



University
of Glasgow

Taylor, Mark (2013) Assessing the use and effectiveness of antipsychotic medication. MD thesis

<http://theses.gla.ac.uk/4227/>

Copyright and moral rights for this thesis are retained by the author

A copy can be downloaded for personal non-commercial research or study, without prior permission or charge

This thesis cannot be reproduced or quoted extensively from without first obtaining permission in writing from the Author

The content must not be changed in any way or sold commercially in any format or medium without the formal permission of the Author

When referring to this work, full bibliographic details including the author, title, awarding institution and date of the thesis must be given.

Assessing the use and effectiveness of antipsychotic medication

Thesis for MD degree, University of Glasgow

Dr Mark Taylor

Acknowledgements: the author would like to thank Dr Jonathan Cavanagh, for his erudite supervision during this project. This work would not have been possible without the patients who generously participated, and the research collaborators with whom I was privileged to work alongside. I must also thank Kathleen McArthur, and finally my family for their love and support.

CONTENTS

Summary of the Thesis	6
List of peer reviewed publications arising from the thesis	8
Abbreviations used in the thesis	9
List of Figures and Tables	11
Chapter 1: Introduction	14
Schizophrenia - an overview	15
Schizophrenia - presentation and course	17
Risks associated with schizophrenia	20
Costs and care of schizophrenia	20
Antipsychotic use in Scotland	21
Chapter 2: Outcomes in schizophrenia	26
The pre-medication era	26
The antipsychotic era	27
Specific factors linked to outcome	29
The nature of relapse	33
Effectiveness versus efficacy of antipsychotic medication	36
Aren't all antipsychotic medications the same?	39
Effectiveness studies of antipsychotic medications	40

Chapter 3: Describing the use of antipsychotic medication in Glasgow using a	
city-wide case register	46
Aim	48
Method	48
Results	49
Discussion	56
Strengths and limitations of the study	58
Implications	59
Chapter 4: A six month prospective study of five oral antipsychotic	
medications	61
Aims	62
Method	63
Results	65
Discussion	70
Strengths and limitations of the study	72
Conclusions	75
Chapter 5: A two year retrospective comparison of five oral antipsychotic	
medications	76
Aims	77
Method	78
Results	80
Discussio	85
Strengths and limitations of the study	88

Chapter 6: A retrospective long term comparison of three long acting (depot)	
injectionable of antipsychotic medications	89
Aims	91
Method	91
Results	95
Discussion	105
Strengths and limitations of the study	107
Conclusions	109
Chapter 7: Developing and validating a new side effect scale for antipsychotic	
medications	110
Aims	112
Method	112
Results	116
Discussion	121
Strengths and limitations of the study	123
Chapter 8: Discussion and context of results	124
Choice of antipsychotic medication	124
Tolerability of antipsychotic medication	128
Optimum dose of antipsychotic medication	131
Optimum duration of antipsychotic treatment	132
Antipsychotic polypharmacy	133
Clozapine	136
Long acting (depot) injections of antipsychotic medication	141
Conclusions and implications for clinical practice	152

Directions for future research	156
References	158
Appendix One	168
Appendix Two	171
Appendix Three	173

Summary of the Thesis

Background

Antipsychotic medications are widely prescribed for schizophrenia and other related psychiatric conditions, but can have serious financial costs and adverse effects. The evidence base concerning the efficacy; effectiveness; and adverse effects of antipsychotic medications is extensive but variable in quality and applicability, and controversy continues to exist as to whether the newer medications are superior to the older antipsychotics. Locally derived data on the use and effectiveness of these medications can inform their future use, and complement the national and international studies.

Aims & objectives

To review the pertinent literature regarding antipsychotic medication, and to examine the use and clinical effectiveness of antipsychotic medication in a local context. Also to develop a valid but pragmatic scale to monitor the adverse side effects of antipsychotic medications.

Methods

A pre-existing case register was analysed to describe the contemporary patterns of antipsychotic usage. For the original data containing studies, one prospective and two retrospective attributions of clinical global impression (CGI) scores, as well as continuation and hospitalization rates were examined. The side effect scale (GASS) was devised after literature review and patient consultation, and tested on consenting patients in comparison to a well established existing scale (LUNSERS) and on healthy individuals.

Results

Data from the Glasgow city case register shows antipsychotics are widely and appropriately prescribed there but polypharmacy is common. In the prospective 6 month study, olanzapine and risperidone produced significant improvements in CGI but lack of power precluded similar conclusions with amisulpride, clozapine, and quetiapine. In the retrospective studies, clozapine was clinically superior to other oral antipsychotics but there was no significant clinical difference between the main 3 depot or long acting antipsychotics studied. The new side-effect scale – the GASS - was found to be easy to use and as discriminating as the LUNSERS.

Discussion

There can be difficulties generalizing data from short term RCTs to routine clinical practice. However this thesis demonstrates that simple but robust measures such as the CGI or GASS can be used to structure and inform everyday clinical practice. Consistent with the evolving debate on the relative merits of individual medications, this thesis showed there was little difference in clinical effectiveness between various oral antipsychotics, with the exception of clozapine. The lack of a significant difference between the old and newer long acting injectable antipsychotics is a new finding, and this area merits further study.

