro-Psychopharmacology and Biological Psychiatry*, 32(3): 849-857.

Erdogan A, Kocabasoglu N, Yalug I, Ozbay G, Senturk H (2004), Management of marked liver enzyme increase during clozapine treatment: a case report and review of the literature. *International Journal of Psychiatry in Medicine*, 34(1): 83-89.

European Medicines Agency (2008), Revised priority list for studies into off-patent paediatric medicinal products. http://www.emea.europa.eu/pdfs/human/paediatrics/22698308en.pdf . Accessed 29 September 2008.

References

Findling RL (2002), Use of quetiapine in children and adolescents. *Journal of Clinical Psychiatry*, 63(Suppl 13): 27-31.

Findling RL, Aman MG, Eeerdekens M, Derivan A, Lyons B (2004), Long-term, open-label study of risperidone in children with severe disruptive behaviors and below-average IQs. *American Journal of Psychiatry*, 161: 677-684.

Findling RL & McNamara NK (2004), Atypical antipsychotics in the treatment of children and adolescents: clinical applications. *Journal of Clinical Psychiatry*, 65(Suppl 6): 30-44.

Findling RL, McNamara NK, Branicky L, Schluchter MD, Lemon E, Blumer JL (2000), A double-blind pilot study of risperidone in the treatment of conduct disorder. *Journal of the American Academy of Child and Adolescent Psychiatry*, 39(4): 509-516.

Findling RL, McNamara NK, Youngstrom EA, Branicky LA, Demeter CA, Schulz C (2003), A prospective, open-label trial of olanzapine in adolescents with schizophrenia. *Journal of the American Academy of Child and Adolescent Psychiatry*, 42(2): 170-175.

Findling RL, Robb A, Nyilas M, Forbes RA, Jin N, Ivanova S, Marcus R, McQuade RD, Iwamoto T, Carson WH (2008), A multiple-center, randomized, double-blind, placebo-controlled study of oral aripiprazole for treatment of adolescents with schizophrenia. *American Journal of Psychiatry*, 165: 1432-1441.

References

Findling RL, Schulz SC, Reed MD, Blumer JL (1998), The antipsychotics. A pediatric perspective. *Pediatric Clinics of North America*, 45(5): 1205-1232.

Frazier JA, Gordon CT, McKenna K, Lenane MC, Jih D, Rapoport JL (1994), An open label trial of clozapine in 11 adolescents with childhood-onset schizophrenia. *Journal of the American Academy of Child and Adolescent Psychiatry*, 33(5): 658-663.

Frangou S & Byrne P (2000), How to manage the first episode of schizophrenia. *British Medical Journal*, 321: 522-523.

Fuller MA, Simon MR, Freedman L (1996), Risperidone-associated hepatotoxicity. *Journal of Clinical Psychopharmacology*, 16(1): 84-85.

Gaertner I, Altendorf K, Batra A, Gaertner HJ (2001), Relevance of liver enzyme elevations with four different neuroleptics: a retrospective review of 7,263 treatment courses. *Journal of Clinical Psychopharmacology*, 21: 215-222.

Gaffney GR, Perry PJ, Lund BC, Bever-stille KA, Arndt S, Kuperman S (2002), Risperidone versus clonidine in the treatment of children and adolescents with Tourette's syndrome. *Journal of the American Academy of Child and Adolescent Psychiatry*, 41(3): 330-336.

Gagliano A, Germanò E, Pustorino G, Impallomeni C, D'Arrigo C, Calamoneri F, Spina E (2004), Risperidone treatment of children with autistic disorder: effectiveness, tolerability, and pharmacokinetic implications. *Journal of Child and Adolescent Psychopharmacology*, 14(1): 39-47.

Geddes J, Freemantle N, Harrison P, Bebbington P (2000), Atypical antipsychotics in the treatment of schizophrenia: systemic overview and meta-regression analysis. *British Medical Journal*, 321: 1371-1376.

Geller WK & Zuiderwijk P (1998), Risperidone-induced hepatotoxicity? *Journal of the American Academy of Child and Adolescent Psychiatry*, 37(3): 246-247.

Gencer O, Emiroglu FNI, Miral S, Baykara B, Baykara A, Dirik E (2008), Comparison of long-term efficacy and safety of risperidone and haloperidol in children and adolescents with autistic disorder. *European Child and Adolescent Psychiatry*, 17: 217-225.

Gillberg C (2000), Typical neuroleptics in child and adolescent psychiatry. *European Child and Adolescent Psychiatry*, 9: I/2-I/8.

Gilbert D, Batterson RB, Sethuraman G, Sallee FR (2004), Tic reduction with risperidone versus pimozide in a randomized, double-blind, crossover trial. *Journal of the American Academy of Child and Adolescent Psychiatry*, 43(2): 206-214.

Glazer WM (2000). Review of incidence studies of tardive dyskinesia with typical antipsychotics. *Journal of Clinical Psychiatry*, 61(Suppl 2): 15-20.

Goldstein LE, Sporn J, Brown S, Kim H, Finkelstein J, Gaffey GK, Sachs G, Stern TA (1999), New–onset diabetes mellitus and diabetic ketoacidosis associated with olanzapine treatment. *Psychosomatics*, 40(5): 438-443.

Gonzalez-Heydrich J, Raches D, Wilens TE, Leichtner A, Mezzacappa E (2003), Retrospective study of hepatic enzyme elevations in children treated with olanzapine, divalproex, and their combination. *Journal of the American Academy of Child and Adolescent Psychiatry*, 42(10): 1227-1233.

Gothelf D, Apter A, Reidman J, Brand-Gothelf A, Bloch Y, Gal G, Kikinzon L, Tyano S, Weizman R, Ratzoni G (2003), Olanzapine, risperidone and haloperidol in the treatment of adolescent patients with schizophrenia. *Journal of Neural Transmission*, 110: 545-560.

Gracious BL & Findling RL (2001), Antipsychotic medications for children and adolescents. *Pediatric Annals*, 30(3): 138-145.

Green AI, Patel JK, Goisman RM, Allison DB, Blackburn G (2000), Weight gain from novel antipsychotic drugs: need for action. *General Hospital Psychiatry*, 22: 224-235.

Greenhill LL, Vitiello B, Abikoff H, Levine J, March JS, Riddle MA, Capasso L, Cooper TB, Davies M, Fisher P, Findling RL, Fried J, Labellarte MJ, McCracken JT, McMahon D, Robinson J, Skrobala A, Scahill L, Varipatis E, Walkup JT, Zito JM (2003), Developing methodologies for monitoring long-term safety of psychotropic medications in children: report on the NIMH conference, September 25, 2000. *Journal of the American Academy of Child and Adolescent Psychiatry*, 42(6): 651-655.

Haddad PM & Anderson IM (2002), Antipsychotic-related QTc prolongation, Torsade de Pointes and sudden death. *Drugs*, 62(11): 1649-1671.

Haddad PM & Wieck A (2004), Antipsychotic-induced hyperprolactinaemia: mechanisms, clinical features and management. *Drugs*, 64(20): 2291-2314.

Hägg S, Joelsson L, Mjörndal T, Spigset O, Oja G, Dahlqvist R (1998), Prevalence of diabetes and impaired glucose tolerance in patients treated with clozapine compared with patients treated with conventional depot neuroleptic medications. *Journal of Clinical Psychiatry*, 59(6): 294-299.

Hammerman S, Lam C, Caroff SN (2006), Neuroleptic malignant syndrome and aripiprazole. *Journal of the American Academy of Child and Adolescent Psychiatry*, 45(6): 639-641.

Hanft A, Eggleston CF, Bourgeois JA (2004), Neuroleptic malignant syndrome in an adolescent after brief exposure to olanzapine. *Journal of Child and Adolescent Psychopharmacology*, 14(3): 481-487.

Harrington R (2002), Affective Disorders, in Rutter M & Taylor E (ed.). *Child and Adolescent Psychiatry 4th edition*. Blackwell Publishing Company, UK; pp. 475.

Harris EC & Barraclough B (1998), Excess mortality of mental disorder. *British Journal of Psychiatry*, 176: 11-53.

Harrison-Woolrych M, Garcia-Quiroga J, Ashton J, Herbison P (2007), Safety and usage of atypical antipsychotic medicines in children: a nationwide prospective cohort study. *Drug Safety*, 30(7): 569-579.

Henderson DC, Cagliero E, Gray C, Nasrallah RA, Hayden DL, Schoenfeld DA, Goff DC (2000), Clozapine, diabetes mellitus, weight gain, and lipid abnormalities: a five-year naturalistic study. *American Journal of Psychiatry*, 157: 975-981.

Hennekens CH & Buring JE (1987), in Mayrent SL (ed.). *Epidemiology in Medicine 1st edition*. Lippincott Williams & Wilkins, USA; pp 17

Hernández-Díaz S, Hernán A, Meyer K, Werler MM, Mitchell AA (2003), Case-Crossover and Case-Time-Control designs in birth defects epidemiology. *American Journal of Epidemiology*, 158(4): 385-391.

Hollis C (2002), Schizophrenia and Allied Disorders, in Rutter M & Taylor E (ed.). *Child and Adolescent Psychiatry 4th edition*. Blackwell Publishing Company, UK; pp. 612-613.

Hollowell J (1997), The General Practice Research Database: quality of morbidity data. *Population Trends*, 87: 36-40.

Holtmann M, Kopf D, Mayer M, Bechtinger E, Schmidt MH (2003a), Risperidone-associated steatohepatitis and excessive weight-gain. *Pharmacopsychiatry*, 36: 207-209.

Holtmann M, Meyer AE, Pitzer M, Schmidt MH (2003b), Risperidone-induced marked elevation of serum creatine-kinase in adolescence. *Pharmacopsychiatry*, 36: 317-318.

Horacek J, Bubenikova-Valesova V, Kopecek M, Palenicek T, Dockery C, Mohr P, Höschl C (2006), Mechanism of action of atypical antipsychotic drugs and the neurobiology of schizophrenia. *CNS Drugs*, 20(5): 389-409.

Hummer M, Kurz M, Kurzthaler I, Oberbauer H, Miller C, Fleischhacker W (1997), Hepatotoxicity of clozapine. *Journal of Clinical Psychopharmacology*, 17(4): 314-317.

Ichikawa J & Melzter HY (1999), Relationship between dopaminergic and serotonergic neuronal activity in the frontal cortex and the action of typical and atypical

antipsychotic drugs. *European Archives of Psychiatry and Clinical Neuroscience*, 249(Suppl 4): IV90-IV98.

ICH Harmonised Tripartite Guideline (1994), Clinical Safety Data Management: Definitions and Standards for Expedited Reporting 1994. http://www.ich.org/LOB/media/MEDIA436.pdf Accessed 03 January 2008.

Impicciatore P, Choonara I, Clarkson A, Provasi D, Pandolfini C, Bonati M (2001), Incidence of adverse drug reactions in paediatric in/out-patients: a systematic review and meta-analysis of prospective studies. *British Journal of Clinical Pharmacology*, 52: 72-83.

Jacobs ES, Dickstein DP, Liebelt EL (2001), Novel psychotropic medications in children: new toxicities to master. *Pediatric Emergency Care*, 17(3): 226-231.

Jerrell JM & McIntyre RS (2008), Adverse events in children and adolescents treated with antipsychotic medications. *Human Psychopharmacology*, 23(4): 283-290.

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

Jick H, Jick SS, Derby LE (1991), Validation of information recorded on general practitioner based computerised data resource in the United Kingdom. *British Medical Journal*, 302: 766-768.

Jick H, Terris BZ, Derbe LE, Jick SS (1992), Further validation of information recorded on a general practitioner based computerized data resource in the United Kingdom. *Pharmacoepidemiology and Drug Safety*, 1(6): 347-349.

Jones PB, Barnes TRE, Davies L, Dunn G, Lloyd H, Hayhurst KP, Murray RM, Markwick A, Lewis SW (2006), Randomized controlled trial of the effect of quality of life of second- vs first-generation antipsychotic drugs in schizophrenia. *Archives of General Psychiatry*, 63: 1079-1087.

Kalverdijk LJ, Hilde T, van den Berg PB, Buiskool J, Wagenaar L, Minderaa RB, de Jong-van den Berg L (2008), Use of antipsychotic drugs among Dutch youths between 1997 and 2005. *Psychiatric Services*, 59(5): 554-560.

Kane JM (2004), Tardive dyskinesia rates with atypical antipsychotics in adults: prevalence and incidence. *Journal of Clinical Psychiatry*, 65(Suppl 9): 16-20.

Kane J, Honigfeld G, Singer J, Meltzer H (1988), Clozapine for the treatment-resistant schizophrenic. A double-blind comparison with chlorpromazine. *Archives of General Psychiatry*, 45(9): 789-796.

Kaplan SL, Rimms RM, Busner J (1994), Prescribing practices of outpatient child psychiatrists. *Journal of the American Academy of Child and Adolescent Psychiatry*, 33(1): 35-44.

Kapur S (1996), 5-HT_2 antagonism and EPS benefits: is there a causal connection? *Psychopharmacology*, 124: 35-39.

Kemner C, Willemsen-Swinkels SHN, De Jonge M, Tuynman-Qua H, Van Engeland H (2002), Open-label study of olanzapine in children with pervasive developmental disorder. *Journal of Clinical Psychopharmacology*, 22: 455-460.

Killian JG, Kerr L, Lawrence C, Celermajer DS (1999), Myocarditis and cardiomyopathy associated with clozapine. *Lancet*, 354: 1841-1845

King B, Zwi K, Nunn K, Longworth J, Dossetor D (2003), Use of risperidone in a paediatric population: an observational study. *Journal of Paediatrics and Child Health*, 39: 523-527.

Kinon BJ & Lieberman JA (1996). Mechanisms of action of atypical antipsychotic drugs: a critical analysis. *Psychopharmacology*, 124: 2-34.

Klein DJ, Cottingham EM, Sorter M, Barton BA, Morrison JA (2006), A randomized, double-blind, placebo-controlled trial of metformin treatment of weight gain associated with initiation of atypical antipsychotic therapy in children and adolescents. *American Journal of Psychiatry*, 163: 2072-2079.

Koller EA, Cross JT, Schneider B (2004), Risperidone-associated diabetes mellitus in children. *Pediatrics*, 113(2): 421.

Koller E & Malozowski S (2001), Atypical antipsychotic drugs and hyperglycemia in adolescents. *Journal of the American Medical Association*, 286(20): 2547-2548.

Koller E, Schneider B, Bennett K, Dubitsky G (2001), Clozapine-associated diabetes. *American Journal of Medicine*, 111: 716-723.

Kornegay CJ, Vasilakis-Scaramozza V, Jick H (2002), Incident diabetes associated with antipsychotic use in the United Kingdom General Practice Research Database. *Journal of Clinical Psychiatry*, 63: 758-762.

Kumra S, Frazier JA, Jacobsen LK, McKenna K, Gordon CT, Lenane MC, Hamberger SD, Smith AK, Albus KE, Alaghband-Rad J, Rapoport JL (1996), Childhood-onset schizophrenia: a double-blind clozapine-haloperidol comparison. *Archives of General Psychiatry*, 53: 1090-1097.

Kumra S, Herion D, Jacobsen LK, Briguglia C, Grothe D (1997), Case study: risperidone-induced hepatotoxicity in pediatric patients. *Journal of the American Academy of Child and Adolescent Psychiatry*, 36(5): 701-705.

Kumra S, Jacobsen LK, Lenane M, Karp BI, Frazier JA, Smith AK, Bedwell J, Lee P, Malanga CJ, Hamburger S, Rapoport JL (1998), Childhood-onset schizophrenia: an

open-label study of olanzapine in adolescents. *Journal of the American Academy of Child and Adolescent Psychiatry*, 37: 377-385.

Kumra S, Oberstar JV, Sikich L, Findling RL, McClellan JM, Vinogradov S, Schulz SC (2008), Efficacy and tolerability of second-generation antipsychotics in children and adolescents with schizophrenia. *Schizophrenia Bulletin*, 34(1): 60-71.

La Grenade L, Graham D, Trontell A (2001), Myocarditis and cardiomyopathy associated with clozapine use in the United States. *New England Journal of Medicine*, 345: 224-225

Labellarte MJ, Crosson JE, Riddle MA (2003), The relevance of prolonged QTc measurement to pediatric psychopharmacology. *Journal of the American Academy of Child and Adolescent Psychiatry*, 42(6): 642-650.

Lader M (2006), Lethal complications of antipsychotic drug complication. *Clinical Risk*, 12(3): 113-117

Laita P, Cifuentes A, Doll A, Llorente C, Cortés I, Parellada M, Moreno D, Ruiz-Sancho A, Graell M, Arango C (2007), Antipsychotic-related abnormal involuntary movements and metabolic and endocrine side effects in children and adolescents. *Journal of Child and Adolescent Psychopharmacology*, 17(4): 487-501.

Lane H, Liu Y, Huang C, Chang Y, Wu P, Lu C, Chang W (2006), Risperidone related weight gain: genetic and nongenetic predictors. *Journal of Clinical Psychopharmacology*, 26(2): 128-134.

Leckman JF & Cohen DJ (2002), Tic Disorders, in Rutter M & Taylor E (ed.). *Child and Adolescent Psychiatry 4th edition*. Blackwell Publishing Company, UK; pp. 593.

Lekhwani M, Nair C, Nikhinson I, Ambrosini PJ (2004), Psychotropic prescription practices in child psychiatric inpatients 9 years old and younger. *Journal of Child and Adolescent Psychopharmacology*, 14(1): 95-103.

Leucht S, Pitschel-Walz G, Abraham D, Kissling W (1999), Efficacy and extrapyramidal side-effects of the new antipsychotics olanzapine, quetiapine, risperidone, and sertindole compared to conventional antipsychotics and placebo. A meta-analysis of randomized controlled trials. *Schizophrenia Research*, 35: 51-68.

Leucht S, Wahlbeck K, Hamann J, Kissling W (2003), New generation antipsychotics versus low-potency antipsychotics: a systematic review and meta-analysis. *The Lancet*, 361: 1581-1589

Levenson J (1985), Neuroleptic malignant syndrome. *American Journal of Psychiatry*, 142(10): 1137-1145.

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

Lewis R (1998), Typical and atypical antipsychotics in adolescent schizophrenia: efficacy, tolerability and differential sensitivity to extrapyramidal symptoms. *Canadian Journal of Psychiatry*, 43: 596-604.

Lieberman JA (2006). Comparative effectiveness of antipsychotic drugs. *Archives of General Psychiatry*, 63: 1069-1072.

Lieberman J, Jody D, Geisler S, Alvir J, Loebel A, Szymanski S, Woerner M, Borenstein M (1993), Time course and biologic correlates of treatment response in first-episode schizophrenia. *Archives of General Psychiatry*, 50(5): 369-376.

Lieberman JA, Stroup S, McEvoy J, Swartz MS, Rosenhack RA, Perkins DO, Keefe RS, Davis SM, Davis CE, Lebowitz BD, Severe J, Hsiao JK (2005), Clinical antipsychotic trials of intervention effectiveness (CATIE) investigators. Effectiveness of antipsychotic drugs in patients with chronic schizophrenia. *New England Journal of Medicine*, 353: 1209-1223

Liebzeit KA, Markowitz JS, Caley CJ (2001), New onset diabetes and atypical antipsychotics. *European Neuropsychopharmacology*, 11: 25-32.

Llinares Tello F, Pratz HC, Ros NB, Martínez EP, Grana EC, Polo JNN, Baines JPO (2005), Acute cholestatic hepatitis probably associated with risperidone. *International Journal of Psychiatry in Medicine*, 35(2): 199-205.

Logue DD, Gonzalez N, Heligman SD, McLaughlin JV, Belcher HM (2007), Hyperglycemia in a 7-year-old child treated with aripiprazole. *American Journal of Psychiatry*, 164(1): 173.

Lohr JB & Braff DL (2003), The value of referring to recently introduced antipsychotics as "second generation". *American Journal of Psychiatry*, 160: 1371-1372.

Lombroso PJ, Scahill L, King R, Lynch K, Chappell PB, Peterson B, McDougle CJ, Leckman JF (1995), Risperidone treatment of children and adolescents with chronic tic disorders: a preliminary report. *Journal of the American Academy of Child and Adolescent Psychiatry*, 34(9): 1147-1152.

Loranger AW (1984), Sex differences in age at onset of schizophrenia. *Archives of General Psychiatry*, 41(2): 157-161.

Lord C & Bailey A (2002), Autistic Spectrum Disorder, in Rutter M & Taylor E (ed.). *Child and Adolescent Psychiatry 4th edition*. UK: Blackwell Publishing Company; pp. 636-637.