Conclusions

Structured routine monitoring of outcomes is possible in the NHS with regard to antipsychotic medication. Oral and LAI (or depot) antipsychotic medications continue to be differentiated more by their adverse side effect profile rather than their relative effectiveness, with the exception of clozapine. A new short, inclusive, and valid side-effect monitoring scale – the GASS - is introduced.

List of peer reviewed publications arising from the thesis:

1. Mark Taylor, Jonathan Cavanagh, Richard Hodgson and Jari Tiihonen. Examining the effectiveness of antipsychotic medication in first-episode psychosis. *J Psychopharmacol* 2012. doi: 10.1177/026988111243925
2. Taylor M, Turner M, Watt L, Brown D, Martin M, and Fraser K. “Atypical anti-psychotics in the real world – a naturalistic comparative outcome study” *Scottish Medical Journal*, 50 (3): 102-6. 2005.
3. Taylor M, Shajahan P, and Lawrie S “Comparing the use and discontinuation of antipsychotics in clinical practice – an observational study” *Journal of Clinical Psychiatry* 69(2): 240-245. 2008 Feb
4. Taylor M and Shajahan P. 1st generation long acting antipsychotic injections. Chapter 4, *Antipsychotic Long acting Injections*. Oxford University Press. 2011. ISBN 978-0-19-958604-2.
5. Shajahan P, Spence E, Taylor M, Daniel D, and Pelosi A. Comparison of the effectiveness of depot antipsychotics in routine clinical practice. *The Psychiatrist*, Jul 2010; 34: 273 - 279.
6. Waddell L and Taylor M. “A new self rating scale for detecting atypical or second generation antipsychotic side effects” ” *J Psychopharmacol* 2008; 22; 238

Abbreviations used in the thesis

AIMS	abnormal involuntary movements scale
ANNSERS	antipsychotic non-neurological side effect rating scale
BNF	british national formulary
CATIE	clinical antipsychotic trial of intervention effectiveness
CGI	clinical global impression
CI	confidence interval
CNS	central nervous system
CUtLASS	cost utility of the latest antipsychotic drugs in schizophrenia study
DDD	defined daily dose
DSM	diagnostic and statistical manual of mental disorders
DUP	duration of untreated psychosis
EPR	electronic patient record
EPS	extra-pyramidal side-effects
EUFEST	european first episode schizophrenia trial
FDA	food and drug administration (of USA)
FGA	first generation antipsychotic
GASS	Glasgow antipsychotic side-effect scale
HR	hazard ratio
LUNSERS	liverpool university side effect rating scale
MHA	mental health act
ICD	international classification of diseases
IQ	intelligence quotient
ISD	information services division (of the Scottish Government)
KG	kilogram
LAI	long acting injection (of antipsychotic)

LOCF last observation carried forward

NHS national health service

NICE national institute for health and clinical excellence (UK)

NIMH national institute for mental health

NNT number needed to treat

NS not significant

PANSS positive and negative syndrome scale

PsyCIS psychosis clinical information system

RCT randomized controlled trial

RLAI risperidone long acting injection

RR relative risk

SD standard deviation

SE side effects

SEG socio-economic group

SGA second generation antipsychotic

SOHO schizophrenia outpatient health outcome

TD tardive dyskinesia

TEOSS Treatment of Early Onset Schizophrenia Spectrum Disorders

WHO world health organisation

List of Figures and Tables

1. Figure 1. Direct antipsychotic medication costs to NHS Scotland, over time.
2. Figure 2. Number of prescriptions for typical and atypical antipsychotics in Scotland over time.
3. Figure 3. Trends over time for the five most commonly prescribed antipsychotic medications.
4. Table 1. Predictors of outcome (adapted with permission from Lewis and Buchanan, 2003)
5. Figure 4. Illustration of the difficulties in recruiting into a randomised controlled trial (RCT) with strict inclusion and exclusion criteria.
6. Table 2. Diagnostic mix of the ICD 10 F21-F29 group in the PsyCIS case register
7. Table 3. Socioeconomic group (SEG) status of the PsyCIS population expressed as a percentage of the whole (%).
8. Table 4. Social characteristics of the PsyCIS population expressed as a percentage of the whole (%)
9. Table 5. Regular pharmacotherapy within the PsyCIS population (%) in 2010
10. Table 6. Antipsychotic combinations in the PsyCIS cohort, 2010.
11. Table 7. Use of the Mental Health (Scotland) Act, 2003 - 'MHA' - long term treatment orders, and current formulation of prescribed medication (in 2010).
12. Table 8. Most frequently prescribed medications, by illness duration, within the PsyCIS cohort.

13. Table 9. Reasons given by treating psychiatrist for patient / medication selection, at the time of switch / initiation.
14. Table 10. Mean rated levels of pathology at baseline assessment.
15. Table 11. Improvement after six months treatment – mean drop in ratings and percent change from baseline
16. Table 12. Reasons given by treating psychiatrist for discontinuation of medication
17. Table 13. Diagnoses and use of SGA medication
18. Table 14. Average dose of SGA (rounded to the nearest 0.5mg)
19. Table 15. Characteristics of individuals with schizophrenia newly started on a SGA
20. Table 16. Discontinuation and hospital admission rates, as well as duration of treatment.
21. Figure 6: Study profile for retrospective analysis of depot medication
22. Table 17. Clinical profile of patients started on depot antipsychotics
23. Table 18. Proportion of patients in depot medication study who improved according to CGI-I (<5)
24. Figure 7. Survival curves in depot medication study - Time to treatment discontinuation due to all causes (A), inefficacy (B), and side-effects (C) and time to hospitalisation (D).
25. Table 19: Clinical Global Impression scores and duration of treatment (unadjusted)
26. Table 20. Existing side-effect rating scales
27. Table 21. Glasgow Antipsychotic Side-effect Scale (GASS)
28. Figure 8. Spread of GASS scores in patients and normal comparisons
29. Table 22. Mean ages and GASS scores of participants

30. Figure 9. PsyCIS cases (n=5221) use of maintenance antipsychotic medication (%) by diagnosis
31. Figure 10. Trends in individual LAI use over time, 2003-2007, in Scotland (data provided by the Information Services Division (ISD) of the Scottish Government.
32. Figure 11. Summary of all mirror image studies examining time in hospital, comparing FGA-LAIs with oral antipsychotic medications (with permission). Distribution (%) of total inpatient stay between previous-treatment and FGA-LAI treatment periods for each mirror image study (n=11) with each horizontal bar totalling 100%.

CHAPTER 1

INTRODUCTION

Before undertaking an in-depth analysis of the use and comparative effectiveness of antipsychotic medications, it is worthwhile summarising the main clinical disorder associated with their use, namely schizophrenia. This is important as it places a clinical context around the later discussion of antipsychotic medication.

Antipsychotic medications are commonly employed in the treatment of various psychotic conditions such as schizo-affective disorder; acute polymorphic or brief reactive psychosis; and bipolar disorder, the majority of the scientific research data on antipsychotic medication focuses on schizophrenia rather than these other forms of psychosis which explains why the reviews in this thesis focus solely on schizophrenia. However, in clinical practice the initial diagnosis is not always clear or straightforward and diagnostic shift between the various psychoses can occur over time. For this reason it was considered pragmatic and reflective of everyday clinical practice to include cases of psychosis rather be constrained to narrow schizophrenia in the original research studies reported here. Furthermore, the original studies described in this thesis are designed to be inclusive and naturalistic rather than have multiple exclusion criteria.

Schizophrenia – an overview

Schizophrenia is a heterogeneous syndrome that presents in adolescence or early adulthood and has a fluctuating course. According to studies by the World Health Organization (WHO), schizophrenia represents one of the top ten causes of worldwide disability, with a point prevalence of 0.2–0.7%, as suggested by large community surveys. Epidemiological studies suggest that there are approximately two new cases of schizophrenia according to the International Classification of Diseases (ICD) definition and about one new case of schizophrenia according to the Diagnostic and Statistical Manual of Mental Disorders (DSM) definition per 10,000 of the population every year. Over the decades, definitions of schizophrenia according to ICD and DSM criteria have changed but even so, schizophrenia remains a relatively common mental disorder, with a lifetime risk approaching one per cent. The disorder is slightly more common in men (Lawrie and Johnstone, 2011).

In terms of the historical descriptions of schizophrenia, one of the important early figures was John Haslam, who in 1809 noted an encroaching apathy after puberty with progressive deterioration in cases of youthful insanity. No review of schizophrenia is complete without mention of Emil Kraepelin, who in 1919 dichotomised the insanity of early adult life into a cyclical manic depressive psychosis and an unremitting ‘dementia praecox’, or youthful dementia, which led in turn to a misconceived pessimistic prognosis for schizophrenia. Eugen Bleuler, working in Switzerland throughout the 1930s coined the term ‘schizophrenia’ to represent a schism or disconnection between the functions of the mind. Unfortunately this term also led to unhelpful caricatures of schizophrenia as a Jekyll-and-Hyde-type split personality.

Bleuler attempted to characterise youthful insanity by proposing that the following were primary symptoms of schizophrenia (later known as the 'four As'):

- Abnormal associations (of thought)
- Ambivalence (in decision making)
- Abnormal affect or emotional tone
- Autistic thought or behaviour

Kurt Schneider went on in a further attempt to clarify the diagnosis of schizophrenia by suggesting they were pathognomonic symptoms of 'first rank' importance – the so-called 'first rank symptoms'. Although this was unsuccessful, the first rank symptoms remain influential and comprise of:

- *Thought insertion, withdrawal or broadcasting.* Alien thoughts are inserted or one's own thoughts are taken out of one's head or feel as though they are broadcast to others. Similar to the complaint of having one's mind read.
- *Delusions of external control (passivity experiences).* Here the sufferer feels his or her thoughts, actions or feelings are controlled by an external agency. These thoughts actions or feelings are sometimes referred to as 'made'.
- *Delusional percept.* This is a rare phenomenon which is a primary delusion arising fully formed from an unrelated normal perception.
- *Thought echo (echo de la pensée).* An auditory hallucination, with a voice repeating the individual's thoughts at the same time or immediately after they have happened.
- *Third-person auditory hallucinations or running commentary.* The hallucination refers to the patient as 'he' or 'she', or gives a running commentary on their actions.