Lyons JS, MacIntyre JC, Lee ME, Carpinello S, Zuber MP, Fazio ML (2004), Psychotropic medications prescribing patterns for children and adolescents in New York's public mental health system. *Community Mental Health Journal*, 40(2): 101-118.

Macfarlane B, Davies S, Mannan K, Sarsam R, Pariente D, Dooley J (1997), Fatal acute fulminant liver failure due to clozapine: a case report and review of clozapine-induced hepatotoxicity. *Gastroenterology*, 112(5): 1707-1709.

Mackin P, Watkinson HM, Young AH (2005), Prevalence of obesity, glucose homeostasis disorders and metabolic syndrome in psychiatric patients taking typical or atypical antipsychotic drugs: a cross-sectional study. *Diabetologia*, 48: 215-221.

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

Malone RP, Sheikh R, Zito JM (1999), Novel antipsychotic medications in the treatment of children and adolescents. *Psychiatric Services*, 50(2): 171-174.

Malone RP, Cater J, Sheikh RM, Choudhury MS, Delaney MA (2001), Olanzapine versus haloperidol in children with autistic disorder: an open pilot study. *Journal of the American Academy of Child and Adolescent Psychiatry*, 40(8): 887-894.

Mané A, Baeza I, Morer A, Lázaro ML, Bernardo M (2005), Neuroleptic malignant syndrome associated with risperidone in a male with early-onset schizophrenia. *Journal of Child and Adolescent Psychopharmacology*, 15: 844-845.

Martin A, Landau J, Leebens P, Ulizio K, Cicchetti D, Scahill L, Leckman JF (2000), Risperidone-associated weight gain in children and adolescents: a retrospective chart review. *Journal of Child and Adolescent Psychopharmacology*, 10(4): 259-268.

Martin A & Leslie D (2003), Trends in psychotropic medication costs for children and adolescents, 1997-2000. *Archives of Pediatrics and Adolescent Medicine*, 157(10): 997-1004.

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

McClellan JM & Werry JS (2003), Evidence-based treatments in child and adolescent psychiatry: an inventory. *Journal of the American Academy of Child and Adolescent Psychiatry*, 42(12): 1388-1400.

McCracken JT, McGough J, Shah B, Cronin P, Hong D, Aman MG, Arnold LE, Lindsay R, Nash P, Hollway J, McDougle CJ, Posey D, Swiezy N, Kohn A, Scahill L, Martin A, Koenig K, Volkmar F, Carroll D, Lancor A, Tierney E, Ghuman J, Gonzalez NM, Grados M, Vitiello B, Ritz L, Davies M, Robinson J, McMahon D (2002), Risperidone in children

with autism and serious behavioral problems. *New England Journal of Medicine*, 347(5): 314-321.

McIntyre RS & Jerrell JM (2008), Metabolic and cardiovascular adverse events associated with antipsychotic treatment in children and adolescents. *Archives of Pediatrics and Adolescent Medicine*, 162(10): 929-935.

Medicines and Healthcare Products Regulatory Agency (2005) *The General Practice Research Database*. GPRD User Manual.

Meltzer HY (2004), What's atypical about atypical antipsychotic drugs? *Current Opinion in Pharmacology*, 4: 53-57.

Meyer JM (2002), A retrospective comparison of weight, lipid, and glucose changes between risperidone- and olanzapine-treated inpatients: metabolic outcomes after 1 year. *Journal of Clinical Psychiatry*, 63: 425-433.

MHRA Prescribing information for thioridazine. http://www.mhra.gov.uk/home/idcplg?IdcService=GET_FILE&dDocName=CON019553&RevisionSelectionMethod=LatestReleased. Accessed 13 June 2008.

Miller DD, Caroff SN, Davis SM, Rosenhack RA, McEvoy JP, Saltz BL, Riggio S, Chakos MH, Swartz MS, Keefe RSE, Stroup TS, Lieberman JA (2008), Extrapyramidal side-

effects of antipsychotics in a randomised trial. *British Journal of Psychiatry*, 193: 279-288.

Montoliu L & Crawford T (2002), Prescribing practices of general practitioners for children with mental health problems. *Child and Adolescent Mental Health*, 7(3): 128-130.

Murray ML, de Vries CS, Wong ICK (2004), A drug utilisation study of antidepressants in children and adolescents using the General Practice Research Database. *Archives of Disease in Childhood*, 89: 1098-1102.

Najjar F, Welch C, Grapentine WL, Sachs H, Siniscalchi J, Price LH (2004), Trends in psychotropic drug use in a child psychiatric hospital from 1991-1998. *Journal of Child and Adolescent Psychopharmacology*, 14(1): 87-93.

Naruse H, Nagahata M, Nakane Y, Shirahashi K, Takesada M, Yamazaki K (1982), A multi-center double-blind trial of pimozide (Orap), haloperidol and placebo in children with behavioral disorders, using crossover design. *Acta Paedopsychiatrica*, 48: 173-184.

Nazareth I, King M, Haines A, Rangel L, Myers S (1993), Accuracy of diagnosis on general practice computer system. *British Medical Journal*, 307: 32-34.

References

National Institute for Health and Clinical Excellence (2002). *Schizophrenia core interventions in the treatment and management of schizophrenia in primary and secondary care. Clinical Guideline 1.* http://guidance.nice.org.uk/CG1/niceguidance/pdf/English. Accessed 17 April 2007.

Newcomer JW, Haupt DW, Fucetola R, Melson AK, Schweiger JA, Cooper BP, Selke G (2002). Abnormalities in glucose regulation during antipsychotic treatment of schizophrenia. *Archives of General Psychiatry*, 59: 337-345.

Nitenson NC, Kando JC, Frankenburg FR, Zararini MC (1995), Fever associated with clozapine administration. *The American Journal of Psychiatry*, 152(7): 1102.

Olfson M, Blanco C, Liu L, Moreno C, Laje G (2006), National trends in the outpatient treatment of children and adolescents with antipsychotic drugs. *Archives of General Psychiatry*, 63: 679 -685.

Osby U, Correia N, Brandt L, Ekbom A, Sparen P (2000), Mortality and causes of death in schizophrenia in Stockholm County, Sweden. *Schizophrenia Research*, 45: 21-28.

Pappagallo M & Silva R (2004), The effect of atypical antipsychotic agents on prolactin levels in children and adolescents. *Journal of Child and Adolescent Psychopharmacology*, 14(3): 359-371.

Patel NC, Crismon ML, Hoagwood K, Johnsrud MT, Rascati KL, Wilson JP (2006a), Physician specialty associated with antipsychotic prescribing for youths in the Texas Medicaid program. *Medical Care*, 44(1): 87-90.

Patel NC, Crismon ML, Shafer A (2006b), Diagnoses and antipsychotic treatment among youths in a public mental health system. *Annals of Pharmacotherapy*, 40: 205-211.

Patel NC, Sanchez RJ, Johnsrud MT, Crismon ML (2002), Trends in antipsychotic use in a Texas Medicaid population of children and adolescents: 1996 to 2000. *Journal of Child and Adolescent Psychopharmacology*, 12(3): 221-229.

Pelonero AL, Levenson JL, Pandurangi AK (1998), Neuroleptic malignant syndrome: a review. *Psychiatric Services*, 49(9): 1163-1172.

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

Perry R, Pataki C, Munoz-Silva DM, Armenteros J, Silva RR (1997), Risperidone in children and adolescents with pervasive developmental disorder: pilot trial and follow-up. *Journal of Child and Adolescent Psychopharmacology*, 7(3): 167-179.

Pi-Sunyer FX (1993), Medical hazards of obesity. *Annals of Internal Medicine*, 119(7, part 2): 665-660.

Piscitelli SC, Frazier JA, McKenna K, Albus KE, Grothe DR, Gordon CT, Rapoport JL (1994), Plasma clozapine and haloperidol concentrations in adolescents with childhood-onset schizophrenia: association with response. *Journal of Clinical Psychiatry*, 55(9, Suppl B): 94-97.

Pool D, Bloom W, Mielke DH, Roniger JJ, Gallant DM (1976), A controlled evaluation of Loxitane in seventy-five adolescent schizophrenic patients. *Current Therapeutic Research* 1976; 19: 99-104.

Potenza MN, Janice P, Stephen J, McDougle C (1999), Olanzapine treatment of children, adolescents, and adults with pervasive developmental disorders: an open-label pilot study. *Journal of Clinical Psychopharmacology*, 19(1): 37-44.

Powers P, Santana CA, Bannon YS (2002), Olanzapine in the treatment of anorexia nervosa: an open label trial. *International Journal of Eating Disorders*, 32: 146-154.

Prusiner SB (2001), Shatturk lecture – Neurodegenerative diseases and prions. *New England Journal of Medicine*, 344(20): 1516-1526.

Ragucci KR & Wells BJ (2001), Olanzapine-induced diabetic ketoacidosis. *Annals of Pharmacotherapy*, 35(12): 1556-1558.

References

Rang HP, Dale MM, Ritter JM (1999), *Pharmacology*. Churchill Livingstone, UK; pp 542-544; 546-457

Rani FA, Byrne PJ, Murray ML, Carter P, Wong ICK (2008a), Paediatric Atypical antipsychotic Monitoring Safety study (PAMS): Pilot study in children and adolescents in secondary- and tertiary-care settings. *Drug Safety* (Accepted 11 November 2008)

Rani F, Murray ML, Byrne PJ, Wong ICK (2008b), Epidemiologic features of antipsychotic prescribing to children and adolescents in primary care in the United Kingdom. *Pediatrics*, 121(5): 1002-1009.

Ray WA & Meador KG (2002), Antipsychotics and sudden death: is thioridazine the only bad actor? *British Journal of Psychiatry*, 180:483-484.

Reilly JG, Ayis SA, Ferrier IN, Jones SJ, Thomas SHL (2000), QTc-interval abnormalities and psychotropic drug therapy in psychiatric patients. *The Lancet*, 355: 1048-1052.

Report of an international consensus meeting (1990), Criteria of drug-induced liver disorders. *Journal of Hepatology*, 11: 272-276.

Rey JM & Sawyer MG (2003), Are psychostimulant drugs being used appropriately to treat child and adolescent disorders? *British Journal of Psychiatry*, 182: 284 -286.

Rigalleau V, Gatta B, Bonnaudt S, Masson M, Bourgeois ML, Vergnot V, Gin H (2000), Diabetes as a result of atypical anti-psychotic drugs – a report of three cases. *Diabetic Medicine*, 17: 484-486.

Robb AS, Chang W, Lee HK, Cook MS (2000), Risperidone-induced Neuroleptic malignant syndrome in an adolescent. *Journal of Child and Adolescent Psychopharmacology*, 10(4): 327-330.

Rodríguez LAG, Duque A, Castellsague J, Perez-Gutthann S, Stricker BHC (1999), A cohort study on the risk of acute liver injury among users of ketoconazole and other antifungal drugs. *British Journal of Clinical Pharmacology*, 48: 847-852.

Rodríguez LAG & Gutthann SP (1998), Use of the UK General Practice Research Database for pharmacoepidemiology. *British Journal of Clinical Pharmacology*, 45: 419-425.

Ross RG, Novins D, Farley GK, Adler LE (2003), A 1-year open-label trial of olanzapine in school-age children with schizophrenia. *Journal of Child and Adolescent Psychopharmacology*, 13(3): 301-309.

Royal College of Paediatrics and Child Health (2004), *Safer and Better Medicines for Children. Developing the Clinical and Research Base of Paediatric Pharmacology in the United Kingdom. A review commissioned by The Medical Research Council, the Department of Health, and the Association of British Pharmaceutical Industry.*

http://www.rcpch.ac.uk/Publications/Publications-list-by-date. Accessed 07 February 2008.

Ruschena D, Mullen PE, Burgess P, Cordner SM, Barry-Walsh J, Drummer OH, Palmer S, Browne C, Wallace C (1998), Sudden death in psychiatric patients. *British Journal of Psychiatry*, 172: 331-336.

Sachdev P, Kruk J, Kneebone M, Kissane D (1995), Clozapine-induced neuroleptic malignant syndrome: review and report of new cases. *Journal of Clinical Psychopharmacology*, 15(5): 365-371.

Safer DJ (2004), A comparison of risperidone-induced weight gain across the age span. *Journal of Clinical Psychopharmacology*, 24: 429-436.

Saito E, Correll CU, Gallelli K, McMeniman M, Parikh UH, Malhotra AK, Kafantaris V (2004), A prospective study of hyperprolactinemia in children and adolescents treated with atypical antipsychotic agents. *Journal of Child and Adolescent Psychopharmacology*, 14(3): 350-358.

Saito E & Kafantaris V (2002), Can diabetes mellitus be induced by medication? *Journal of Child and Adolescent Psychopharmacology*, 12(3): 231-236.

Sallee FR, Nesbitt L, Jackson C, Sine L, Sethuraman G (1997), Efficacy of haloperidol and pimozide in children and adolescents with Tourette's disorder. *American Journal of Psychiatry*, 154(8): 1057-1062.

Sathpathy S & Winsberg B. Extrapyramidal symptoms in children on atypical antipsychotic drugs. *Journal of Clinical Psychopharmacology*, 23(6): 675-677.

Scahill L & Lynch KA (1998), Atypical neuroleptics in children and adolescents. *Journal of Child and Adolescent Psychiatric Nursing*, 11(1): 38-43.

Scahill L & Skrypeck A (1997), The use of traditional neuroleptics in children and adolescents. *Journal of Child and Adolescent Psychiatric Nursing*, 10(3): 41-45.

Schirm E, Tobi H, Zito JM, de Jong-van den Berg LTW (2001), Psychotropic medication in children: a study from the Netherlands. *Pediatrics*, 108(2): e25.

Seeman P & Lee T (1975), Antipsychotic drugs: direct correlation between clinical potency and presynaptic action on dopamine neurons. *Science*, 188: 1217-1219.

Selva KA & Scott SM (2001), Diabetic ketoacidosis associated with olanzapine in an adolescent patient. *Journal of Pediatrics*, 138(6): 936-938.

Sharma R, Trappler B, Ng YK, Leeman CP (1996), Risperidone-induced neuroleptic malignant syndrome. *The Annals of Pharmacotherapy*, 30: 775-778.

Sikich L, Hamer RM, Bashford RA, Sheitman BB, Lieberman JA (2004), A pilot study of risperidone, olanzapine, and haloperidol in psychotic youth: a double-blind, randomized, 8-week trial. *Neuropsychopharmacology*, 29: 133-145.

Skarpathiotakis M & Westreich N (2005), NMS after clozapine initiation. *Journal of the American Academy of Child and Adolescent Psychiatry*, 44(11): 1101-1102.

Spalding S (2004), Aripiprazole and atypical Neuroleptic malignant syndrome. *Journal of the American Academy of Child and Adolescent Psychiatry*, 43(12): 1457-1458.

Spencer EK & Campbell M (1994), Children with schizophrenia: diagnosis phenomenology and pharmacotherapy. *Schizophrenia Bulletin*, 20: 713-725.

Staller JA, Wade MJ, Baker M (2005), Current prescribing patterns in outpatient child and adolescent psychiatric practice in central New York. *Journal of Child and Adolescent Psychopharmacology*, 15(1): 57-61.

Stigler KA, Potenza MN, McDougle CJ (2001), Tolerability profile of atypical antipsychotics in children and adolescents. *Paediatric Drugs*, 3(12): 927-942.

Stigler KA, Potenza MN, Posey DJ, McDougle CJ (2004), Weight gain associated with atypical antipsychotic use in children and adolescents. *Pediatric Drugs*, 6(1): 33-44.

Straus SMJM, Bleumink GS, Dieleman JP, van der Lei J, 't Jong GW, Kingma H, Sturkenboom MCJM, Strickler BHC (2004), Antipsychotics and the risk of sudden cardiac death. *Archives of Internal Medicine*, 164: 1293-1297.

Stolley PD & Laporte J (2003), The Public Health, the University, and Pharmacoepidemiology, in Strom B (ed.). *Pharmacoepidemiology 3rd edition.* John Wiley & Sons, USA; pp 86.

Strom B (2003), What is Pharmacoepidemiology?, in Strom B (ed.). *Pharmacoepidemiology 3rd edition.* John Wiley & Sons, USA; 3-5.

Sutcliffe AG & Wong ICK (2006), Rational prescribing for children. *British Medical Journal*, 332: 1464 -1465.

Svensson TH (2003), Preclinical effects of conventional and atypical antipsychotic drugs: defining the mechanisms of action. *Clinical Neuroscience Research*, 3: 34-46.

Szigethy E, Wiznitzer M, Branicky LA, Maxwell K, Findling RL (1999), Risperidone-induced hepatotoxicity in children and adolescents? A chart review study. *Journal of Child and Adolescent Psychopharmacology*, 9(2): 93-98.

Tamminga CA (2003), The science of antipsychotics: mechanistic insight. *CNS Spectrums*, 11(Suppl 2): 5-9.

Thatcher GW, Cates M, Blair B (1995), Clozapine induced toxic hepatitis. *American Journal of Psychiatry*, 152: 296-297.

The General Practice Research Database. http://www.gprd.com. Accessed 03 July 2007.

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

Turgay A, Binder C, Snyder R, Fisman S (2005), Long-term safety and efficacy of risperidone for the treatment of disruptive behavior disorders in children with subaverage IQs. *Pediatrics*, 110(3): e34

Uppsala Monitoring Centre. Causality assessment of suspected adverse drug reactions. http://www.who-umc.org/DynPage.aspx?id=22682 . Accessed: 20 May 2007.

Van Staa T & Abenhaim L (1994), The quality of information recorded on a UK database of primary care records: A study of hospitalizations due to hypoglycemia and other conditions. *Pharmacoepidemiology and Drug Safety*, 3(1): 15-21.

Variant Creutzfeldt-Jacob Disease (2002), http://www.cjd.ed.ac.uk/cjdtype.htm#variant Accessed 03 November 2008.

Vercammen L, Buyse GM, Proost JEF, Van Hove JLK (2003), Neuroleptic malignant syndrome in juvenile neuronal ceroid lipofuscinosis associated with low-dose risperidone therapy. *Journal of Inherited Metabolic Disease*,26(6): 611-612.

Vetter VL, Elia J, Erickson C, Berger S, Blum N, Uzark K, Webb CL (2008), Cardiovascular monitoring of children and adolescents with heart disease receiving medications for attention deficit/hyperactivity disorder: a scientific statement from the American Heart Association Council on cardiovascular disease in the Young Congenital Cardiac Defects Committee and the Council on Cardiovascular Nursing. *Circulation*, 117: 2407-2423.

Vitiello B, Riddle MA, Greenhill LL, March JS, Levine J, Schachar RJ, Abikoff H, Zito J, McCracken JT, Walkup JT, Findling RL, Robinson JM, Cooper TB, Davies M, Varipatis E, Labellarte MJ, Scahill L, Capasso L (2003), How can we improve the assessment of safety in child and adolescent psychopharmacology? *Journal of the American Academy of Child and Adolescent Psychiatry*, 42(6): 634-641.

Wahlbeck K, Cheine M, Essali A (1999a), Evidence of clozapine's effectiveness in schizophrenia: a systematic review and meta-analysis of randomized trials. *American Journal of Psychiatry*, 156: 990-999.

Wahlbeck K, Cheine MV, Essali A (1999b), Clozapine versus typical neuroleptic medication for schizophrenia. *The Cochrane Database of Systematic Reviews*, Issue 4. Art. No.: CD000059. DOI: 10.1002/14651858.CD000059

References

Walley T & Mantgani A (1997), The UK General Practice Research Database. *Lancet*, 350: 1097-1099.

Webb P, Bain C, Pirozzo S (2005), *Essential Epidemiology: An Introduction for students and health professionals*. Cambridge University Press UK; pp 49; 58.

Wheatley M, Plant J, Reader H, Brown G, Cahill C (2004), Clozapine treatment of adolescents with posttraumatic stress disorder and psychotic symptoms. *Journal of Clinical Psychopharmacology*, 24: 167-173.

Whittington CJ, Kendall T, Fonagy P, Cottrell D, Cotgrove A, Boddington E (2004), Selective serotonin reuptake inhibitors in childhood depression: systematic review of published versus unpublished data. *Lancet*, 363: 1341-1345.

Wirshing DA, Spellberg BJ, Erhart SM, Marder SR, Wirshing WC (1998), Novel antipsychotics and new onset diabetes. *Biological Psychiatry*, 44(8): 778-783.