Schizophrenia – presentation and course

Schizophrenia typically manifests in young people in their twenties, is usually lifelong and is characterised by “positive symptoms” such as auditory hallucinations, bizarre delusions, and disrupted speech (‘thought disorder’), and by “negative symptoms” such as social withdrawal, de-motivation, self neglect, and the appearance of flat emotional tone or affect. Subtle intellectual dysfunction, particularly in terms of impaired frontal lobe function such as executive function; planning; and verbal skills is also frequently evident clinically (Lawrie and Johnstone, 2011).

The ICD 10 (WHO, 1992) diagnostic criteria for schizophrenia are given below, but a requirement for diagnosis is that one clear symptom, or two if less clear-cut, should be present for most of a one-month period or more.

- Thought echo and social withdrawal or thought broadcasting.
- Delusions of passivity, external control, referring to the body, or specific thoughts actions or sensations and delusional perception.
- Running commentary style hallucinations.
- Persistent inappropriate delusions. These are abnormal delusional beliefs that are culturally inappropriate and completely impossible in reality. These constitute ‘first rank’ symptoms of schizophrenia – see above.
- Persistent hallucinations of any other sort when accompanied by fleeting delusions or over-valued ideas.
- Thought disorder, including breaks or interpolations in thought, leading to incoherent or irrelevant speech or neologisms.
- Catatonia, including mutism, posturing, stupor and excitement.

- Negative symptoms, such as marked apathy, poverty of speech and blunting or incongruous emotional tone.

The developmental pathways that may result in schizophrenia are highly complex and poorly understood. They include family history of schizophrenia (St Clair *et al*, 1990); obstetric complications (Eagles *et al*, 1990) and developmental difficulties (Miller *et al*, 2002); abuse (Janssen *et al*, 2004); major life events (Miller *et al*, 2001); and parental loss (Morgan *et al*, 2007). Rates of schizophrenia are also increased in urban, poor, immigrant and ethnic minority populations (Allardyce *et al*, 2006). Nearer to the time of disease onset, social factors such as cannabis use (Semple *et al*, 2005) and acute life events (Miller *et al*, 2001) appear aetiologically relevant.

Although many people do achieve remission of symptoms, the associated difficulties can be persistent and/or the individual diagnosed with schizophrenia can experience repeated episodes in between periods of remission. It is increasingly recognised that recovery from schizophrenia is more than the reduction or remission of symptoms *per se* (Yeomans *et al*, 2010). The Scottish Recovery Network has defined recovery as “... *being able to live a meaningful and satisfying life, as defined by each person, in the presence or absence of symptoms*”.

About three quarters of people who meet diagnostic criteria for schizophrenia will experience a relapse at some point later in life. Unplanned disengagement from treatment is a significant risk for relapse (Robinson *et al*, 1999) and poorer social integration predicts a lesser recovery following a first or second episode of

psychosis (Drake *et al*, 2000). Relapse is linked to increasing disability via loss of important relationships and work and educational opportunities. A poor outcome is more likely in men, individuals who misuse drugs, people with low IQ and where there is long duration of untreated psychosis. Low levels of academic and social functioning prior to the onset of schizophrenia and more severe symptoms at presentation also predicts poor outcome as does having more prominent negative symptoms and a poor response to antipsychotic medication (Marshall *et al*, 2005) – all these factors are more thoroughly reviewed in the next chapter.

The interpersonal context is a crucial aspect of recovery. Individuals who live in supportive home environments and have more friends are more likely to experience a fuller recovery from an acute episode of schizophrenia. However, many individuals lose their friends and families' support and may become subject to poverty, stigma and isolation and may end up facing discrimination and violence. About one half will have substance misuse problems (Cantwell R, 2003) and an overlapping half will have anxiety states and/or depression (Karatzias T *et al*, 2007).

People diagnosed with schizophrenia have life expectancy around 10-20 years shorter than the general population, with most patients smoking cigarettes, often heavily, many drinking alcohol to excess, and a poor diet and sedentary lifestyle being typical (eg Hamer M *et al*, 2008).

Risks associated with schizophrenia

There is much stigma surrounding the diagnosis of schizophrenia. Stereotypes of people diagnosed with schizophrenia as violent individuals populate the imagination of the media and general public. Although violence committed by people with schizophrenia is rare and the proportion of violence in society attributable to schizophrenia is very small, there is a marginally increased risk of committing violence for someone with schizophrenia, compared to a member of the general public (Fahy T, 2002).

More common and worrying is that individuals diagnosed with schizophrenia are more likely to hurt themselves. Five per cent of people with schizophrenia will commit suicide, and well recognised risk factors including male sex, illness severity and comorbidity, whilst the only consistent protective factor being delivery of, and adherence to, effective treatment (Hor and Taylor, 2010). This is one of the reasons that an independent review of the pharmacological treatment for schizophrenia, ie antipsychotic medication, is considered important. Incidence of attempted suicide following a first episode psychosis amongst adolescents is 32% (Falcone *et al*, 2007). Crucially linked to suicide are the feelings of depression and hopelessness that arise from perceptions of schizophrenia as a chronic, disabling, stigmatising diagnosis.

Costs and care of schizophrenia

There is significant expenditure in relation to the care of individuals diagnosed with schizophrenia and their families. In England this was estimated as £6.7 billion in 2004/05. The direct cost of treatment was about £2 billion. Indirect costs to society amounted to nearly £4.7 billion, of which £3.4 billion was attributed to lost

productivity due to unemployment, absence from work and premature mortality. The cost of informal care and private expenditures borne by families was £615 million, and that of lost productivity of carers was estimated to be £32 million. About £570 million was paid out in benefits and the cost of administering this was around £14 million (Mangalore R and Knapp M, 2006). Provided below (see Figure 1) are some details of the direct costs of antipsychotic medication in Scotland, and although these figures are impressively high, they are dwarfed by the larger costs (both direct and the harder to measure indirect costs) of refractory or undertreated schizophrenia and its consequences.

Nearly half of all mental hospital beds in Europe are occupied by people with a primary diagnosis of schizophrenia. Individuals with schizophrenia remain poorly serviced: the National Institute of Mental Health Epidemiologic Catchment Area survey from the USA reported that 40 per cent receive no care whatsoever in any given year. People with schizophrenia constitute roughly one-third of the homeless population in both Europe and the USA. The advent of community care has dramatically reduced the numbers of patients who live their lives in hospital, and has not resulted in an increase in the homeless hostel population (Geddes *et al*, 1994). Many patients are now treated solely by their general practitioner without input from specialist services (Lang *et al*, 1997). The care needs of older patients with schizophrenia are also often neglected (McNulty *et al*, 2003).

Antipsychotic use in Scotland

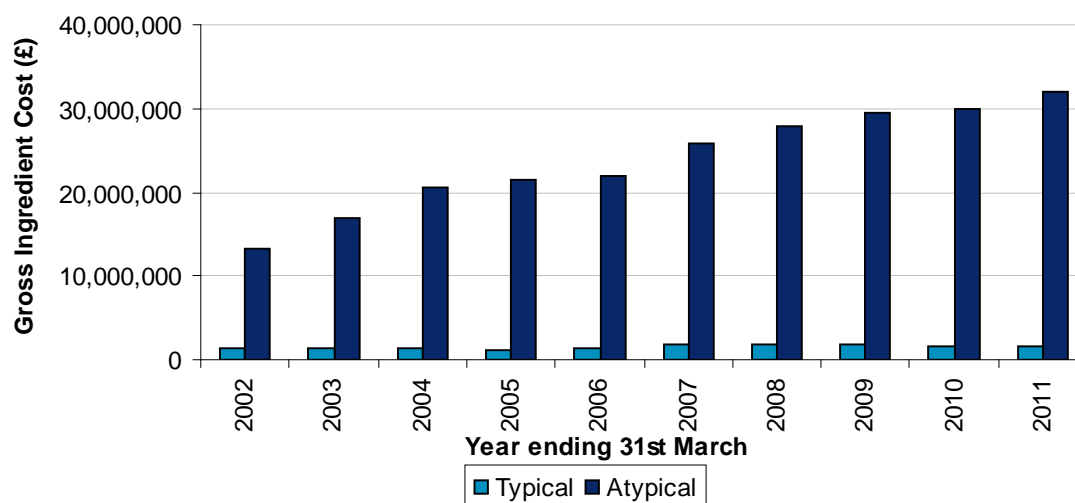
Antipsychotic medication is the cornerstone of treatment for schizophrenia. Traditionally these medications have been licensed only for the treatment of schizophrenia. Over the last two decades or more however, antipsychotics have

been increasingly used off license in other mental disorders and over the last decade have received official license in the UK and elsewhere for the treatment of bipolar disorder. The widespread use of antipsychotic medication in mental healthcare is documented in chapter 3 of this thesis, and is evident from the following Scottish Government statistics (Figures 1, 2, and 3), reproduced with permission from Prescribing Information System (Ross MacLean), Information Services Division Scotland.

Regarding nomenclature, later in this thesis the term 'typical antipsychotics' as mentioned below, will be substituted by 'first generation antipsychotics' or 'FGAs'; and atypical antipsychotics' will be termed 'second generation antipsychotics' or 'SGAs'.

Figure 1

Direct antipsychotic medication costs to NHS Scotland, over time.



The increasing use of atypical or SGA medications over time has significant cost implications for NHS Scotland, as demonstrated in Figure 1. For example, the

direct acquisition costs of atypicals or SGAs rose in 2006 from nearly £22 million to nearly £32 million only five years later.

Figure 2.

Number of prescriptions for typical and atypical antipsychotics in Scotland over time.