Wong ICK & Murray ML (2005), The potential of UK clinical databases in enhancing paediatric medication research. *British Journal of Clinical Pharmacology*, 59(6): 750-755.

Wong ICK, Murray ML, Camilleri-Novak D, Stephens P (2004), Increased prescribing trends of paediatric psychotropic medications. *Archives of Disease in Childhood*, 89: 1131-1132.

Wood L & Martinez C (2004), The General Practice Research Database. *Drug Safety*, 27(12): 871-881.

Woods SW, Martin A, Spector SG, McGlashan TH (2002), Effects of development on olanzapine-associated adverse events. *Journal of the American Academy of Child and Adolescent Psychiatry*,41(12): 1439-1446.

Worrall R, Wilson A, Cullen M (1995), Dystonia and drug-induced hepatitis in a patient treated with clozapine. *American Journal of Psychiatry*, 152: 647-648.

Wudarsky M, Nicolson R, Hamburger SD, Spechler L, Gochman P, Bedwell J, Lenane MC, Rapoport JL (1999), Elevated prolactin in pediatric patients on typical and atypical antipsychotics. *Journal of Child and Adolescent Psychopharmacology*, 9(4): 239-245.

Yan J (2007), Risperidone approved to treat schizophrenia in children. *Psychiatric News*, 42(18): 1

Zalsman G, Lewis R, Konas S, Loesbtein O, Goldberg P, Burguillo F, Nahshoni E, Munitz H (2004), Atypical neuroleptic malignant syndrome associated with risperidone

treatment in two adolescents. *International Journal of Adolescent Medicine and Health*,16(2): 179-182.

Zarate CA (2001), Sudden cardiac death and antipsychotic drugs. *Archives of General Psychiatry*, 58: 1168-1171.

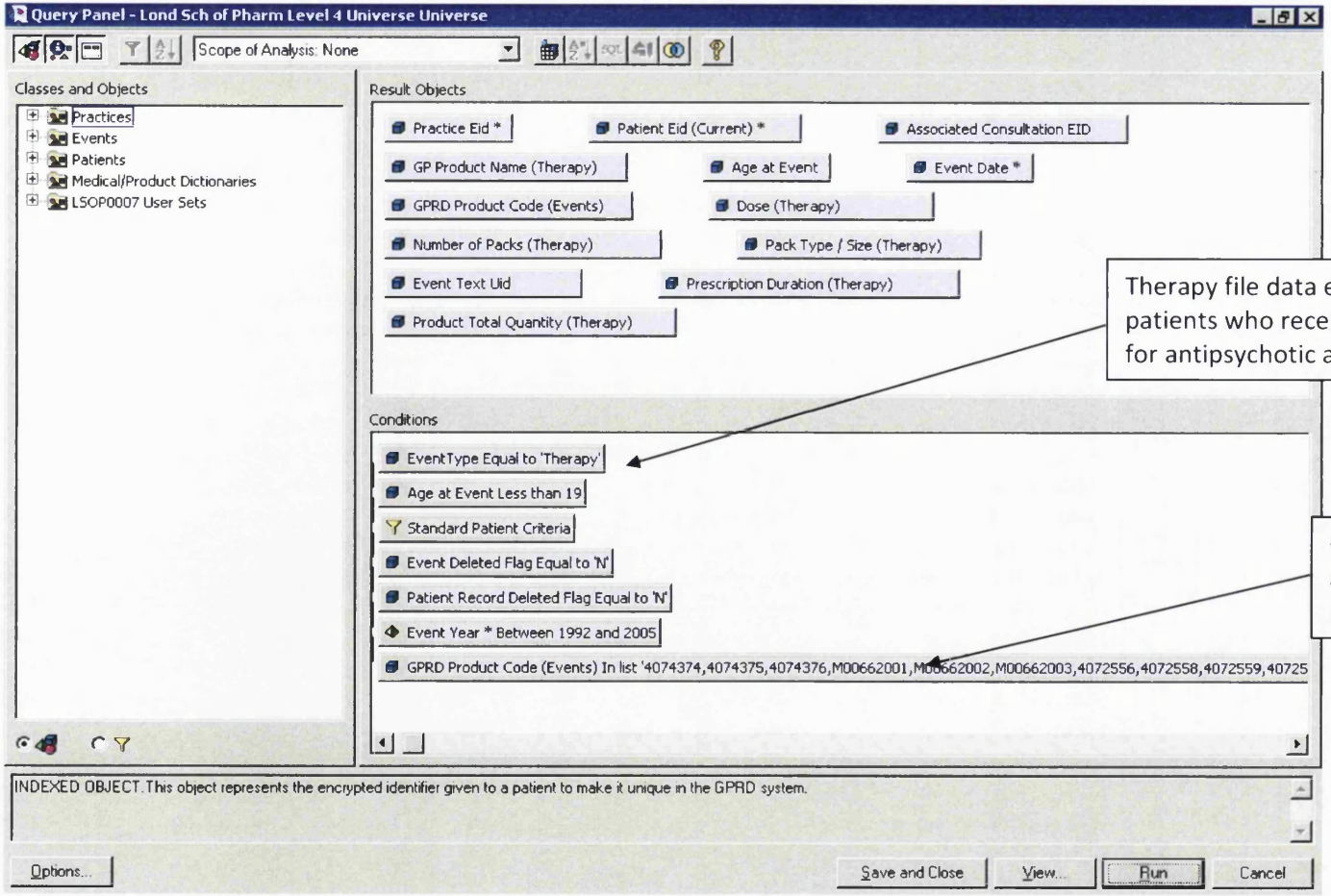
Zito JM, Safer DJ, dosReis S, Gardner JF, Boles M, Lynch F (2000), Trends in the prescribing of psychotropic medications to preschoolers. *Journal of the American Medical Association*, 283(8): 1025-1030.

Appendices

Appendix A: GPRD Product codes of antipsychotic drugs

Please refer to the Appendix data CD for the full list of Product codes of antipsychotic drugs

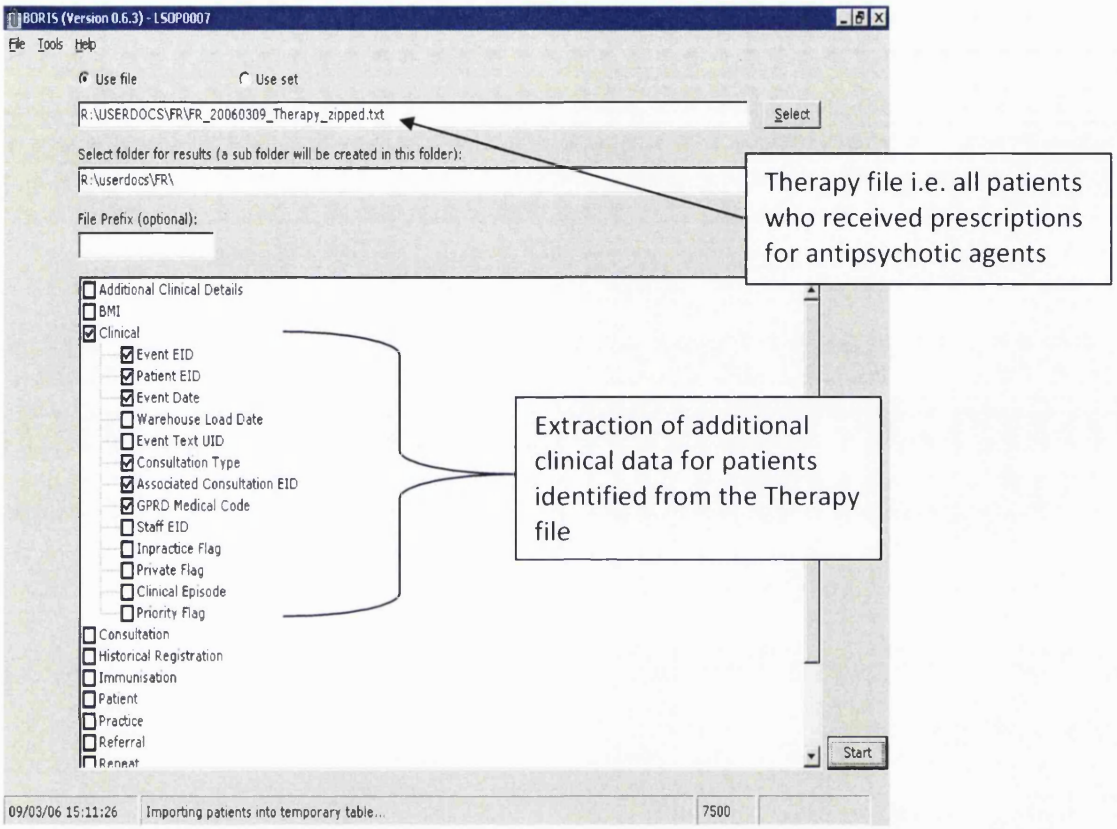
Appendix B: Screen shot of a GPRD query using Business Objects



Therapy file data extraction i.e. all patients who received prescriptions for antipsychotic agents

GPRD product codes for antipsychotic agents (Appendix A)

Appendix C: Screen shot of a GPRD query using BORIS



Appendix D: Example of an electronic patient profile

GPRD

Excellence in Public Health Research

GPRD Patient Profile Report

Patient No:	1			
ID:361048S-221148	FAM.ID:3767	Up to Standard date: 01/07/1998	REG: 02/09/1994	Permanent
Male	YOB: 1982	Marit.Stat:Unknown	Age in 2007: 25	
Trnsfr out Date:		Trnsfr out Rsn:		

Patient Events

Event Type*: 'CL' = Clinical; 'Rf' = Referral; 'Ts' = Test; 'Im'= Immunisation; 'Th' = Therapy; 'Rp' = Repeat. ** If event type is Test ('Ts'), the "Other Event Information" column contains results and units. If event type is Referral ('Rf'), the same column contains the organisation type. If event type is Immunisation ('Im') the column contains immunisation status.

Event Date	Event Type*	Read Term / Product Name	Dictionary Codes	MedDRA PT	Immunisation Type (Compound)	Other Event Information**
14/06/94	CL	Closed fracture of the radial shaft	S232100	Radius fracture		
14/11/94	Im	Measles/rubella vaccination	66M2.00		MR (No Data)	Given
26/11/95	CL	BCG vaccination	663..11	Immunisation		
18/02/97	Im	First diphtheria vaccination	6641.00		DIPHTHERIA (No Data)	Given
18/02/97	Im	First polio vaccination	6681.00		POLIO (No Data)	Given
18/02/97	Im	First tetanus vaccination	6661.00		TETANUS (No Data)	Given
15/08/99	CL	Nondependent alcohol abuse	E250.00	Alcoholism		
25/04/00	CL	Telephone encounter	9N31.00			
27/04/00	CL	Had a chat to patient	6CB..00			
09/05/00	CL	C/O - feeling depressed	1B17.11	Depression		
09/05/00	CL	C/O - feeling depressed	1B17.11	Depression NEC		
26/06/00	CL	Patient reviewed	6A...00			
26/06/00	Th	SULPIRIDE tablets 200mg (SULPIRIDE)				

** If event type is Test ('Ts'), the "Other Event Information" column contains results and units. If event type is Referral ('Rf'), the same column contains the organisation type. If event type is Immunisation ('Im') the column contains immunisation status.

1

Event Date	Event Type*	Read Term / Product Name	Dictionary Codes	MedDRA PT	Immunisation Type (Compound)	Other Event Information**
30/06/00	CL	Patient reviewed	6A...00			
06/07/00	CL	Patient reviewed	6A...00			
06/07/00	CL	Transient insomnia	E274100	Insomnia		
06/07/00	CL	Transient insomnia	E274100	Insomnia NEC		
06/07/00	Th	ZOLPIDEM tablets 10mg (ZOLPIDEM)				
12/07/00	CL	Hallucinations	1B1E.00	Hallucination		
12/07/00	CL	Hallucinations	1B1E.00	Hallucination NOS		
07/08/00	Th	SULPIRIDE tablets 200mg (SULPIRIDE)				
07/08/00	Th	ZOLPIDEM tablets 10mg (ZOLPIDEM)				
25/08/00	CL	MED4 Doctors statement	9DF..00			
25/08/00	CL	Tremor symptom	1B22.11	Tremor		
25/08/00	CL	Tremor symptom	1B22.11	Tremor NEC		
25/08/00	Th	TRIHEXYPHENIDYL HYDROCHLORIDE tablets 2mg (BENZHEXOL)				
01/09/00	Rp	N/A				
01/09/00	Th	OLANZAPINE orodispersible tablet 10mg ()				
04/09/00	Th	ZOLPIDEM tablets 10mg (ZOLPIDEM)				
08/09/00	CL	MED5 - doctor's special stat	9D2..00			
08/09/00	CL	Toothache	J05y.11	Toothache		
08/09/00	Th	AMOXICILLIN capsules 250mg (AMOXYCILLIN)				
15/11/00	Th	OLANZAPINE orodispersible tablet 10mg ()				
21/11/00	Rp	N/A				
21/11/00	Th	OLANZAPINE orodispersible tablet 10mg ()				

** If event type is Test ('Ts'), the "Other Event Information" column contains results and units. If event type is Referral ('Rf'), the same column contains the organisation type. If event type is Immunisation ('Im') the column contains immunisation status.

Event Date	Event Type*	Read Term / Product Name	Dictionary Codes	MedDRA PT	Immunisation Type (Compound)	Other Event Information**
28/12/00	Th	OLANZAPINE orodispersible tablet 10mg ()				
30/01/01	Th	OLANZAPINE orodispersible tablet 10mg ()				
26/02/01	CL	Telephone encounter	9N31.00			
26/02/01	Th	OLANZAPINE orodispersible tablet 10mg ()				
26/03/01	Th	OLANZAPINE orodispersible tablet 10mg ()				
26/04/01	Th	OLANZAPINE orodispersible tablet 10mg ()				
25/05/01	Rp	N/A				
25/05/01	Th	OLANZAPINE orodispersible tablet 10mg ()				
18/06/01	CL	Letter from specialist	9N36.00			
18/06/01	Th	QUETIAPINE starter pack ()				
25/06/01	Th	QUETIAPINE tablets 150mg (QUETIAPINE)				
05/07/01	CL	Telephone encounter	9N31.00			
23/09/01	CL	Paroxysmal supraventricular tachycardia	G570.00	Supraventricular tachycardia		
19/11/01	CL	Schizophrenic disorders	E10..00	Schizophrenia		
19/11/01	CL	Schizophrenic disorders	E10..00	Schizophrenia NOS		
23/11/01	CL	O/E - blood pressure reading	246..00	Blood pressure		
23/11/01	CL	Patient reviewed	6A...00			
30/11/01	CL	Blood withdrawal	7L17.00			
01/12/01	Ts	Basophil count	42L..00	Basophil count		10.03
01/12/01	Ts	Eosinophil count	42K..00	Eosinophil count		10.33
01/12/01	Ts	Haematocrit - PCV	425..00	Haematocrit		0.42 %
01/12/01	Ts	Haemoglobin estimation	423..00	Haemoglobin		14.8 g/dL

** If event type is Test ('Ts'), the "Other Event Information" column contains results and units. If event type is Referral ('Rf'), the same column contains the organisation type. If event type is Immunisation ('Im') the column contains immunisation status.

Event Date	Event Type*	Read Term / Product Name	Dictionary Codes	MedDRA PT	Immunisation Type (Compound)	Other Event Information**
01/12/01	Ts	Lymphocyte count	42M..00	Lymphocyte count		12.03
01/12/01	Ts	Mean corpusc. haemoglobin(MCH)	428..00	Mean cell haemoglobin		30.2 pg
01/12/01	Ts	Mean corpusc. Hb. conc. (MCHC)	429..00	Mean cell haemoglobin concentration		35.3 g/L
01/12/01	Ts	Mean corpuscular volume (MCV)	42A..00	Mean cell volume		85.6 fL
01/12/01	Ts	Monocyte count	42N..00	Monocyte count		10.79
01/12/01	Ts	Neutrophil count	42J..00	Neutrophil count		15.72
01/12/01	Ts	Platelet count	42P..00	Platelet count		334
01/12/01	Ts	Red blood cell (RBC) count	426..00	Red blood cell count		14.89
01/12/01	Ts	Total white cell count	42H..00	White blood cell count		18.9
01/12/01	Ts	Total white cell count	42H..00	White blood cell count NOS		18.9
07/12/01	CL	Blood withdrawal	7L17.00			
07/12/01	Ts	Basophil count	42L..00	Basophil count		10.02
07/12/01	Ts	Eosinophil count	42K..00	Eosinophil count		10.31
07/12/01	Ts	Haematocrit - PCV	425..00	Haematocrit		0.46 %
07/12/01	Ts	Haemoglobin estimation	423..00	Haemoglobin		15.7 g/dL
07/12/01	Ts	Lymphocyte count	42M..00	Lymphocyte count		12.5
07/12/01	Ts	Mean corpusc. haemoglobin(MCH)	428..00	Mean cell haemoglobin		30.1 pg
07/12/01	Ts	Mean corpusc. Hb. conc. (MCHC)	429..00	Mean cell haemoglobin concentration		34.5 g/L
07/12/01	Ts	Mean corpuscular volume (MCV)	42A..00	Mean cell volume		87.2 fL
07/12/01	Ts	Monocyte count	42N..00	Monocyte count		10.58
07/12/01	Ts	Neutrophil count	42J..00	Neutrophil count		12.64
07/12/01	Ts	Platelet count	42P..00	Platelet count		291

** If event type is Test ('Ts'), the 'Other Event Information' column contains results and units. If event type is Referral ('RF'), the same column contains the organisation type. If event type is Immunisation ('Im') the column contains immunisation status.

Event Date	Event Type*	Read Term / Product Name	Dictionary Codes	MedDRA PT	Immunisation Type (Compound)	Other Event Information**
07/12/01	Ts	Red blood cell (RBC) count	426..00	Red blood cell count		15.21
07/12/01	Ts	Total white cell count	42H..00	White blood cell count		16.2
07/12/01	Ts	Total white cell count	42H..00	White blood cell count NOS		16.2
10/12/01	CL	Had a chat to patient	8CB..00			
10/12/01	Ts	Basophil count	42L..00	Basophil count		10.02
10/12/01	Ts	Eosinophil count	42K..00	Eosinophil count		10.31
10/12/01	Ts	Haematocrit - PCV	425..00	Haematocrit		0.46 %
10/12/01	Ts	Haemoglobin estimation	423..00	Haemoglobin		15.7 g/dL
10/12/01	Ts	Lymphocyte count	42M..00	Lymphocyte count		12.5
10/12/01	Ts	Mean corpusc. haemoglobin(MCH)	428..00	Mean cell haemoglobin		30.1 pg
10/12/01	Ts	Mean corpusc. Hb. conc. (MCHC)	429..00	Mean cell haemoglobin concentration		34.5 g/L
10/12/01	Ts	Mean corpuscular volume (MCV)	42A..00	Mean cell volume		87.2 fL
10/12/01	Ts	Monocyte count	42N..00	Monocyte count		10.58
10/12/01	Ts	Neutrophil count	42J..00	Neutrophil count		12.84
10/12/01	Ts	Platelet count	42P..00	Platelet count		291
10/12/01	Ts	Red blood cell (RBC) count	426..00	Red blood cell count		15.21
10/12/01	Ts	Total white cell count	42H..00	White blood cell count		16.2
10/12/01	Ts	Total white cell count	42H..00	White blood cell count NOS		16.2
12/12/01	CL	Advice	67I..00			
12/12/01	CL	Blood withdrawal	7L17.00			
19/12/01	CL	Blood withdrawal	7L17.00			
19/12/01	CL	O/E - blood pressure reading	246..00	Blood pressure		

** If event type is Test ('Ts'), the "Other Event Information" column contains results and units. If event type is Referral ('Rf'), the same column contains the organisation type. If event type is Immunisation ('Im') the column contains immunisation status.