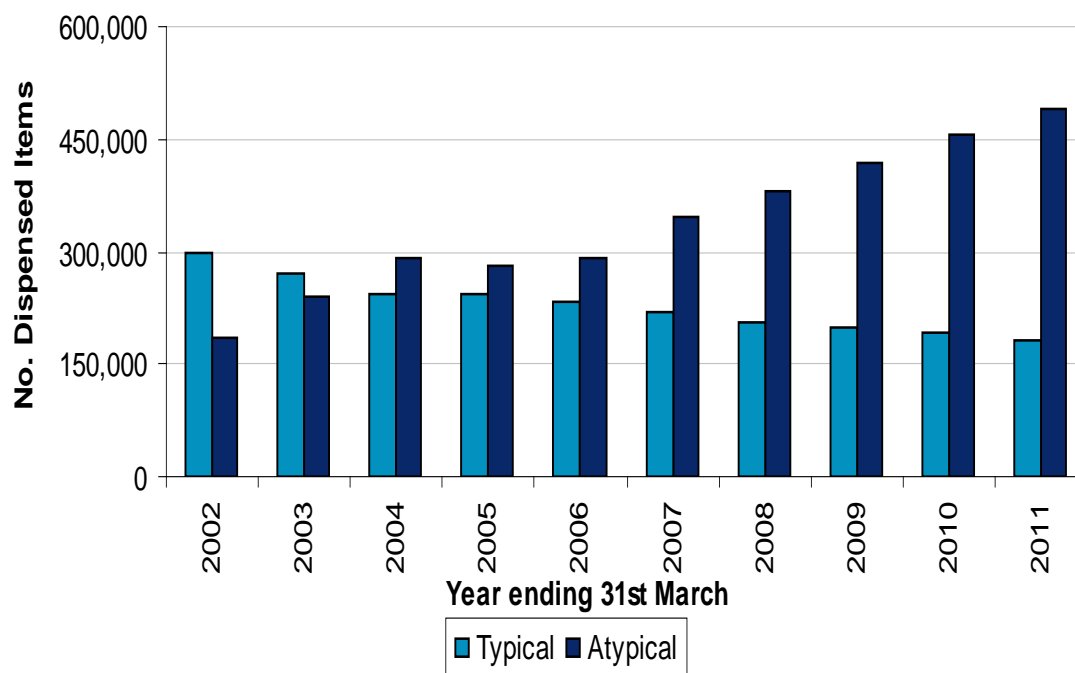


Figure 2 indicates that for 2011 over 600,000 separate items or prescriptions for all antipsychotic medications were written across Scotland. Also evident is that from 2006 to 2011, there has been a dramatic 59% increase in the use of the more expensive atypical or SGA medications *pari passu* with a 22% reduction in the use of the older and cheaper typical or FGA medications.

Figure 3.

Trends over time for the five most commonly prescribed antipsychotic medications.

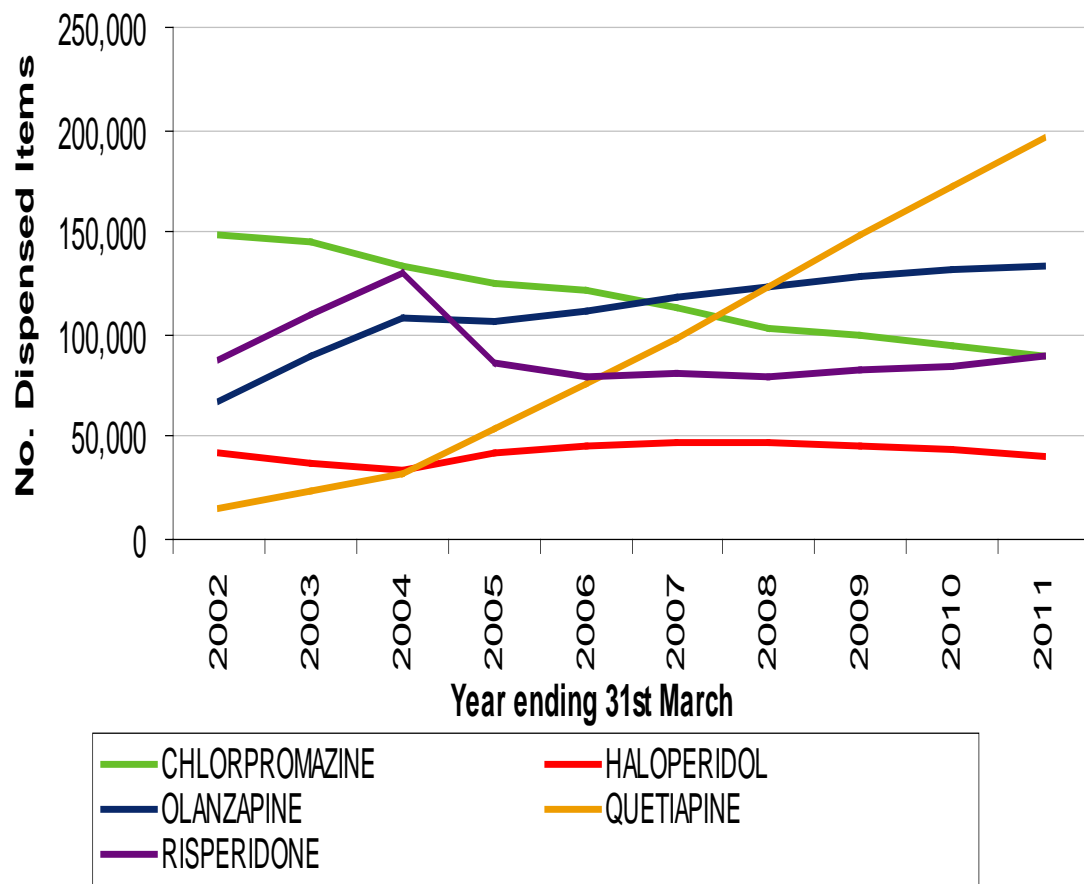


Figure 3 indicates that quetiapine has greatly increased its market share over the last 5 years, whilst chlorpromazine use has continued to fall over a similar period. Based on personal clinical experience and anecdotal evidence it is conjectured that this is due to a switch in the choice of off-label (ie unlicensed) use of a non-addictive sedative medication. It is worth noting from Figure 3, that (at the time of writing) chlorpromazine; haloperidol; and risperidone were available as generic medications (ie cheap); and that both quetiapine and olanzapine were shortly due

to come off patent. Thus it is anticipated that direct acquisition costs for the most frequently prescribed antipsychotic medications will actually fall in the next few years.