Event Date	Event Type*	Read Term / Product Name	Dictionary Codes	MedDRA PT	Immunisation Type (Compound)	Other Event Information**
27/12/01	CL	Blood withdrawal	7L17.00			
27/12/01	CL	O/E - blood pressure	246..12	Blood pressure		
27/12/01	CL	O/E - blood pressure reading	246..00	Blood pressure		
27/12/01	Ts	Basophil count	42L..00	Basophil count		10.01
27/12/01	Ts	Eosinophil count	42K..00	Eosinophil count		10.32
27/12/01	Ts	Haematocrit - PCV	425..00	Haematocrit		0.44 %
27/12/01	Ts	Haemoglobin estimation	423..00	Haemoglobin		15.3 g/dL
27/12/01	Ts	Lymphocyte count	42M..00	Lymphocyte count		11.87
27/12/01	Ts	Mean corpusc. haemoglobin(MCH)	428..00	Mean cell haemoglobin		29.7 pg
27/12/01	Ts	Mean corpusc. Hb. conc. (MCHC)	429..00	Mean cell haemoglobin concentration		34.6 g/L
27/12/01	Ts	Mean corpuscular volume (MCV)	42A..00	Mean cell volume		85.7 fL
27/12/01	Ts	Monocyte count	42N..00	Monocyte count		10.33
27/12/01	Ts	Neutrophil count	42J..00	Neutrophil count		12.58
27/12/01	Ts	Platelet count	42P..00	Platelet count		276
27/12/01	Ts	Red blood cell (RBC) count	426..00	Red blood cell count		15.15
27/12/01	Ts	Total white cell count	42H..00	White blood cell count		15.1
27/12/01	Ts	Total white cell count	42H..00	White blood cell count NOS		15.1
02/01/02	CL	Blood withdrawal	7L17.00			
09/01/02	CL	Blood withdrawal	7L17.00			
16/01/02	CL	Blood withdrawal	7L17.00			
23/01/02	CL	Blood withdrawal	7L17.00			
30/01/02	CL	Blood withdrawal	7L17.00			

** If event type is Test ('Ts'), the "Other Event Information" column contains results and units. If event type is Referral ('Rf'), the same column contains the organisation type. If event type is Immunisation ('Im') the column contains immunisation status.

Event Date	Event Type*	Read Term / Product Name	Dictionary Codes	MedDRA PT	Immunisation Type (Compound)	Other Event Information**
06/02/02	CL	Blood withdrawal	7L17.00			
13/02/02	CL	Blood withdrawal	7L17.00			
20/02/02	CL	Blood withdrawal	7L17.00			
27/02/02	CL	Blood withdrawal	7L17.00			
06/03/02	CL	Blood withdrawal	7L17.00			
13/03/02	CL	Blood withdrawal	7L17.00			
20/03/02	CL	Blood withdrawal	7L17.00			
27/03/02	CL	Blood withdrawal	7L17.00			
03/04/02	CL	Blood withdrawal	7L17.00			
03/04/02	CL	O/E - blood pressure reading	246..00	Blood pressure		
10/04/02	CL	Blood withdrawal	7L17.00			
17/04/02	CL	Blood withdrawal	7L17.00			
24/04/02	CL	Blood withdrawal	7L17.00			
03/05/02	CL	Blood withdrawal	7L17.00			
08/05/02	CL	Blood withdrawal	7L17.00			
15/05/02	CL	Blood withdrawal	7L17.00			
22/05/02	CL	Blood withdrawal	7L17.00			
29/05/02	CL	Blood withdrawal	7L17.00			
05/06/02	CL	Blood withdrawal	7L17.00			
12/06/02	CL	Blood withdrawal	7L17.00			
19/06/02	CL	Blood withdrawal	7L17.00			
26/06/02	CL	Blood withdrawal	7L17.00			

** If event type is Test ('Ts'), the "Other Event Information" column contains results and units. If event type is Referral ('Rf'), the same column contains the organisation type. If event type is Immunisation ('Im') the column contains immunisation status.

Event Date	Event Type*	Read Term / Product Name	Dictionary Codes	MedDRA PT	Immunisation Type (Compound)	Other Event Information**
03/07/02	CL	Blood withdrawal	7L17.00			
17/07/02	CL	Blood withdrawal	7L17.00			
31/07/02	CL	Blood withdrawal	7L17.00			
14/08/02	CL	Blood withdrawal	7L17.00			
29/08/02	CL	Blood withdrawal	7L17.00			
11/09/02	CL	Blood withdrawal	7L17.00			
11/09/02	CL	C/O: a rash	1D14.00	Rash		
11/09/02	CL	C/O: a rash	1D14.00	Rash NOS		
11/09/02	Th	CANESTEN -HC cream 1% + 1% (CLOTRIMAZOLE)				
11/09/02	Th	CANESTEN -HC cream 1% + 1% (HYDROCORTISONE)				
19/09/02	CL	Drug addiction therapy	6B23.00			
25/09/02	CL	Blood withdrawal	7L17.00			
30/09/02	CL	Blood withdrawal	7L17.00			
09/10/02	CL	Blood withdrawal	7L17.00			
23/10/02	CL	Telephone encounter	9N31.00			
06/11/02	CL	Blood withdrawal	7L17.00			
06/12/02	CL	Blood withdrawal	7L17.00			
18/12/02	CL	Did not attend - no reason	9N42.00			
02/01/03	CL	Blood withdrawal	7L17.00			
03/02/03	CL	Blood withdrawal	7L17.00			
03/03/03	CL	Blood withdrawal	7L17.00			
26/03/03	CL	Telephone encounter	9N31.00			

** If event type is Test ('Ts'), the "Other Event Information" column contains results and units. If event type is Referral ('Rf'), the same column contains the organisation type. If event type is Immunisation ('Im') the column contains immunisation status.

Event Date	Event Type*	Read Term / Product Name	Dictionary Codes	MedDRA PT	Immunisation Type (Compound)	Other Event Information**
27/03/03	CL	Blood withdrawal	7L17.00			
10/04/03	CL	Telephone encounter	9N31.00			
23/04/03	CL	Simple schizophrenia	E100.00	Schizophrenia simple		
23/04/03	CL	Telephone encounter	9N31.00			
02/05/03	CL	Blood withdrawal	7L17.00			
13/05/03	Rp	N/A				
16/05/03	Th	CHLORPROMAZINE tablets 50mg (CHLORPROMAZINE)				
02/06/03	CL	Did not attend - no reason	9N42.00			
02/06/03	CL	Telephone encounter	9N31.00			
03/06/03	CL	Blood withdrawal	7L17.00			
04/06/03	Th	CHLORPROMAZINE tablets 50mg (CHLORPROMAZINE)				
04/06/03	Ts	Basophil count	42L..00	Basophil count		10.01
04/06/03	Ts	Eosinophil count	42K..00	Eosinophil count		10.31
04/06/03	Ts	Haematocrit - PCV	425..00	Haematocrit		1.434
04/06/03	Ts	Haemoglobin estimation	423..00	Haemoglobin		15.4 g/dL
04/06/03	Ts	Lymphocyte count	42M..00	Lymphocyte count		11.67
04/06/03	Ts	Mean corpusc. haemoglobin(MCH)	428..00	Mean cell haemoglobin		30.2 pg
04/06/03	Ts	Mean corpuscular volume (MCV)	42A..00	Mean cell volume		85.1 fL
04/06/03	Ts	Monocyte count	42N..00	Monocyte count		10.38
04/06/03	Ts	Neutrophil count	42J..00	Neutrophil count		13.56
04/06/03	Ts	Platelet count	42P..00	Platelet count		246
04/06/03	Ts	Red blood cell (RBC) count	426..00	Red blood cell count		15.1

** If event type is Test ('Ts'), the "Other Event Information" column contains results and units. If event type is Referral ('Rf'), the same column contains the organisation type. If event type is Immunisation ('Im') the column contains immunisation status.

Event Date	Event Type*	Read Term / Product Name	Dictionary Codes	MedDRA PT	Immunisation Type (Compound)	Other Event Information**
04/06/03	Ts	Total white cell count:	42H..00	White blood cell count		16.1
04/06/03	Ts	Total white cell count:	42H..00	White blood cell count NOS		16.1
12/06/03	CL	Patient reviewed	6A...00			
13/06/03	CL	Blood withdrawal	7L17.00			
14/06/03	Ts	Basophil count	42L..00	Basophil count		10.01
14/06/03	Ts	Eosinophil count	42K..00	Eosinophil count		10.36
14/06/03	Ts	Gamma - G.T. level	44G4.00	Gamma-glutamyltransfera se		29 iu/L
14/06/03	Ts	Haematocrit - PCV	425..00	Haematocrit		1.446
14/06/03	Ts	Haemoglobin estimation	423..00	Haemoglobin		15.4 g/dL
14/06/03	Ts	Liver function test	44D6.00			No Data Entered
14/06/03	Ts	Lymphocyte count	42M..00	Lymphocyte count		12.02
14/06/03	Ts	Mean corpusc. haemoglobin(MCH)	428..00	Mean cell haemoglobin		30.1 pg
14/06/03	Ts	Mean corpuscular volume (MCV)	42A..00	Mean cell volume		87.3 fL
14/06/03	Ts	Monocyte count	42N..00	Monocyte count		10.67
14/06/03	Ts	Neutrophil count	42J..00	Neutrophil count		13.32
14/06/03	Ts	Plasma total protein	44MA.00	Protein		74 g/L
14/06/03	Ts	Plasma total protein	44MA.00	Protein NOS		74 g/L
14/06/03	Ts	Plasma total protein	44MA.00	Protein total		74 g/L
14/06/03	Ts	Platelet count	42P..00	Platelet count		246
14/06/03	Ts	Random blood sugar	44T1.00	Blood glucose		5.3 mmol/L
14/06/03	Ts	Red blood cell (RBC) count	426..00	Red blood cell count		15.11
14/06/03	Ts	Serum albumin	44M4.00	Blood albumin		49 g/L

** If event type is Test ('Ts'), the "Other Event Information" column contains results and units. If event type is Referral ('RF'), the same column contains the organisation type. If event type is Immunisation ('Im') the column contains immunisation status.

Event Date	Event Type*	Read Term / Product Name	Dictionary Codes	MedDRA PT	Immunisation Type (Compound)	Other Event Information**
14/06/03	Ts	Serum alkaline phosphatase	44F..00	Blood alkaline phosphatase		183 iu/L
14/06/03	Ts	Serum alkaline phosphatase	44F..00	Blood alkaline phosphatase NOS		183 iu/L
14/06/03	Ts	Serum creatinine	44J3.00	Blood creatinine		101 umol/L
14/06/03	Ts	Serum potassium	44I4.00	Blood potassium		4.4 mmol/L
14/06/03	Ts	Serum sodium	44I5.00	Blood sodium		139 mmol/L
14/06/03	Ts	Total bilirubin	44E3.00	Blood bilirubin		12 umol/L
14/06/03	Ts	Total white cell count	42H..00	White blood cell count		16.4
14/06/03	Ts	Total white cell count	42H..00	White blood cell count NOS		16.4
17/06/03	Ts	TSH - thyroid stim. hormone	442A.00	Blood thyroid stimulating hormone		1.12 mu/L
07/07/03	CL	Blood withdrawal	7L17.00			
11/07/03	CL	Patient reviewed	6A...00			
11/07/03	Th	CHLORPROMAZINE tablets 50mg (CHLORPROMAZINE)				
11/07/03	Th	ZOPICLONE tablets 7.5mg (ZOPICLONE)				
15/07/03	CL	Telephone encounter	9N31.00			
15/07/03	Th	CHLORPROMAZINE tablets 50mg (CHLORPROMAZINE)				
18/07/03	CL	Admit psychiatric emergency	8H23.00			
18/07/03	CL	Paranoid states	E12..00	Delusional disorder, paranoid type		
18/07/03	CL	Paranoid states	E12..00	Delusional disorder, persecutory type		
21/07/03	CL	Alcoholic psychoses	E01..00	Alcoholic psychosis		
28/07/03	CL	Telephone encounter	9N31.00			
28/07/03	Th	CHLORPROMAZINE tablets 50mg (CHLORPROMAZINE)				
28/07/03	Th	ZOPICLONE tablets 7.5mg (ZOPICLONE)				

** If event type is Test ('Ts'), the "Other Event Information" column contains results and units. If event type is Referral ('RF'), the same column contains the organisation type. If event type is Immunisation ('Im') the column contains immunisation status.

Event Date	Event Type*	Read Term / Product Name	Dictionary Codes	MedDRA PT	Immunisation Type (Compound)	Other Event Information**
05/08/03	Th	CHLORPROMAZINE tablets 50mg (CHLORPROMAZINE)				
05/08/03	Th	ZOPICLONE tablets 7.5mg (ZOPICLONE)				
13/08/03	CL	Blood withdrawal	7L17.00			
13/08/03	CL	Telephone encounter	9N31.00			
13/08/03	Th	CHLORPROMAZINE tablets 50mg (CHLORPROMAZINE)				
13/08/03	Th	ZOPICLONE tablets 7.5mg (ZOPICLONE)				
23/08/03	CL	Unfit for work	13JJ.00	Retirement		
09/09/03	CL	Blood withdrawal	7L17.00			
12/09/03	CL	Medication review	8B21400			
12/09/03	Rp	N/A				
12/09/03	Th	AMISULPRIDE tablets 100mg ()				
12/09/03	Th	AMISULPRIDE tablets 200mg (AMISULPRIDE)				
12/09/03	Th	ZOPICLONE tablets 7.5mg (ZOPICLONE)				
26/09/03	Th	AMISULPRIDE tablets 100mg ()				
26/09/03	Th	AMISULPRIDE tablets 200mg (AMISULPRIDE)				
07/10/03	CL	Blood withdrawal	7L17.00			
08/11/03	CL	Blood withdrawal	7L17.00			
11/11/03	Th	AMISULPRIDE tablets 100mg ()				
11/11/03	Th	AMISULPRIDE tablets 200mg (AMISULPRIDE)				
11/11/03	Th	ZOPICLONE tablets 7.5mg (ZOPICLONE)				
02/12/03	CL	Blood withdrawal	7L17.00			
09/12/03	Th	AMISULPRIDE tablets 100mg ()				

** If event type is Test ('Ts'), the "Other Event Information" column contains results and units. If event type is Referral ('Rf'), the same column contains the organisation type. If event type is Immunisation ('Im') the column contains immunisation status.

Event Date	Event Type*	Read Term / Product Name	Dictionary Codes	MedDRA PT	Immunisation Type (Compound)	Other Event Information**
09/12/03	Th	AMISULPRIDE tablets 200mg (AMISULPRIDE)				
06/01/04	Th	AMISULPRIDE tablets 100mg ()				
06/01/04	Th	AMISULPRIDE tablets 200mg (AMISULPRIDE)				
22/01/04	CL	Blood withdrawal	7L17.00			
02/02/04	Th	AMISULPRIDE tablets 100mg ()				
02/02/04	Th	AMISULPRIDE tablets 200mg (AMISULPRIDE)				
03/03/04	Th	AMISULPRIDE tablets 100mg ()				
03/03/04	Th	AMISULPRIDE tablets 200mg (AMISULPRIDE)				
05/03/04	CL	Blood withdrawal	7L17.00			
25/03/04	CL	Blood withdrawal	7L17.00			
06/04/04	Th	AMISULPRIDE tablets 100mg ()				
06/04/04	Th	AMISULPRIDE tablets 200mg (AMISULPRIDE)				
05/05/04	CL	Blood withdrawal	7L17.00			
05/05/04	Th	AMISULPRIDE tablets 100mg ()				
05/05/04	Th	AMISULPRIDE tablets 200mg (AMISULPRIDE)				
03/06/04	CL	Blood withdrawal	7L17.00			
03/06/04	CL	Telephone encounter	9N31.00			
15/06/04	Th	AMISULPRIDE tablets 100mg ()				
15/06/04	Th	AMISULPRIDE tablets 200mg (AMISULPRIDE)				
30/06/04	CL	Blood withdrawal	7L17.00			
12/07/04	Th	AMISULPRIDE tablets 100mg ()				
12/07/04	Th	AMISULPRIDE tablets 200mg (AMISULPRIDE)				

** If event type is Test ('Ts'), the "Other Event Information" column contains results and units. If event type is Referral ('Rf'), the same column contains the organisation type. If event type is Immunisation ('Im') the column contains immunisation status.

Event Date	Event Type*	Read Term / Product Name	Dictionary Codes	MedDRA PT	Immunisation Type (Compound)	Other Event Information**
05/06/04	Th	AMISULPRIDE tablets 100mg ()				
05/06/04	Th	AMISULPRIDE tablets 200mg (AMISULPRIDE)				
01/09/04	CL	Blood withdrawal	7L17.00			
01/09/04	Rp	N/A				
01/09/04	Th	AMISULPRIDE tablets 100mg ()				
01/09/04	Th	AMISULPRIDE tablets 200mg (AMISULPRIDE)				
01/09/04	Ts	Basophil count	42L..00	Basophil count		10.02
01/09/04	Ts	Eosinophil count	42K..00	Eosinophil count		10.56
01/09/04	Ts	Full blood count - FBC	424..00	Full blood count		No Data Entered
01/09/04	Ts	Haematocrit	4259.00	Haematocrit		1.424
01/09/04	Ts	Haemoglobin estimation	423..00	Haemoglobin		14.9 g/dL
01/09/04	Ts	Lymphocyte count	42M..00	Lymphocyte count		12.42
01/09/04	Ts	Mean corpusc. haemoglobin(MCH)	428..00	Mean cell haemoglobin		30.1 pg
01/09/04	Ts	Mean corpuscular volume (MCV)	42A..00	Mean cell volume		85.7 fL
01/09/04	Ts	Monocyte count	42N..00	Monocyte count		10.66
01/09/04	Ts	Neutrophil count	42J..00	Neutrophil count		15.82
01/09/04	Ts	Platelet count	42P..00	Platelet count		276
01/09/04	Ts	Red blood cell (RBC) count	426..00	Red blood cell count		14.96
01/09/04	Ts	Total white cell count	42H..00	White blood cell count		19.5
01/09/04	Ts	Total white cell count	42H..00	White blood cell count NOS		19.5
03/09/04	CL	Unfit for work	13JJ.00	Retirement		
03/09/04	CL		9H8..00			

** If event type is Test ('Ts'), the "Other Event Information" column contains results and units. If event type is Referral ('Rf'), the same column contains the organisation type. If event type is Immunisation ('Im') the column contains immunisation status.

Event Date	Event Type*	Read Term / Product Name	Dictionary Codes	MedDRA PT	Immunisation Type (Compound)	Other Event Information**
10/09/04	CL	Cigarette smoker	137P.00	Smoker		
10/09/04	CL	C/O - cough	171..11	Cough		
10/09/04	CL	O/E - blood pressure reading	246..00	Blood pressure		
10/09/04	CL	Patient reviewed	6A...00			
10/09/04	CL	Smoking cessation advice	6CAL.00			
10/09/04	Th	AMOXICILLIN capsules 250mg (AMOXYCILLIN)				
10/09/04	Th	BRICANYL TURBOHALER 500mcg (TERBUTALINE)				
27/09/04	CL	Blood withdrawal	7L17.00			
30/09/04	Th	AMISULPRIDE tablets 100mg ()				
30/09/04	Th	AMISULPRIDE tablets 200mg (AMISULPRIDE)				
08/10/04	CL	Abnormal weight loss - symptom	1625.11	Weight decreased		
08/10/04	CL	O/E - weight	22A..00	Weight		
08/10/04	CL	Postural hypotension	G970.11	Orthostatic hypotension		
08/10/04	CL	Postural hypotension	G970.11	Postural hypotension		
28/10/04	Th	AMISULPRIDE tablets 100mg ()				
28/10/04	Th	AMISULPRIDE tablets 200mg (AMISULPRIDE)				
29/10/04	CL	Blood withdrawal	7L17.00			
07/12/04	Th	AMISULPRIDE tablets 100mg ()				
07/12/04	Th	AMISULPRIDE tablets 200mg (AMISULPRIDE)				
08/12/04	CL	Blood withdrawal	7L17.00			
08/12/04	Ts	ALT/SGPT serum level	44G3.00	Alanine aminotransferase		22 iu/L
08/12/04	Ts	Liver function test	44D0.00			No Data Entered

** If event type is Test ('Ts'), the 'Other Event Information' column contains results and units. If event type is Referral ('Rf'), the same column contains the organisation type. If event type is Immunisation ('Im') the column contains immunisation status.

Event Date	Event Type*	Read Term / Product Name	Dictionary Codes	MedDRA PT	Immunisation Type (Compound)	Other Event Information**
08/12/04	Ts	Renal function tests	451..00	Renal function test		No Data Entered
08/12/04	Ts	Renal function tests	451..00	Renal function tests NOS		No Data Entered
08/12/04	Ts	Serum albumin	44M4.00	Blood albumin		48 g/L
08/12/04	Ts	Serum alkaline phosphatase	44F..00	Blood alkaline phosphatase		124 iu/L
08/12/04	Ts	Serum alkaline phosphatase	44F..00	Blood alkaline phosphatase NOS		124 iu/L
08/12/04	Ts	Serum bilirubin level	44E..00	Blood bilirubin		12 umol/L
08/12/04	Ts	Serum creatinine	44J3.00	Blood creatinine		85 umol/L
08/12/04	Ts	Serum gamma-glutamyl transferase level	44G9.00			24 iu/L
08/12/04	Ts	Serum potassium	44I4.00	Blood potassium		4.3 mmol/L
08/12/04	Ts	Serum sodium	44I5.00	Blood sodium		138 mmol/L
08/12/04	Ts	Serum total protein	44M3.00	Protein		74 g/L
08/12/04	Ts	Serum total protein	44M3.00	Protein NOS		74 g/L
08/12/04	Ts	Serum total protein	44M3.00	Protein total		74 g/L
08/12/04	Ts	Serum TSH level	442W.00			1.24 mu/L
31/12/04	CL	Did not attend - no reason	9N42.00			
04/01/05	CL	Blood withdrawal	7L17.00			
05/01/05	Th	AMISULPRIDE tablets 100mg ()				
05/01/05	Th	AMISULPRIDE tablets 200mg (AMISULPRIDE)				
07/01/05	CL	Blood withdrawal	7L17.00			
07/01/05	CL	Patient reviewed	6A...00			
07/01/05	Ts	Basophil count	42L..00	Basophil count		10.02
07/01/05	Ts	Eosinophil count	42K..00	Eosinophil count		10.32

** If event type is Test ('Ts'), the "Other Event Information" column contains results and units. If event type is Referral ('Rf'), the same column contains the organisation type. If event type is Immunisation ('Im') the column contains immunisation status.

Event Date	Event Type*	Read Term / Product Name	Dictionary Codes	MedDRA PT	Immunisation Type (Compound)	Other Event Information**
07/01/05	Ts	Full blood count - FBC	424..00	Full blood count		No Data Entered
07/01/05	Ts	Haematocrit	4255.00	Haematocrit		1.456
07/01/05	Ts	Haemoglobin estimation	423..00	Haemoglobin		16.1 g/dL
07/01/05	Ts	Lymphocyte count	42M..00	Lymphocyte count		12.99
07/01/05	Ts	Mean corpusc. haemoglobin(MCH)	428..00	Mean cell haemoglobin		30.3 pg
07/01/05	Ts	Mean corpuscular volume (MCV)	42A..00	Mean cell volume		85.9 fL
07/01/05	Ts	Monocyte count	42N..00	Monocyte count		10.66
07/01/05	Ts	Neutrophil count	42J..00	Neutrophil count		16.49
07/01/05	Ts	Platelet count	42P..00	Platelet count		307
07/01/05	Ts	Red blood cell (RBC) count	426..00	Red blood cell count		15.31
07/01/05	Ts	Total white cell count	42H..00	White blood cell count		20.5
07/01/05	Ts	Total white cell count	42H..00	White blood cell count NOS		20.5
25/01/05	CL		6A6..00			
03/02/05	CL	Blood withdrawal	7L17.00			
09/02/05	CL	Medication review	8B31400			
09/02/05	Th	AMISULPRIDE tablets 100mg ()				
09/02/05	Th	AMISULPRIDE tablets 200mg (AMISULPRIDE)				
02/03/05	CL	Blood withdrawal	7L17.00			
04/03/05	Th	AMISULPRIDE tablets 100mg ()				
04/03/05	Th	AMISULPRIDE tablets 200mg (AMISULPRIDE)				
06/04/05	CL	Blood withdrawal	7L17.00			
12/04/05	Th	AMISULPRIDE tablets 100mg ()				

** If event type is Test ('Ts'), the "Other Event Information" column contains results and units. If event type is Referral ('Rf'), the same column contains the organisation type. If event type is Immunisation ('Im') the column contains immunisation status.

Event Date	Event Type*	Read Term / Product Name	Dictionary Codes	MedDRA PT	Immunisation Type (Compound)	Other Event Information**
12/04/05	Th	AMISULPRIDE tablets 200mg (AMISULPRIDE)				
13/05/05	CL	Blood withdrawal	7L17.00			
13/05/05	Th	AMISULPRIDE tablets 100mg ()				
13/05/05	Th	AMISULPRIDE tablets 200mg (AMISULPRIDE)				
14/06/05	CL	Blood withdrawal	7L17.00			
15/06/05	Th	AMISULPRIDE tablets 100mg ()				
15/06/05	Th	AMISULPRIDE tablets 200mg (AMISULPRIDE)				
08/07/05	CL	Blood withdrawal	7L17.00			
15/07/05	Th	AMISULPRIDE tablets 100mg ()				
15/07/05	Th	AMISULPRIDE tablets 200mg (AMISULPRIDE)				
01/08/05	CL	Blood withdrawal	7L17.00			
09/08/05	Th	AMISULPRIDE tablets 100mg ()				
09/08/05	Th	AMISULPRIDE tablets 200mg (AMISULPRIDE)				
01/09/05	Rp	N/A				
01/09/05	Th	AMISULPRIDE tablets 100mg ()				
01/09/05	Th	AMISULPRIDE tablets 200mg (AMISULPRIDE)				
08/09/05	CL	Blood withdrawal	7L17.00			
13/09/05	CL		9OX6.00			
28/09/05	Th	AMISULPRIDE tablets 100mg ()				
28/09/05	Th	AMISULPRIDE tablets 200mg (AMISULPRIDE)				
30/09/05	CL	Did not attend - no reason	9N42.00			
06/10/05	CL	Blood withdrawal	7L17.00			

** If event type is Test ('Ts'), the "Other Event Information" column contains results and units. If event type is Referral ('RF'), the same column contains the organisation type. If event type is Immunisation ('Im') the column contains immunisation status.

Event Date	Event Type*	Read Term / Product Name	Dictionary Codes	MedDRA PT	Immunisation Type (Compound)	Other Event Information**
31/10/05	Th	AMISULPRIDE tablets 100mg ()				
31/10/05	Th	AMISULPRIDE tablets 200mg (AMISULPRIDE)				
18/11/05	CL	Blood withdrawal	7L17.00			
21/11/05	CL	Blood withdrawal	7L17.00			
01/12/05	Th	AMISULPRIDE tablets 100mg ()				
01/12/05	Th	AMISULPRIDE tablets 200mg (AMISULPRIDE)				
16/12/05	CL	Blood withdrawal	7L17.00			
16/12/05	CL	Tinea versicolor	AB10.12	Tinea versicolor		
16/12/05	CL	Tinea versicolor	AB10.12	Tinea versicolour		
16/12/05	Th	NIZORAL cream 2% (KETOCONAZOLE)				
04/01/06	Th	AMISULPRIDE tablets 100mg ()				
04/01/06	Th	AMISULPRIDE tablets 200mg (AMISULPRIDE)				
17/01/06	CL	Blood withdrawal	7L17.00			
16/02/06	CL	Blood withdrawal	7L17.00			
17/02/06	Th	AMISULPRIDE tablets 100mg ()				
17/02/06	Th	AMISULPRIDE tablets 200mg (AMISULPRIDE)				
23/03/06	CL	Blood withdrawal	7L17.00			
27/03/06	Th	AMISULPRIDE tablets 100mg ()				
27/03/06	Th	AMISULPRIDE tablets 200mg (AMISULPRIDE)				
20/04/06	CL	Blood withdrawal	7L17.00			
20/04/06	Th	AMISULPRIDE tablets 100mg ()				
20/04/06	Th	AMISULPRIDE tablets 200mg (AMISULPRIDE)				

** If event type is Test ('Ts'), the 'Other Event Information' column contains results and units. If event type is Referral ('Rf'), the same column contains the organisation type. If event type is Immunisation ('Im') the column contains immunisation status.

Event Date	Event Type*	Read Term / Product Name	Dictionary Codes	MedDRA PT	Immunisation Type (Compound)	Other Event Information**
24/04/08	CL	Notes summary on computer	9344.00			
23/05/08	CL	Blood withdrawal	7L17.00			
23/05/08	CL	Telephone encounter	9N31.00			
25/05/08	Th	AMISULPRIDE tablets 100mg ()				
25/05/08	Th	AMISULPRIDE tablets 200mg (AMISULPRIDE)				
20/06/08	CL	Blood withdrawal	7L17.00			
20/06/08	Ts	Basophil count	42L..00	Basophil count		10.02
20/06/08	Ts	Eosinophil count	42K..00	Eosinophil count		10.6
20/06/08	Ts	Full blood count - FBC	424..00	Full blood count		No Data Entered
20/06/08	Ts	Haematocrit	4259.00	Haematocrit		1.453
20/06/08	Ts	Haemoglobin estimation	423..00	Haemoglobin		15.9 g/dL
20/06/08	Ts	Lymphocyte count	42M..00	Lymphocyte count		13.03
20/06/08	Ts	Mean corpusc. haemoglobin(MCH)	428..00	Mean cell haemoglobin		30.4 pg
20/06/08	Ts	Mean corpuscular volume (MCV)	42A..00	Mean cell volume		88.6 fL
20/06/08	Ts	Monocyte count	42N..00	Monocyte count		10.71
20/06/08	Ts	Neutrophil count	42J..00	Neutrophil count		15.21
20/06/08	Ts	Platelet coun:	42P..00	Platelet count		282
20/06/08	Ts	Red blood cell (RBC) count	426..00	Red blood cell count		15.23
20/06/08	Ts	Total white cell coun:	42H..00	White blood cell count		19.6
20/06/08	Ts	Total white cell coun:	42H..00	White blood cell count NOS		19.6
22/06/08	CL	Cigarette smoker	137P.00	Smoker		
22/06/08	CL	C/O - cough	171..11	Cough		

** If event type is Test ('Ts'), the "Other Event Information" column contains results and units. If event type is Referral ('Rf'), the same column contains the organisation type. If event type is Immunisation ('Im') the column contains immunisation status.

Event Date	Event Type*	Read Term / Product Name	Dictionary Codes	MedDRA PT	Immunisation Type (Compound)	Other Event Information**
22/06/06	CL	Smoking cessation advice	6CAL.00			
22/06/06	Th	AMOXICILLIN capsules 250mg (AMOXYCILLIN)				
24/06/06	Ts	Urine examination	46...00	Urine analysis		No Data Entered
29/06/06	Th	AMISULPRIDE tablets 100mg ()				
29/06/06	Th	AMISULPRIDE tablets 200mg (AMISULPRIDE)				
18/07/06	CL	Blood withdrawal	7L17.00			
04/08/06	Th	AMISULPRIDE tablets 100mg ()				
04/08/06	Th	AMISULPRIDE tablets 200mg (AMISULPRIDE)				
18/08/06	CL	Did not attend - no reason	9N42.00			
25/08/06	Th	AMISULPRIDE tablets 100mg ()				
25/08/06	Th	AMISULPRIDE tablets 200mg (AMISULPRIDE)				
12/09/06	CL	Blood withdrawal	7L17.00			
11/10/06	Rp	N/A				
11/10/06	Th	AMISULPRIDE tablets 100mg ()				
11/10/06	Th	AMISULPRIDE tablets 200mg (AMISULPRIDE)				
13/10/06	CL	Blood withdrawal	7L17.00			
13/11/06	CL	Blood withdrawal	7L17.00			
13/11/06	Th	AMISULPRIDE tablets 100mg ()				
13/11/06	Th	AMISULPRIDE tablets 200mg (AMISULPRIDE)				
05/12/06	CL	Did not attend - no reason	9N42.00			
08/12/06	CL	Did not attend - no reason	9N42.00			
11/12/06	CL	Blood withdrawal	7L17.00			

** If event type is Test ('Ts'), the "Other Event Information" column contains results and units. If event type is Referral ('Rf'), the same column contains the organisation type. If event type is Immunisation ('Im') the column contains immunisation status.

Event Date	Event Type*	Read Term / Product Name	Dictionary Codes	MedDRA PT	Immunisation Type (Compound)	Other Event Information**
13/12/06	Th	AMISULPRIDE tablets 100mg ()				
13/12/06	Th	AMISULPRIDE tablets 200mg (AMISULPRIDE)				
05/01/07	CL	Letter sent to patient	9NC3.00			
09/01/07	CL	Blood withdrawal	7L17.00			
10/01/07	CL	Mental health administration	9H...00			
24/01/07	Th	AMISULPRIDE tablets 100mg ()				
24/01/07	Th	AMISULPRIDE tablets 200mg (AMISULPRIDE)				
09/02/07	CL	Blood withdrawal	7L17.00			
12/02/07	CL	Indirect encounter	9N3..00			
19/02/07	Th	AMISULPRIDE tablets 100mg ()				
19/02/07	Th	AMISULPRIDE tablets 200mg (AMISULPRIDE)				
01/03/07	CL	Blood withdrawal	7L17.00			
07/03/07	CL		6CM2.00			
16/03/07	CL	Blood withdrawal	7L17.00			
16/03/07	CL	Had a chat to patient	6CB..00			
03/04/07	Th	AMISULPRIDE tablets 100mg ()				
03/04/07	Th	AMISULPRIDE tablets 200mg (AMISULPRIDE)				
05/04/07	CL	Blood withdrawal	7L17.00			
12/04/07	CL	Indirect encounter	9N3..00			
26/04/07	CL	Blood withdrawal	7L17.00			
26/04/07	Th	AMISULPRIDE tablets 100mg ()				
26/04/07	Th	AMISULPRIDE tablets 200mg (AMISULPRIDE)				

** If event type is Test ('Ts'), the "Other Event Information" column contains results and units. If event type is Referral ('Rf'), the same column contains the organisation type. If event type is Immunisation ('Im') the column contains immunisation status.

Event Date	Event Type*	Read Term / Product Name	Dictionary Codes	MedDRA PT	Immunisation Type (Compound)	Other Event Information**
10/05/07	Th	AMISULPRIDE tablets 100mg ()				
10/05/07	Th	AMISULPRIDE tablets 200mg (AMISULPRIDE)				
31/05/07	Th	AMISULPRIDE tablets 100mg ()				
31/05/07	Th	AMISULPRIDE tablets 200mg (AMISULPRIDE)				
07/06/07	CL	Blood withdrawal	7L17.00			
18/06/07	CL	Telephone encounter	9N31.00			
26/06/07	CL	Blood withdrawal	7L17.00			
24/07/07	CL	Blood withdrawal	7L17.00			
01/08/07	CL	Encounter administration	9N...11			
08/08/07	Th	AMISULPRIDE tablets 100mg ()				
08/08/07	Th	AMISULPRIDE tablets 200mg (AMISULPRIDE)				
23/08/07	CL	Blood withdrawal	7L17.00			
01/01/00	CL	Hospital reference number	9R6..00			

** If event type is Test ('Ts'), the "Other Event Information" column contains results and units. If event type is Referral ('Rf'), the same column contains the organisation type. If event type is Immunisation ('Im') the column contains immunisation status.

Appendix E: Ethics approvals for the pharmacoepidemiological study of antipsychotic prescribing using the GPRD (Chapter 4)

GPRD
Excellence in Public Health Research

RESTRICTED-COMMERCIAL

Scientific & Ethical Advisory Group

SEAG EVALUATION OF PROTOCOLS

FEED-BACK TO APPLICANTS

CONFIDENTIAL *by e-mail*

PROTOCOL NO: 775

PROTOCOL TITLE: Children anti psychotic prescribing trend and utilisation research (capture)

APPLICANT: Dr Ian Chi Kei Wong, The Centre for Paediatric Pharmacy Research, University of London

APPROVED ☐	APPROVED SUBJECT TO MINOR AMENDMENT (resubmission not required) ☒	REVISION/ RESUBMISSION REQUESTED ☐	REJECTED ☐

COMMENTS

Protocol 775 is approved but the investigators should note the following comments by SEAG and amend the protocol appropriately. Re-submission is not required.

The applicants need to amend their formulae for the calculation of incidence and prevalence so that the denominator includes only children in the relevant age range, with the requisite minimum of 6 months data available.

Also they should be aware that their estimate of incidence will be no more than approximate and may be majorly inaccurate. They are planning to accept children with as little as 6 months data available. There will be children who have used atypical antipsychotics previously but not during the time period covered by the study, who are then falsely defined as incident cases.

DATE: 9 January 2006

C:\2007\0306\GPRD_PEN\DU study\SEAG Approval.doc

Please refer to the Appendix data CD for the protocol for this Ethics application

Safeguarding public health

MHRA

Independent Scientific Advisory Committee
for MHRA database research

ISAC EVALUATION OF PROTOCOLS FOR RESEARCH INVOLVING GPRD DATA

FEED-BACK TO APPLICANTS

CONFIDENTIAL		*by e-mail*	
PROTOCOL NO:	775A		
PROTOCOL TITLE:	Children anti psychotic prescribing trend and utilisation research (capture)		
APPLICANT:	Dr Ian Chi Kei Wong, The Centre for Paediatric Pharmacy Research, University of London		
APPROVED ☒	**APPROVED SUBJECT TO MINOR AMENDMENT** (resubmission not required) ☐	**REVISION/ RESUBMISSION REQUESTED** ☐	**REJECTED** ☐
COMMENTS:	Protocol 775A is approved.		
DATE:	30 March 2007		

Medicines and Healthcare products Regulatory Agency
Market Towers 1 Nine Elms Lane London SW8 5NQ
T 020 7084 2000 F 020 7084 2353 www.mhra.gov.uk

An executive agency of the Department of Health

Please refer to the Appendix data CD for the protocol for this Ethics application amendment

Appendix F: Ethics approval for the pharmacoepidemiological validation of antipsychotic prescribing using the IMS database (Chapter 4)

ims

10 October 2008

Professor Ian Wong
Centre for Paediatric Pharmacy Research
The School of Pharmacy, University of London,
First Floor , BMA House,
Tavistock Square,
London,
WC1H 9JP

Dear Ian,

I am writing to confirm that the Centre for Paediatric Pharmacy Research has submitted a protocol to the Independent Scientific and Ethics Committee established to review uses of the IMS Disease Analyzer database. The Committee approved the use of the database for drug utilisation studies in children as described in that protocol.

Yours sincerely

Peter Stephens
VP Public Health Affairs Europe, Middle East & Africa,
IMS Co-ordinator for ISEAC
IMS Health®
7 Harewood Avenue
London, NW1 6JB, UK
Tel: +44 207 393 5323 Mobile: +44 (0)7711 148653
email: pstephens@uk.imshealth.com
www.imshealth.com

IMS HEALTH
7 Harewood Avenue
London NW1 6JE
United Kingdom

Tel +44(0)20 7393 5300
Fax +44(0)20 7393 5900
www.imshealth.com

IMS A.G. registered & incorporated with limited liability in Zug, Switzerland, registered as a branch in England, Ref. No. BR 1589
Swiss Address:
Dorfplatz 4 6330

Appendix G: Ethics approval for the mortality study (Chapter 5)

Safeguarding public health

MHRA

Independent Scientific Advisory Committee
for MHRA database research

ISAC EVALUATION OF PROTOCOLS FOR RESEARCH INVOLVING GPRD DATA

FEED-BACK TO APPLICANTS

CONFIDENTIAL			*by e-mail*
PROTOCOL NO:	07_021		
PROTOCOL TITLE:	Mortality study of antipsychotics in children and adolescents		
APPLICANT:	Prof Ian Wong, Professor of Paediatric Medicines Research, Centre for Paediatric Pharmacy Research, The School of Pharmacy, Institute of Child Health, Great Ormond Street Hospital for Children		
APPROVED ☐	**APPROVED SUBJECT TO MINOR AMENDMENT (resubmission not required)** ☒	**REVISION/ RESUBMISSION REQUESTED** ☐	**REJECTED** ☐
COMMENTS:	The inclusion criteria are slightly ambiguous - will patients be included only for the period in which they are under 18, or retained so long as they are under 18 at some point during the period studied? It might be helpful to look at GPRD recorded death rates among the wider population at this age, in order to get a sense of how mortality rates at this age group in the GPRD compare with the ONS estimates. This would require a larger cohort, but might be feasible. The crude mortality ratio (CMR) and Standardised Mortality Ratio (SMR) are to be calculated, but the estimates could be very variable as the number of deaths is, hopefully, small.		
DATE:	23 March 2007		

Medicines and Healthcare products Regulatory Agency
Market Towers 1 Nine Elms Lane London SW8 5NQ
T 020 7084 2000 F 020 7084 2353 www.mhra.gov.uk

An executive agency of the Department of Health

Please refer to the Appendix data CD for the protocol for this Ethics application

Appendix H: Questionnaires sent to general practitioners for the mortality study (Chapter 5)

Dear GP,

At the Centre for Paediatric Pharmacy Research, Great Ormond Street Hospital, we are investigating the causes of death in children and adolescents who have been prescribed an antipsychotic drug for the treatment of psychiatric conditions. Previous studies have shown that both the older, typical antipsychotic agents and the newer atypical antipsychotics are used for many psychiatric disorders in this population. As you are aware, there are significant adverse effects and toxicities associated with the antipsychotic agents, including the newer atypical antipsychotics.