From the above brief overview of the use of antipsychotic medication in Scotland, it can be seen that a more in-depth analysis of the use and comparative effectiveness of the most commonly prescribed antipsychotics would not only be of clinical value but also of interest to pharmacy budget holders.

CHAPTER 2

OUTCOMES IN SCHIZOPHRENIA; AND EFFECTIVENESS VERSUS EFFICACY OF ANTIPSYCHOTIC MEDICATION***The pre-medication era***

Early reports of psychosis (e.g. Joan of Arc) exist, but it was the Renaissance-inspired physicians such as Haslam, Esquirol and Morel who provided the first descriptions of a progressive insanity affecting the young. The work of Kraepelin (1919) at the beginning of the 20th century remains highly influential, as it was his careful documentation that led to the differentiation of the two major patterns of youthful insanity: manic depressive (bipolar) psychosis and dementia praecox (premature dementia – now called schizophrenia). Kraepelin emphasized the early onset of dementia praecox and established a trend towards therapeutic pessimism, as he believed that dementia praecox would inevitably deteriorate, whilst the course in bipolar psychosis was viewed as fluctuating but benign. Today, most clinicians appreciate that there is a wide variation in disease course and outcome; indeed, Kraepelin's own series of hospital-based cases revealed spontaneous, complete recovery in approximately 15% of patients.

In an important meta-analysis of 22 early (1895–1925) studies, Hegarty *et al* (1994) found that 25–30% of patients with dementia praecox had a good social outcome after 5 years. In the Iowa 500 study (Tsuang MT *et al*, 1979), only 26% of patients ($n = 200$) with narrowly defined schizophrenia assessed between 1895 and 1925 could be discharged into the community following their first hospitalization. Of those individuals who did not fully recover (approximately 74%),

Fuller (1930) suggests that 25% died, 35% were discharged over a 15-year period, and 39% remained chronically hospitalized throughout the study.

The antipsychotic era

McGlashan's 'Chestnut Lodge' study (1984) found that, compared with patients with chronic affective disorder, patients with chronic schizophrenia were less likely to be working at long-term follow-up, and were more likely to be rehospitalized, exhibit more severe symptoms and show a higher level of disability. Also, a considerably higher proportion of patients with schizophrenia were viewed as continuously incapacitated than those with chronic affective disorder. Combining data from the Chestnut Lodge and Iowa 500 studies reveals that 28% of patients were chronically disabled, 55% lived in sheltered accommodation, and 30% were employed.

Shepherd *et al* (1989) defined remission as full clinical recovery and relapse as re-admission; 22% of patients in their study group remained relapse-free 5 years after a first episode of schizophrenia, while 35% had relapsed. By contrast, Crow *et al* (1986) defined relapse as either the development of psychotic features or a worsening mental state and using these criteria, 45% of patients in the Northwick Park sample group remained relapse-free 2 years after a first episode.

In a study examining social disability in 349 patients over 15 years from first presentation, Wiersma *et al* (2000) concluded that only 17% of patients had no disability, whereas 24% experienced severe disability at long-term follow-up. Gender, age at onset, duration of untreated psychosis (DUP), type of psychosis, and remission during the first 2 years did not predict long-term disability. However,

severity of disability at earlier assessments contributed significantly to variance at 15-year follow-up. Examining mortality, and 15- and 25-year illness trajectories, Harrison *et al* (2001) found that approximately 50% of surviving cases had favourable outcomes, although they noted marked geographical variations. Using regression modelling, they determined that the course of illness during the first 2 years was the strongest predictor of outcomes at 15 years. Interestingly, 16% of early unremitting cases achieved late-phase recovery. The authors concluded that socio-cultural conditions appear to modify long-term course and that early intervention programmes may produce long-term gains.

The greatest variability in disease course is observed in the initial stages of schizophrenia. In an evaluation of first-admission studies from the 1970s and 1980s over a mean follow-up time of 17.4 years, 54% of patients exhibited social recovery despite 32% showing poor clinical outcomes (data adapted from Ram *et al*. 1992). Thus, while clinical and social morbidity can go hand in hand, a significant proportion of patients – often women – will demonstrate social recovery despite ongoing symptoms.