We want to ascertain the cause of death in patients who have died after being prescribed an antipsychotic drug, and to perform a causality assessment to determine the likelihood of the antipsychotic drug causing death. In addition to this, the standardised mortality ratios (SMRs) will be calculated and compared between the typical and the atypical antipsychotics.

We have identified a cohort of patients from the General Practice Research Database who have been prescribed at least one typical or atypical antipsychotic between 1992 and 2004. From this list of patients we have further identified patients who also had a clinical code of death in their records. Such a patient has been identified from your practice and we would be grateful if you would complete the attached questionnaire to aid us in this important research. It is important for you to confirm that the patient has died (for example, patients may have a death code which relates to a family member who has died). All data received will be treated with the utmost confidence and no individual cases will be reported.

As this is an epidemiological study, it is important that we receive the full information requested in order for us to obtain meaningful results. Your cooperation is very much appreciated.

Many thanks in advance

Professor Ian Wong BSc (Hons) Pharmacy, MSc, PhD, MRPharmS
DH National Public Health Career Scientist & Professor of Paediatric Medicines Research
Centre for Paediatric Pharmacy Research
A collaboration between the School of Pharmacy, Institute of Child Health & Great Ormond Street Hospital for Children

Dr Patrick Byrne MB.BS MMedSci FRCPsych
Hon. Research Associate and Consultant in Adolescent Psychiatry
Institute of Psychiatry
King's College

Mortality associated with antipsychotic drug treatment questionnaire

Please tick the relevant box where appropriate

1. Is the patient deceased?
☐ Yes ☐ No

If Yes, then please continue with the questionnaire. If No, then that is all the information that is required, thank you.

2. What was the date of death (dd/mm/yyyy)? _____/_____/_____

3. Where did the patient die?
☐ Home ☐ Hospital ☐ Other ; Please specify_____

4a. If a death certificate is available, what was the cause of death as recorded on the certificate

_____

OR

4b. If no death certificate is available, in your opinion what was the likely cause of death?

_____

5. Was a post-mortem performed?
☐ Yes ☐ No ☐ Unknown

If Yes, please indicate results_____

_____

6. Were there any laboratory test abnormalities prior or at the time of death?
☐ Yes ☐ No ☐ Unknown

If Yes, please indicate when and state results of laboratory abnormalities

_____

_____

7. At the time of death, did the patient have any illnesses which may have contributed to death?

☐ Yes ☐ No

If Yes, please specify: _____

_____

8. If suicide was the cause of death, did the patient show any predictors of suicide prior to death?
☐ Yes ☐ No ☐ Not applicable
If Yes, please tick all that apply
☐ previous suicide attempt ☐ a referral to a psychiatrist in the two years prior to the event
☐ psychiatric diagnosis confirmed: please specify: _____

Please turn over

9. If suicide was the cause of death, what method of suicide was used?
☐ Overdose of prescribed drug ☐ Overdose of non-prescribed drug

Please specify drug: _____

☐ Violence ☐ Other ; Please state: _____

10. Did the patient have an active prescription for an antipsychotic at the time of death?
☐ Yes ☐ No

If Yes, please specify which drug_____

If Yes, please specify indication for the drug_____

11. When was the last prescription for this antipsychotic drug issued (dd/mm/yyyy)? ____/_____/____

12. What dose of the antipsychotic drug was the patient taking at the time of death?

Dose_____ Frequency (eg once daily) _____

12. What was the maximum dose of the antipsychotic drug the patient had ever been prescribed?

Dose_____ Date (dd/mm/yyyy) _____/_____/_____

13. Was the patient taking other prescribed medications at the time of death?
☐ Yes ☐ No

If Yes, please give details on drug, dose and date of last prescription

Drug	Dose	Date of last prescription (dd/mm/yyyy)
_____	_____	_____/_____/_____
_____	_____	_____/_____/_____
_____	_____	_____/_____/_____
_____	_____	_____/_____/_____

Please provide any other information you may feel is relevant

_____

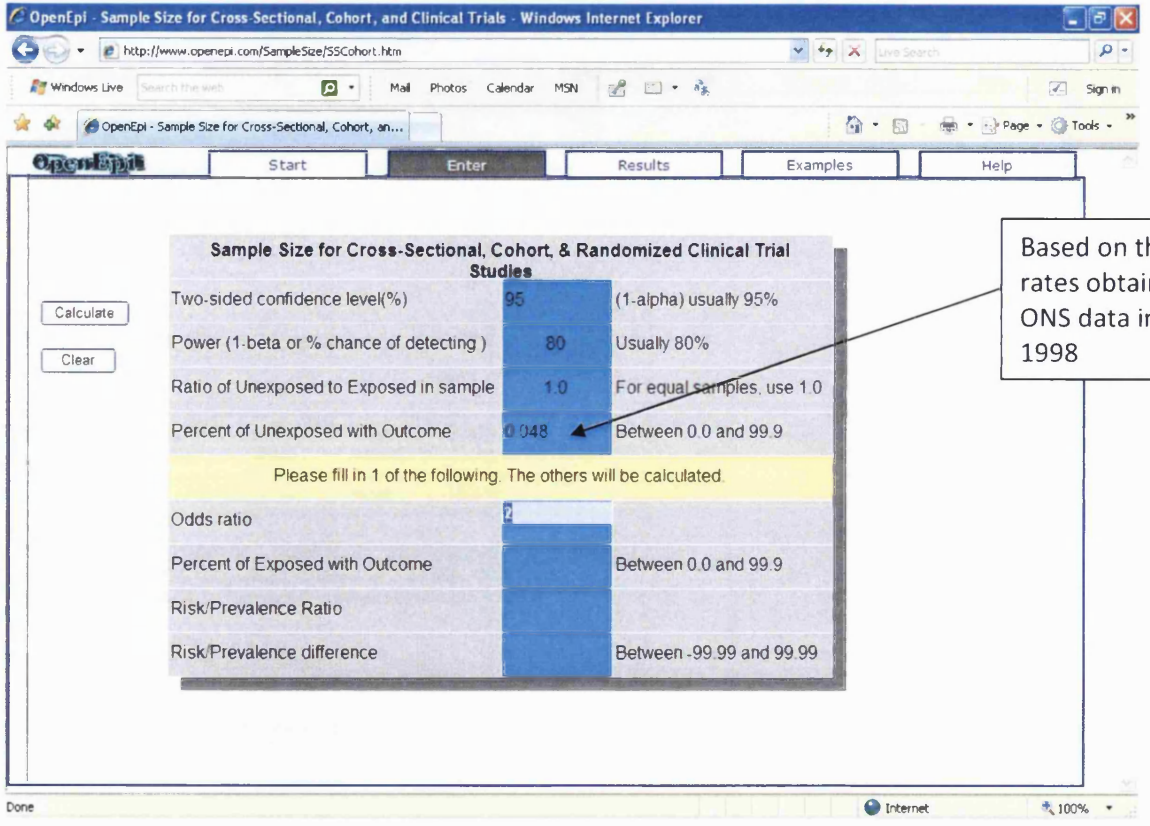
_____

_____

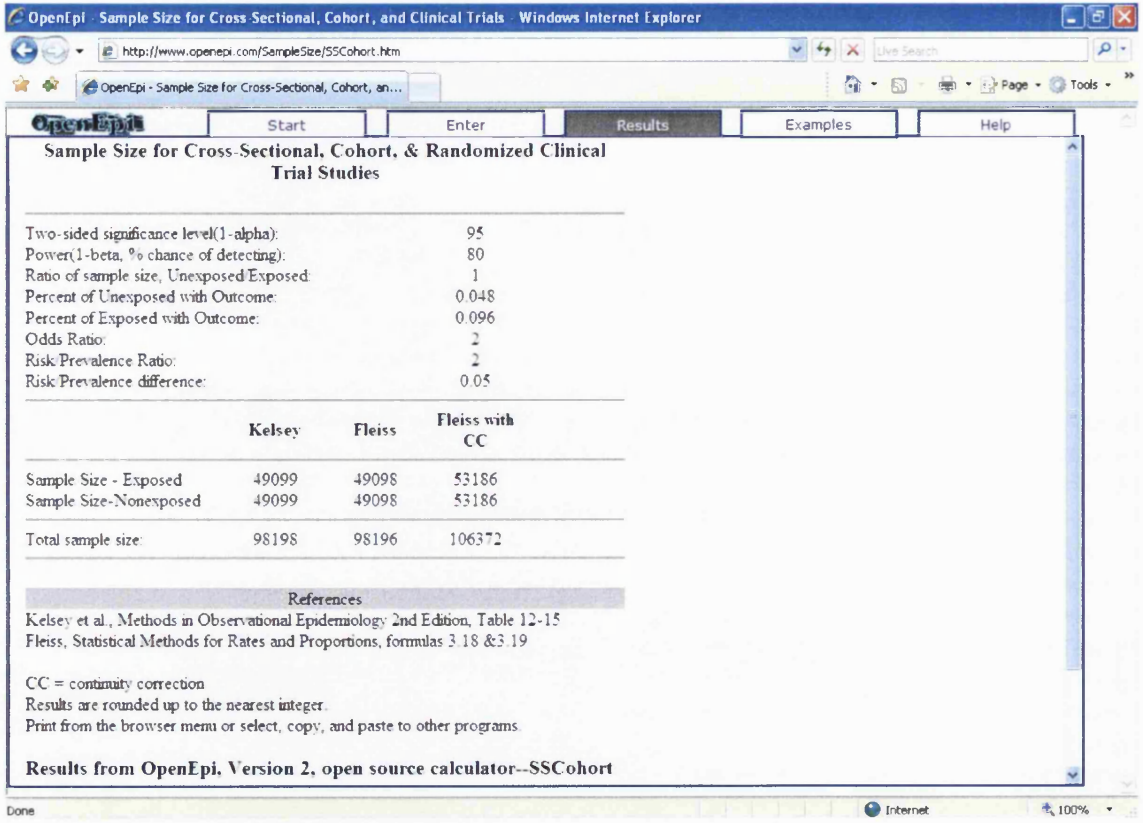
_____

Many thanks for completing the questionnaire

Appendix I: Sample size calculation for mortality rates



Based on the mortality rates obtained from ONS data in the year 1998


OpenEpi - Sample Size for Cross-Sectional, Cohort, and Clinical Trials - Windows Internet Explorer
http://www.openepi.com/SampleSize/SSCohort.htm
OpenEpi - Sample Size for Cross-Sectional, Cohort, an...
Page
Tools
OpenEpi
Start
Enter
Results
Examples
Help
Sample Size for Cross-Sectional, Cohort, & Randomized Clinical Trial Studies
Two-sided significance level(1-alpha): 95
Power(1-beta, % chance of detecting): 80
Ratio of sample size, Unexposed/Exposed: 1
Percent of Unexposed with Outcome: 0.048
Percent of Exposed with Outcome: 0.096
Odds Ratio: 2
Risk/Prevalence Ratio: 2
Risk/Prevalence difference: 0.05
Kelsey
Fleiss
Fleiss with CC
Sample Size - Exposed 49099 49098 53186
Sample Size-Nonexposed 49099 49098 53186
Total sample size: 98198 98196 106372
References
Kelsey et al., Methods in Observational Epidemiology 2nd Edition, Table 12-15
Fleiss, Statistical Methods for Rates and Proportions, formulas 3.18 &3.19
CC = continuity correction
Results are rounded up to the nearest integer.
Print from the browser menu or select, copy, and paste to other programs.
Results from OpenEpi, Version 2, open source calculator--SSCohort
Done
Internet
100%

Appendix J: Ethics approval for the safety study (Chapter 6)

Safeguarding public health

MHRA

Independent Scientific Advisory Committee
for MHRA database research

ISAC EVALUATION OF PROTOCOLS FOR RESEARCH INVOLVING GPRD DATA

FEED-BACK TO APPLICANTS

CONFIDENTIAL			*by e-mail*
PROTOCOL NO:	07_059		
PROTOCOL TITLE:	Incidence of liver damage and diabetes with antipsychotic use in children and adolescents		
APPLICANT:	Prof Ian Wong, Professor of Paediatric Medicines Research, Centre for Paediatric Pharmacy Research, The School of Pharmacy, Institute of Child Health, Great Ormond Street Hospital for Children		
APPROVED ☐	**APPROVED SUBJECT TO MINOR AMENDMENT (resubmission not required)** ☐	**REVISION/ RESUBMISSION REQUESTED** ☒	**REJECTED** ☐
COMMENTS:	Protocol 07_059 is not approved and needs to be revised taking into account the following observations from ISAC. Resubmission is required. Reviewer 1 1. The number of exposed patients is fairly small - 1103 for atypical and 1871 for typical antipsychotics. The incidence of diabetes is around 24 per 100,000 per year. Only small numbers of cases can be expected. A sample size calculation should be done to evaluate whether the study is feasible with this number of exposed cases. 2. For the SIR, the age-specific incidence rates for diabetes by sex are required but it is not clear how these will be obtained. 3. Known causes of acute liver damage such as viral hepatitis, EBV infection, etc. should be sought. Reviewer 2 The applicants do not seem to have considered the power of the study. Is the incidence of liver damage in the population of interest high enough to make the		

Medicines and Healthcare products Regulatory Agency
Market Towers 1 Nine Elms Lane London SW8 5NQ
T 020 7084 2000 F 020 7084 2353 www.mhra.gov.uk

An executive agency of the Department of Health

	study worthwhile and reliable? Some estimate of the power would be helpful. A great deal of weight will be given to the causality assessment of the expert panel. How will the panel function? How will the investigators prevent the introduction of bias into the assessment? What criteria will be used to determine plausibility of relationship to drug? Will the panel be masked as to the identity of the antipsychotic? There is no control group for this study, and the incidence of liver damage and diabetes in the cohort will be compared to the incidence stratified by age and gender in GPRD. Are there no confounders that should be considered? Reviewer 3 The occurrence of the cases should be made without too much error although the cases of diabetes will be made with more error than the cases of liver disease since there is unlikely to be a consistent definition in the cohort; it would be worth exploring the influence of the diagnostic criteria since each case will be reviewed. It would be sensible to assess the duration and severity of each case (and its relationship to drug withdrawal - which I think the applicants are assessing). In assessing the standardised incidence rates in the cohort, the applicants will not be controlling for attendance rates for other conditions - since a diagnosis will be more likely to be made in a higher attending population- and for other comorbidities; it would be worth modelling this rather than assessing crude standardised incidence rates.
DATE:	23 July 2007

Please refer to the Appendix data CD for the protocol for this Ethics application

Appendix K: GPRD Medical codes related to liver abnormalities

Please refer to the Appendix data CD for the full list of Medical codes related to liver abnormalities

Appendix L: GPRD Medical codes related to diabetes mellitus

Please refer to the Appendix data CD for the full list of Medical codes related to diabetes mellitus

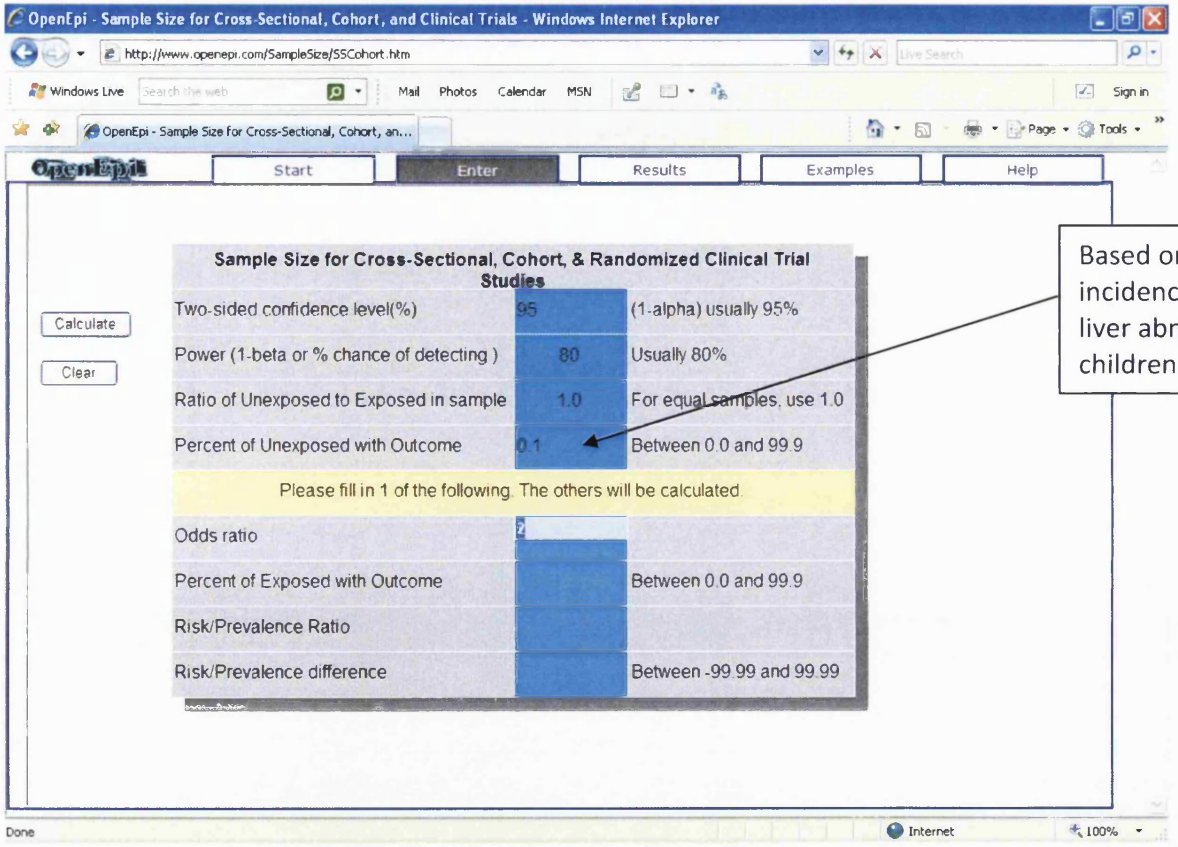
Appendix M: GPRD Product codes of antidiabetic drugs

Please refer to the Appendix data CD for the full list of Product codes of antidiabetic drugs

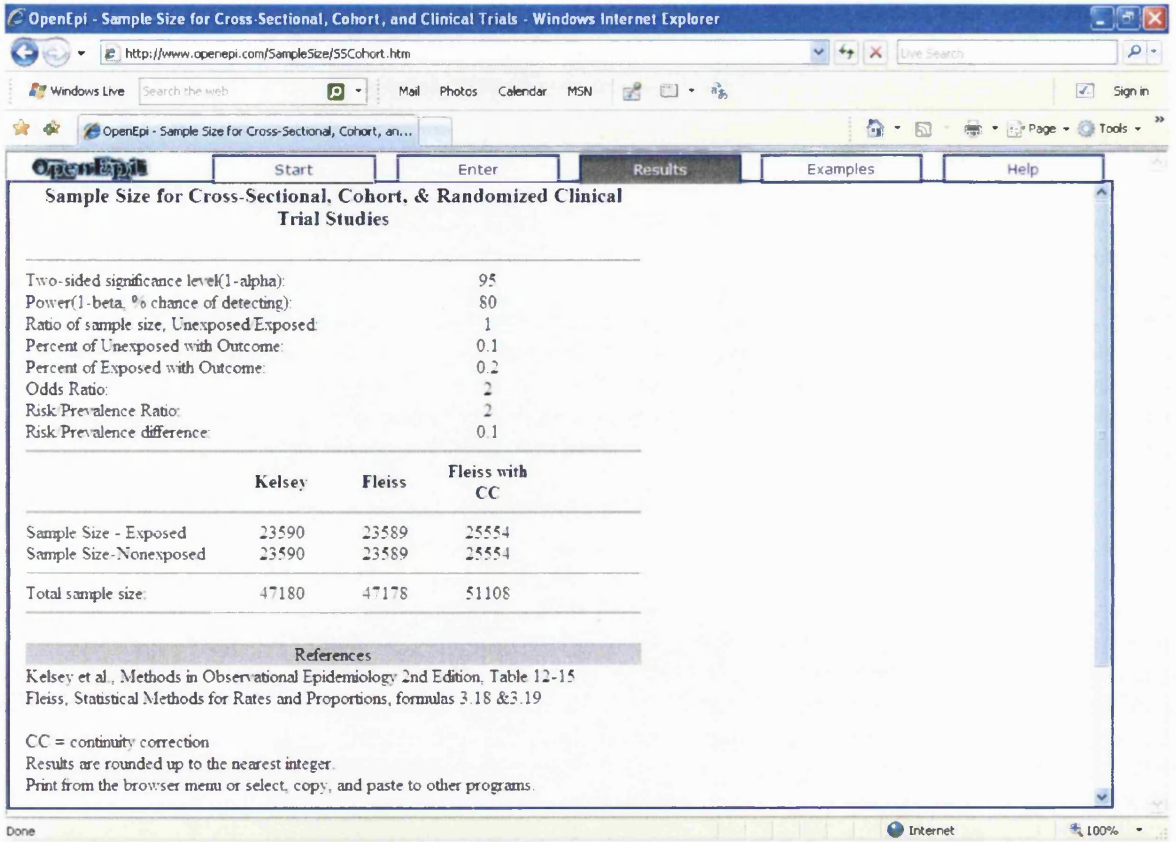
Appendix N: GPRD Medical codes related to extrapyramidal symptoms

Please refer to the Appendix data CD for the full list of Medical codes related to extrapyramidal symptoms

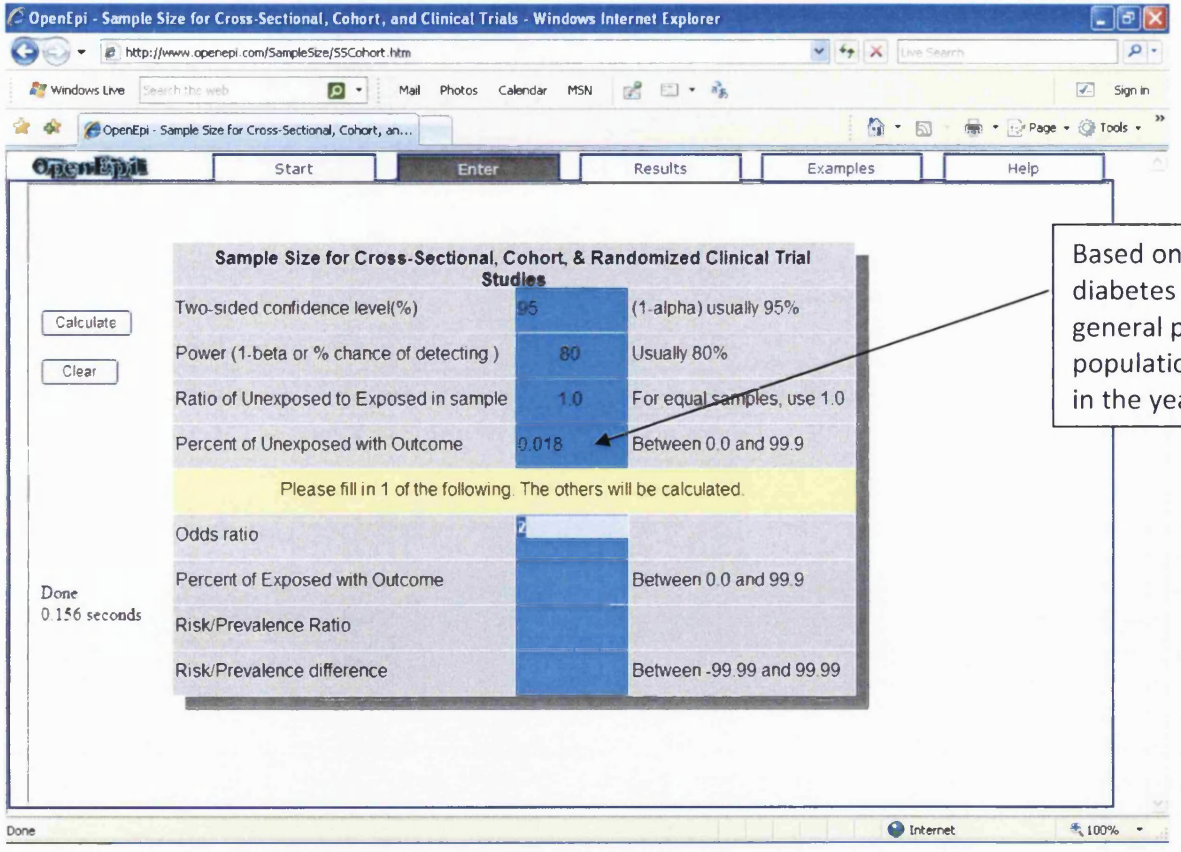
Appendix O: Sample size calculation for incidence of liver abnormalities



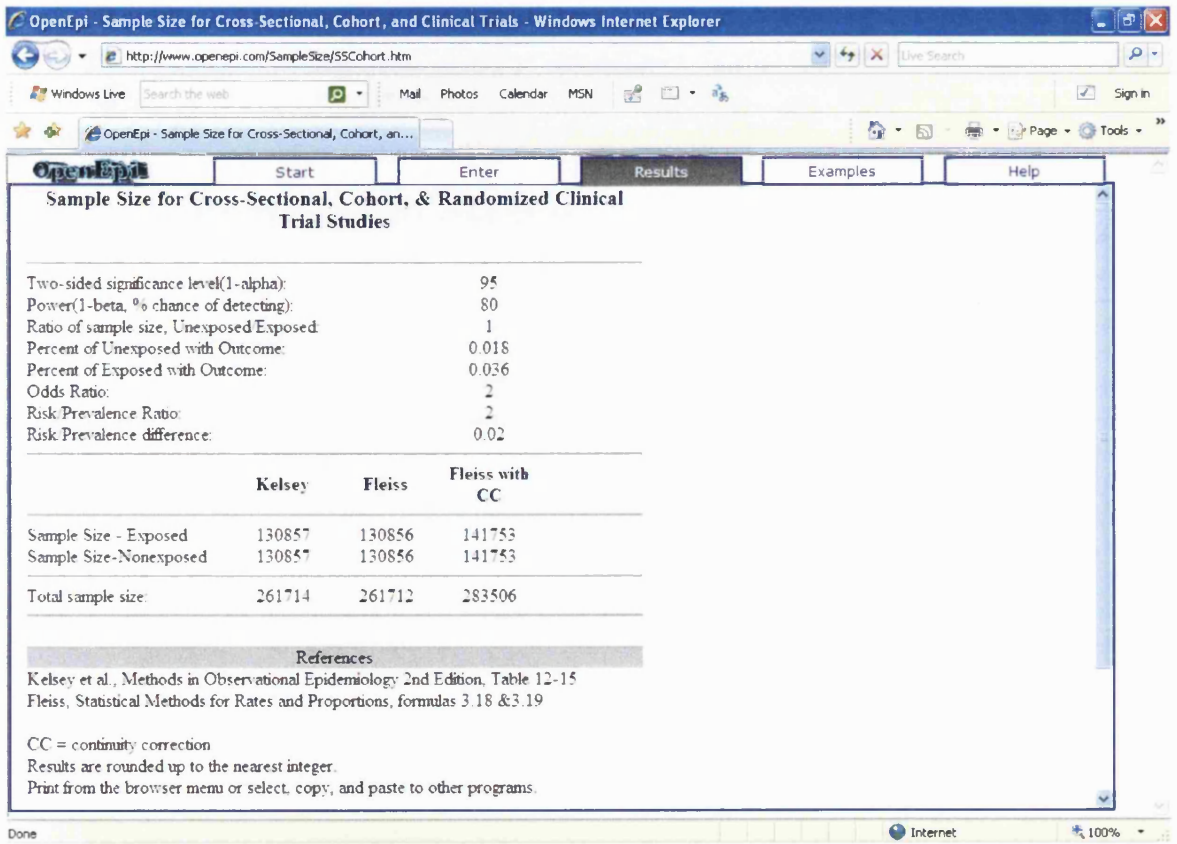
Based on a hypothetical incidence rate of 1 case of liver abnormality per 1,000 children


OpenEpi - Sample Size for Cross-Sectional, Cohort, and Clinical Trials - Windows Internet Explorer
http://www.openepi.com/SampleSize/SSCohort.htm
Start
Enter
Results
Examples
Help
Sample Size for Cross-Sectional, Cohort, & Randomized Clinical Trial Studies
Two-sided significance level(1-alpha): 95
Power(1-beta, % chance of detecting): 80
Ratio of sample size, Unexposed/Exposed: 1
Percent of Unexposed with Outcome: 0.1
Percent of Exposed with Outcome: 0.2
Odds Ratio: 2
Risk/Prevalence Ratio: 2
Risk/Prevalence difference: 0.1
Kelsey
Fleiss
Fleiss with CC
Sample Size - Exposed 23590 23589 25554
Sample Size-Nonexposed 23590 23589 25554
Total sample size: 47180 47178 51108
References
Kelsey et al., Methods in Observational Epidemiology 2nd Edition, Table 12-15
Fleiss, Statistical Methods for Rates and Proportions, formulas 3.18 &3.19
CC = continuity correction
Results are rounded up to the nearest integer.
Print from the browser menu or select, copy, and paste to other programs.
Done
Internet
100%

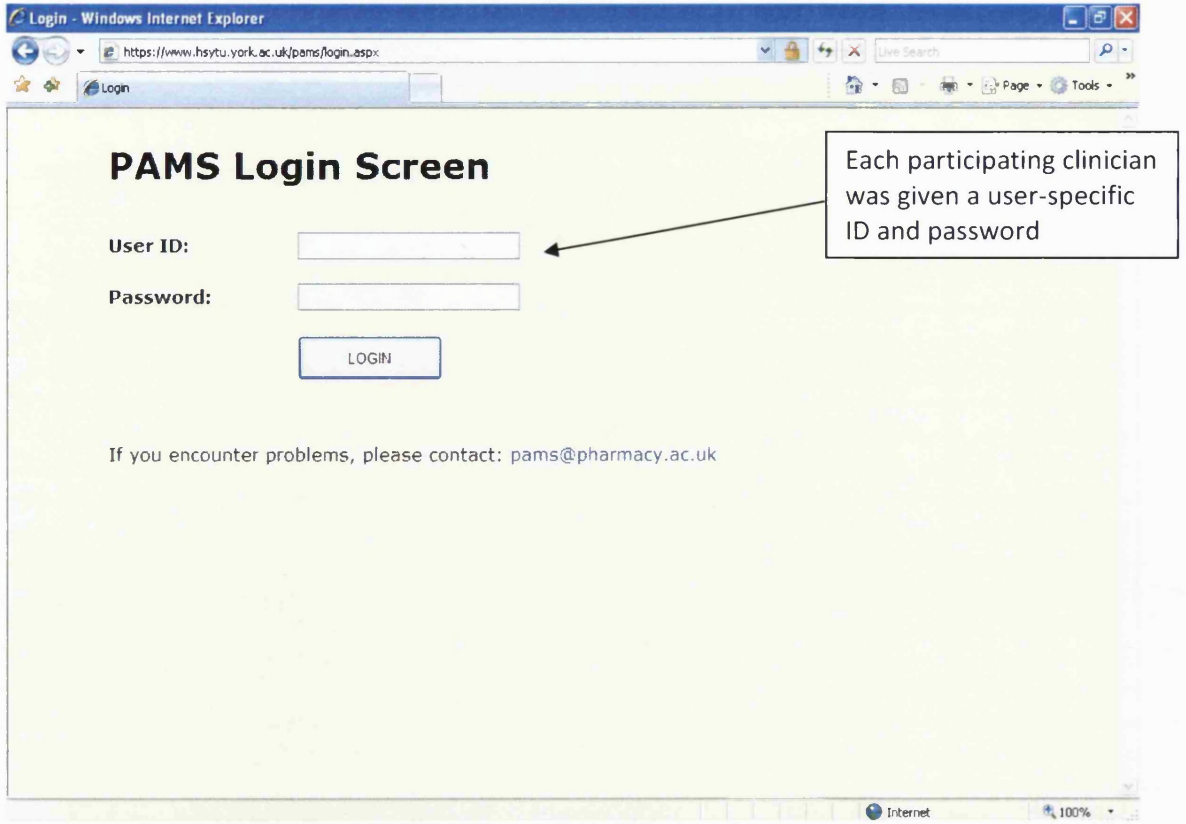
Appendix P: Sample size calculation for the incidence of diabetes mellitus

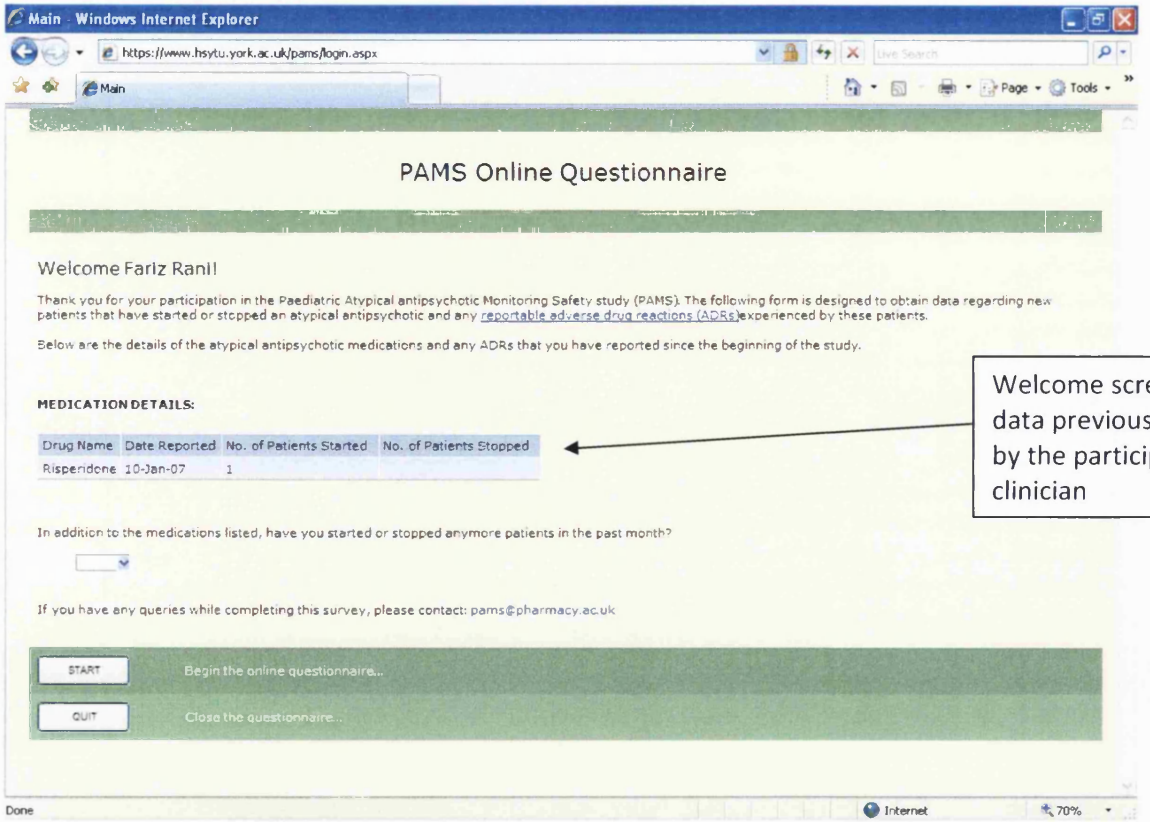


Based on the incidence of diabetes mellitus in the general paediatric population in the GPRD in the year 1998

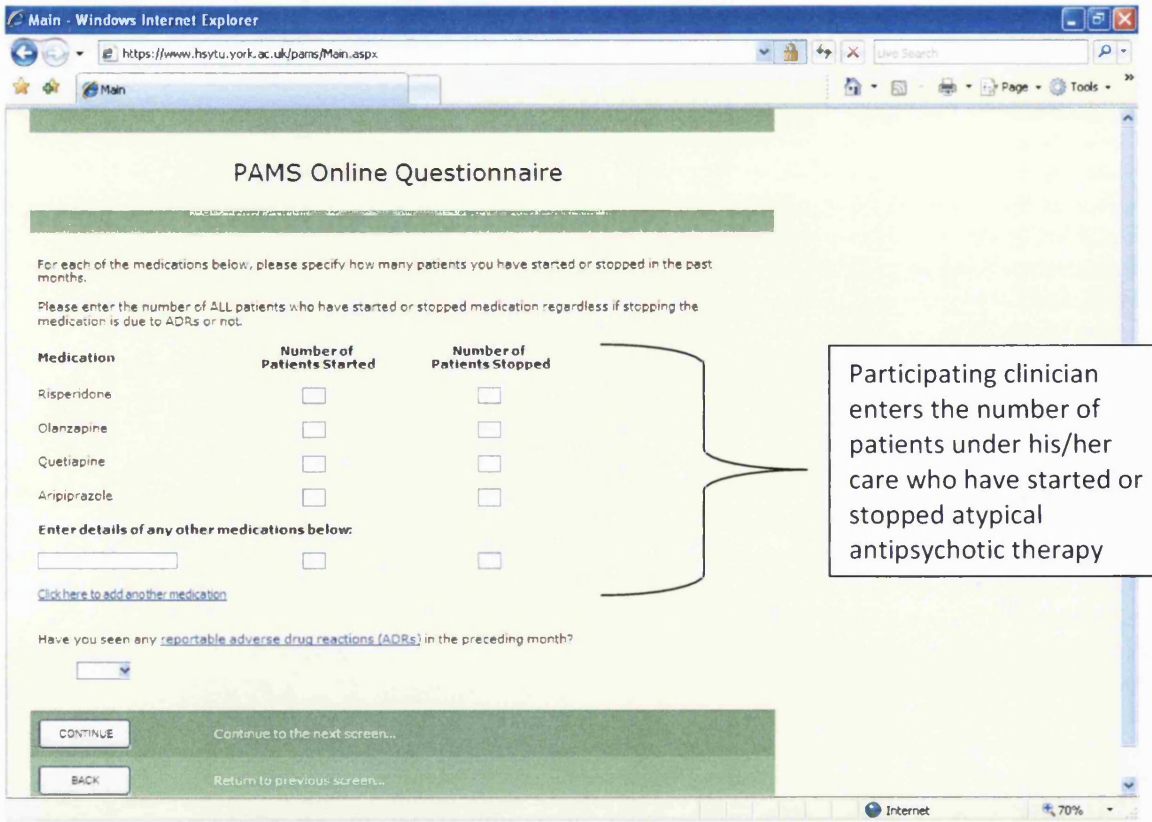

OpenEpi - Sample Size for Cross-Sectional, Cohort, and Clinical Trials - Windows Internet Explorer
http://www.openepi.com/SampleSize/SSCohort.htm
OpenEpi - Sample Size for Cross-Sectional, Cohort, an...
OpenEpi
Start
Enter
Results
Examples
Help
Sample Size for Cross-Sectional, Cohort, & Randomized Clinical Trial Studies
Two-sided significance level(1-alpha): 95
Power(1-beta, % chance of detecting): 80
Ratio of sample size, Unexposed:Exposed: 1
Percent of Unexposed with Outcome: 0.018
Percent of Exposed with Outcome: 0.036
Odds Ratio: 2
Risk/Prevalence Ratio: 2
Risk/Prevalence difference: 0.02
Kelsey
Fleiss
Fleiss with CC
Sample Size - Exposed 130857 130856 141753
Sample Size-Nonexposed 130857 130856 141753
Total sample size: 261714 261712 283506
References
Kelsey et al., Methods in Observational Epidemiology 2nd Edition, Table 12-15
Fleiss, Statistical Methods for Rates and Proportions, formulas 3.18 &3.19
CC = continuity correction
Results are rounded up to the nearest integer.
Print from the browser menu or select, copy, and paste to other programs.
Done
Internet
100%

Appendix Q: PAMS online data collection form

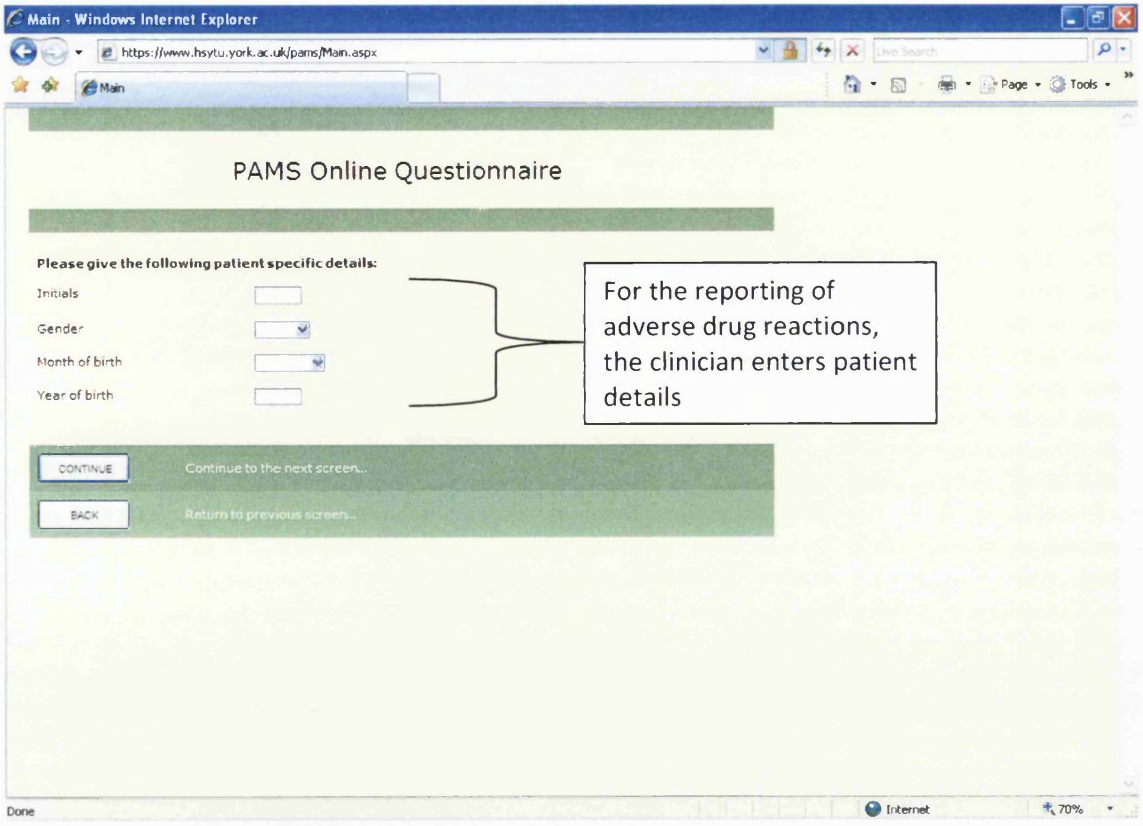


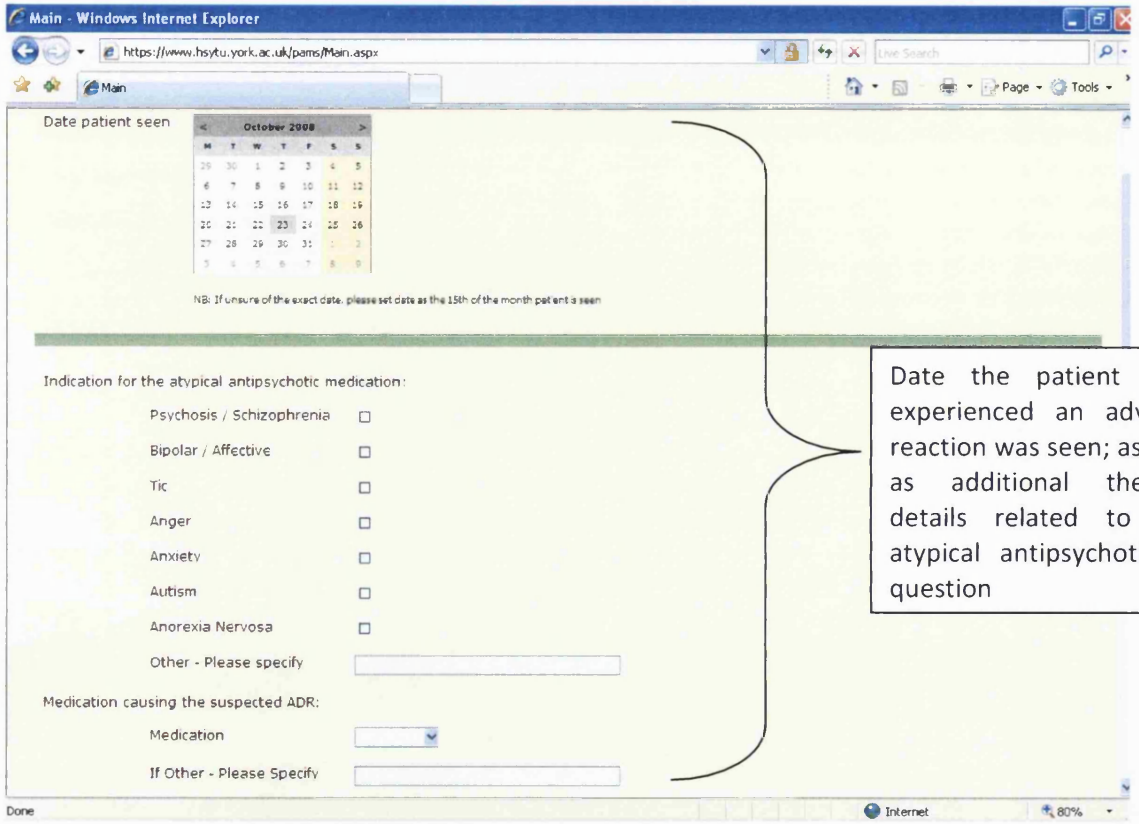


Welcome screen shows all data previously entered by the participating clinician

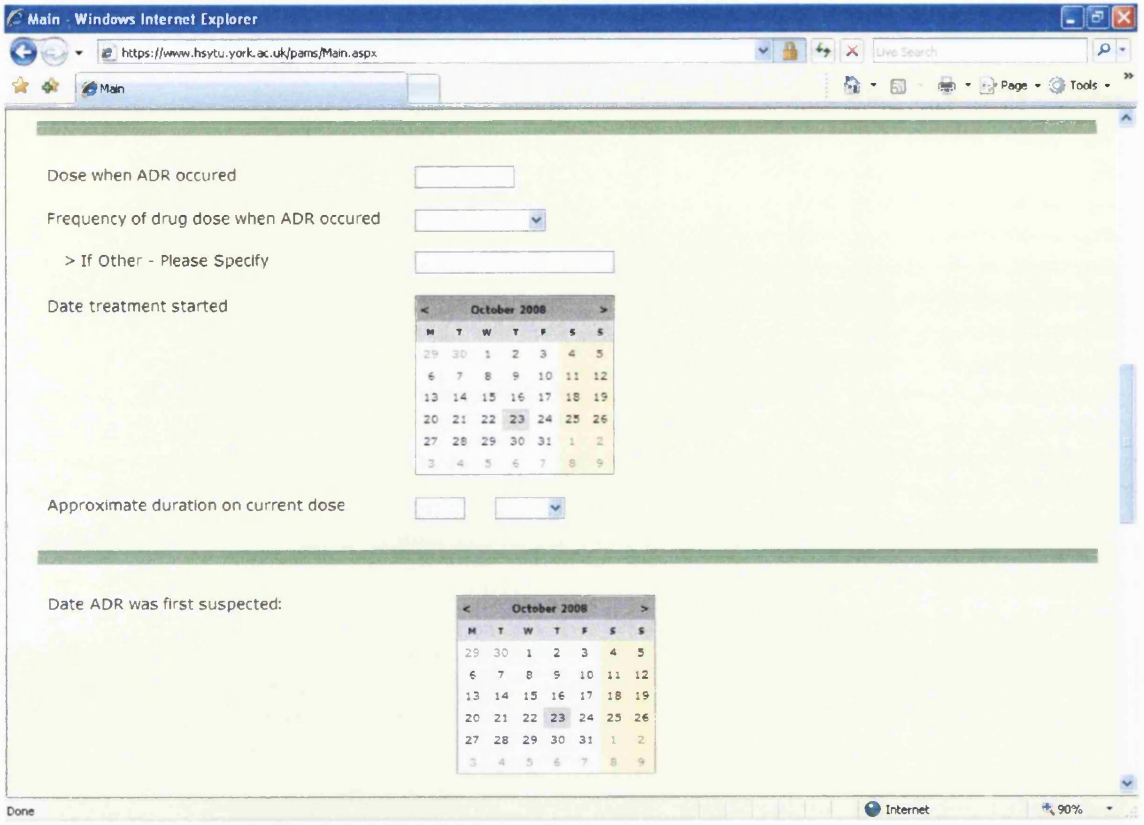


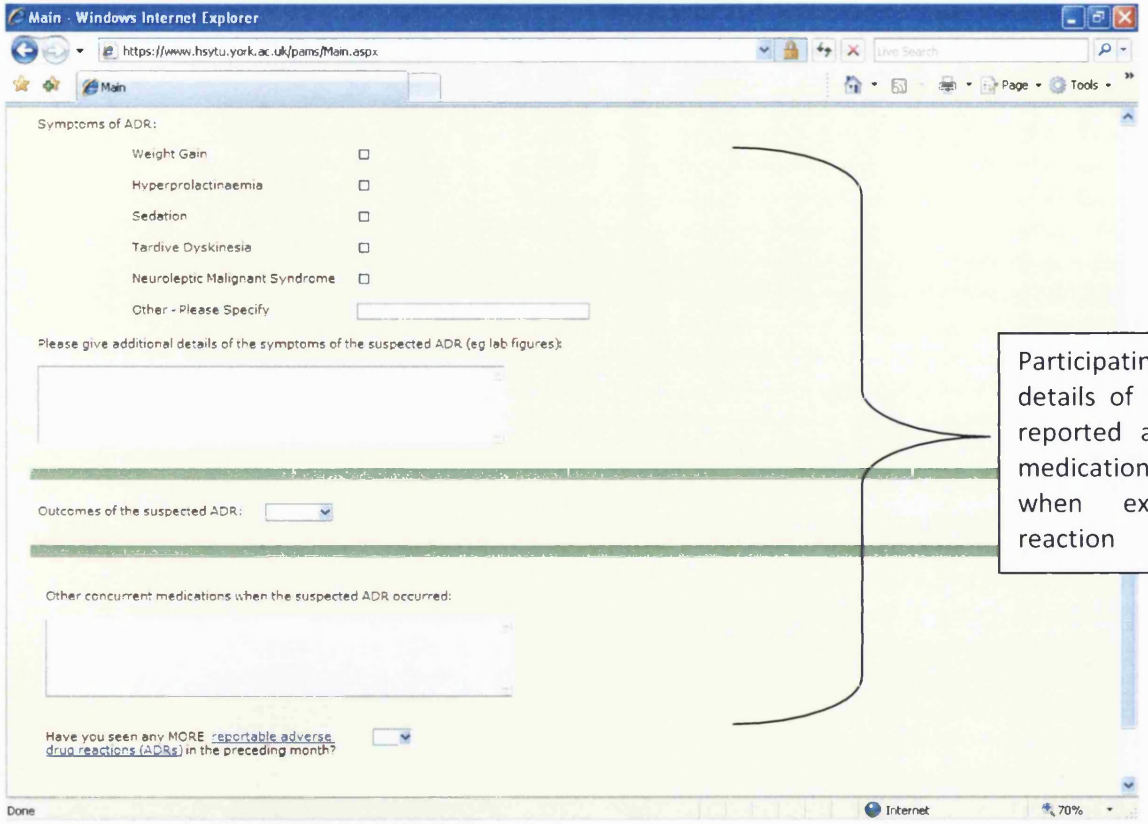
Participating clinician enters the number of patients under his/her care who have started or stopped atypical antipsychotic therapy


Main - Windows Internet Explorer
https://www.hsytu.york.ac.uk/pams/Main.aspx
Main
Page
Tools
PAMS Online Questionnaire
Please give the following patient specific details:
Initials
Gender
Month of birth
Year of birth
CONTINUE
Continue to the next screen...
BACK
Return to previous screen...
Done
Internet
70%
For the reporting of adverse drug reactions, the clinician enters patient details



Date the patient who experienced an adverse reaction was seen; as well as additional therapy details related to the atypical antipsychotic in question


Main - Windows Internet Explorer
https://www.hsytu.york.ac.uk/pams/Main.aspx
Main
Page
Tools
Dose when ADR occured
Frequency of drug dose when ADR occured
> If Other - Please Specify
Date treatment started
October 2008
Approximate duration on current dose
Date ADR was first suspected:
October 2008
Done
Internet
90%



Participating clinician enters additional details of the adverse reaction being reported as well as any concurrent medication the patient was taking when experiencing the adverse reaction

Appendix R: Ethics approval for the PAMS study (Chapter 7)

Charing Cross Research Ethics Committee
Room 3E/03A, 3rd Floor
Charing Cross Hospital
Fulham Palace Road
London W6 8RF

Telephone: 020 8846 7283
Facsimile: 020 8846 7280

Dr Ian CK Wong
Centre for Paediatric Pharmacy Research
The School of Pharmacy
29-39 Brunswick Square
London
WC1N 1AX

16 November 2005

Dear Dr Wong

Full title of study:	**Paediatric Atypical antipsychotic Monitoring Safety study (PAMS)**
REC reference number:	**05/Q0401/133**

The Research Ethics Committee reviewed the above application at the meeting held on 07 November 2005.

Ethical opinion

1. The following points were confirmed at interview:
a) The participants would comprise Paediatricians, not patients.
b) Doctors would keep a running tally of the number of patients who were newly started on an atypical antipsychotic.
c) Doctors would be actively encouraged to follow the Yellow Card System.

The members of the Committee present gave a favourable ethical opinion of the above research on the basis described in the application form, protocol and supporting documentation.

Ethical review of research sites

The Committee agreed that all sites in this study should be exempt from site-specific assessment (SSA). There is no need to complete Part C of the application form or to inform Local Research Ethics Committees (LRECs) about the research. The favourable opinion for the study applies to all sites involved in the research.

Conditions of approval

The favourable opinion is given provided that you comply with the conditions set out in the attached document. You are advised to study the conditions carefully.

RECEIVED
21 NOV 2005

Approved documents

The documents reviewed and approved at the meeting were:

Document	*Version*	*Date*
Application		12 October 2005

Investigator CV		12 October 2005
Protocol	3.5	12 October 2005
Covering Letter		12 October 2005
Summary/Synopsis	2.0	12 October 2005
Letter from Sponsor		11 October 2005
Peer Review		21 April 2005
Questionnaire	3.5	12 October 2005
Letter of invitation to participant	3.5	12 October 2005
Participant Information Sheet	3.5	12 October 2005
Participant Consent Form	3.5	12 October 2005
Statement of Indemnity Arrangements		01 June 2005

Research governance approval

You should arrange for the R&D Department at all relevant NHS care organisations to be notified that the research will be taking place, and provide a copy of the REC application, the protocol and this letter.

All researchers and research collaborators who will be participating in the research at a NHS site must obtain final research governance approval before commencing any research procedures. Where a substantive contract is not held with the care organisation, it may be necessary for an honorary contract to be issued before approval for the research can be given.

Membership of the Committee

The members of the Ethics Committee who were present at the meeting are listed on the attached sheet.

Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees (July 2001) and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

05/Q0401/133	**Please quote this number on all correspondence**

With the Committee's best wishes for the success of this project

Yours sincerely

pp. G. Schlotz

Dr Michael Feher
Chair

Email: TSchlotz@hhnt.org

Enclosures: *List of names and professions of members who were present at the meeting and those who submitted written comments*

Standard approval conditions

Copy to: *Dr Julian Axe*
The School of Pharmacy, University of London.
The School of Pharmacy, University of London.
29 Brunswick Square
London WC1N 1AX

Charing Cross Research Ethics Committee

Attendance at Committee meeting on 07 November 2005

Committee Members:

Name	*Profession*	*Present?*	*Notes*
Dr Michael Feher	Consultant Physician	Yes	
Dr Anwar Alhaq	Clinical Scientist	No	
Dr Mark Atkins	Consultant Virologist	No	
Mrs Jane Bruton	Nurse	No	
Mr John Clifford	Lawyer	Yes	
Mrs Claudia Court	Lay Member	No	
Mr Iain Davidson	Pharmacist	Yes	
Dr Andrew Dicker	General Practitioner	Yes	
Dr Jerry Healy	Consultant Radiologist	No	
Miss Katie Macdonald	Lay Member	Yes	
Dr Graeme Moyle	Associate Director of HIV Research	Yes	
Dr Rosalind Mulholland	Psychiatrist	No	
Miss Anna Smajdor	Lay Member	Yes	
Mr Mike Stafford	Consultant Gynaecologist	Yes	
Mr Peter Thomas	Lay Member	No	
Dr Sabita Uthaya	Paediatrician	Yes	
Dr Steve Yentis	Consultant Anaesthetist	No	

Also in attendance:

Name	*Position (or reason for attending)*
Miss Anita Chakraborty	Committee Co-ordinator

An advisory committee to North West London Strategic Health Authority

Please refer to the Appendix data CD for the protocol for this application

Riverside Research Ethics Committee
Room 3E03A, 3rd Floor
Charing Cross Hospital
Fulham Palace Road
London W6 8RF

Tel: 020 8846 7282
Fax: 020 8846 7280
Email: achakraborty@hhnt.org

Dr Ian Wong
Centre for Paediatric Pharmacy Research
The School of Pharmacy
29-39 Brunswick Square
London WC1N 1AX

13 January 2006

Dear Dr Wong

Full title of study:	**Paediatric Atypical antipsychotic Monitoring Safety study (PAMS)**
REC reference number:	**05/Q0401/133**
Amendment date:	**07/12/2005**

The above amendment was reviewed at the meeting of the Sub-Committee of the Research Ethics Committee held on 09/01/2006.

Ethical opinion

The members of the Committee present gave a favourable ethical opinion of the amendment on the basis described in the notice of amendment form and supporting documentation.

Approved documents

The documents reviewed and approved at the meeting were:

- Notice of Substantial Amendment, 09/12/2005
- Protocol version 3.5
- Protocol version 4.1
- Amendment Sheet, version 1.07/12/2005

Membership of the Committee

The members of the Ethics Committee who were present at the meeting are listed at the end of the letter.

Research governance approval

All investigators and research collaborators in the NHS should notify the R&D Department for the relevant NHS care organisation of this amendment and check whether it affects research governance approval of the research.

Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees (July 2001) and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

04/Q0401/64	Please quote this number on all correspondence

Yours sincerely

Miss Anita Chakraborty
Committee Co-ordinator

List of names and professions of members who were present at the meeting and those who submitted written comments

- Steve Yentis (Chairman)
- Mr J Clifford (Lay Member)

RECEIVED
18 JAN 2006

Please refer to the Appendix data CD for the protocol for this ethics application amendment

RECEIVED
21 AUG 2006

Riverside Research Ethics Committee
Charing Cross Hospital
Fulham Palace Road
London W6 8RF

Tel: 020 8846 7282
Fax: 020 8846 7280

Dr Ian CK Wong
Director of the Centre for Paediatric Pharmacy Research
The School of Pharmacy
29-39 Brunswick Square
London
WC1N 1AX

16 August 2006

Dear Dr Wong

Study title: **Paediatric Atypical antipsychotic Monitoring Safety study (PAMS)**
REC reference: **05/Q0401/133**

Amendment number: **5.0**
Amendment date: **07 July 2006**

The above amendment was reviewed at the meeting of the Sub-Committee of the REC held on 26 July 2006.

Ethical opinion

The members of the Committee present gave a favourable ethical opinion of the amendment on the basis described in the notice of amendment form and supporting documentation.

Approved documents

The documents reviewed and approved at the meeting were:

Document	Version	Date
Protocol	5.0	07 July 2006
Amendment sheet	1.0	07 July 2006
Notice of Substantial Amendment (non-CTIMPs)	5.0	07 July 2006

Membership of the Committee

The members of the Ethics Committee who were present at the meeting are listed at the foot of the next page.

Research governance approval

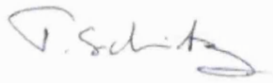
All investigators and research collaborators in the NHS should notify the R&D Department for the relevant NHS care organisation of this amendment and check whether it affects research governance approval of the research.

Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees (July 2001) and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

05/Q0401/133: Please quote this number on all correspondence

Yours sincerely



Tanja Schiotz
Committee Co-ordinator

E-mail: t.schiotz@hhnt.nhs.uk

Copy to: *Clinical Trials Unit, MHRA*

Dr Julian Axe

Riverside Research Ethics Committee

Attendance at Sub-Committee of the REC meeting on 26 July 2006

Committee Members:

Name	*Profession*	*Present?*
Dr Steven Yentis	Consultant Anaesthetist	Yes
Dr Mark Atkins	Consultant Virologist	Yes

Also in attendance:

Miss Katie Slater	Committee Administrator

Please refer to the Appendix data CD for the protocol for this ethics application amendment