It is generally agreed (Saha *et al*, 2007) that the life expectancy of individuals with schizophrenia is shortened and that death from all causes, particularly cardiovascular disease, occurs at a younger age than in the general population. A study by Tsuang *et al* (1980) estimated that life expectancy is reduced by about 10 years among men and by about 9 years among women with schizophrenia and affective disorders.. Also of concern is that at least 5% of patients with schizophrenia commit suicide, with young men in the early stages of their illness

being most at risk (Hor and Taylor, 2010). Of those who commit suicide, two-thirds do so within the first 5 years of illness onset (Wiersma *et al*, 1998).

Specific factors linked to outcome

Factors associated with patient outcomes are shown in Table 1 (adapted with permission from Lewis and Buchanan, 2003). It should be recognized however that these factors account for only around 20% of the variance shown in long-term studies.

Table 1. Predictors of outcome (adapted with permission from Lewis and Buchanan, 2003)

Factor	Good outcome	Poor outcome
Demographic	Female Married	Male Single
Genetic	Family history of affective disorder	Family history of schizophrenia
Onset	Good pre-morbid adjustment Acute onset Life event at onset	Poor pre-morbid function Early onset Insidious onset Long duration of untreated psychosis
Symptoms	Affective symptoms	Negative symptoms Neurological soft signs
Psychosocial	Family/peer support Living in developed country	High expressed emotion in the family Social isolation Substance misuse
Treatment	Early treatment Good initial response Adherence	Non-adherence

Adherence to medication

The typical rates of non-adherence to medication of 40% for oral antipsychotics and 25–40% for depot antipsychotics are similar to those associated with drugs used to treat other chronic medical specialities (Pinikahana *et al*, 2002). Factors most consistently associated with non-adherence include poor insight, negative attitude, previous non-adherence, substance abuse, shorter illness duration, inadequate discharge planning, and poor therapeutic alliance. A small number of non-industry-sponsored studies have indicated that adherence to medication and patient satisfaction are enhanced by the use of SGAs as opposed to older drugs (Dolder *et al*, 2002). Interestingly, Robinson *et al* (2002) found that individuals with poor premorbid cognitive function were more likely to stop taking antipsychotic medications during the first year of treatment; those with Parkinsonian side effects also had a greater chance of discontinuing medication.

Gender

The degree of social impairment of men with schizophrenia is twice that of women with schizophrenia and men are less likely than women to experience complete remission, particularly when first-episode or recent-onset cases are studied (van Os *et al*, 1997). The reasons for these gender differences are not entirely clear, although there would appear to be an interaction with pre-morbid state, age at onset and substance misuse. Women are also more likely than men to manifest affective symptoms.

Symptom profile

Prominent early negative symptoms are associated with poor long-term outcomes (Fenton *et al*, 1991a), although it can be difficult to distinguish between negative

symptoms, poor pre-morbid functioning and over-treatment with antipsychotics. Conversely, paranoid and affective symptoms have been linked with better outcomes (Fenton *et al* 1991b).

Cognitive function and IQ have been shown to deteriorate during the course of schizophrenia (Eberhard *et al*, 2003) which can have a substantial impact on insight and compliance, which can in turn lead to increased relapse rates (Rossell *et al*, 2003) In addition, there is some evidence to suggest that intelligence is an important variable in determining outcomes (Thompson 1985).

Family history

Few studies have examined whether a poor prognosis is related to family history or whether a positive family history of psychosis exacerbates disease course. The Copenhagen high-risk project (Jorgensen *et al*, 1987) and the McGuffin *et al* (1984) twin study provide some evidence for a link between a positive family history of schizophrenia and overall poor outcomes.

Social factors

A number of studies (eg McKenzie *et al*, 1995) have shown that lower social class correlates with poor long-term outcomes, treatment resistance and chronicity. It is not always clear whether this merely represents decreased accessibility to or uptake of healthcare services.

An interesting study from Jamaica (Hickling *et al*, 2001) found that relapse rates after a first episode of schizophrenia were low and that good outcomes were related to high levels of gainful employment and the use of intramuscular antipsychotics. The authors noted that favourable short-term outcomes in

Jamaican patients were in contrast to the high relapse rates found in Afro-Caribbean patients in the UK. Indeed, a generally more favourable outcome for schizophrenia has been shown (Leff J et al, 1992) for patients in the developing world in WHO-sponsored studies.

In a meta-analysis of the effects of family interventions on illness course, Pitschel-Walz *et al* (2001) concluded that relapse rates in schizophrenic patients could be reduced by approximately 20% if the families of those affected were included in treatment strategies.

Duration of untreated psychosis

An 'expert briefing' (2003) from the National Health Development Unit in England concluded that patients experiencing lengthy delays in treatment initiation were more likely to exhibit poor outcomes across a range of measures. However, the briefing also noted that further evidence was required to prove that shortening the DUP led to improved outcomes. Gumley (2003) re-analysed the 1998 Wiersma data and found that individuals with a longer DUP at relapse were almost twice as likely to have experienced both an insidious onset of schizophrenia and a delay in the initiation of antipsychotic treatments.

Substance misuse and dual diagnosis

Swofford *et al* (1996) noted that substance abusers with schizophrenia were twice as likely to be hospitalized and four times as likely to have a relapse as non-drug-using individuals with schizophrenia during a 2-year follow-up study. Additionally, another study (McKenzie *et al*, 2001) showed that men with psychosis were two to three times more likely to abuse substances than women with psychosis; however,

there was no difference in the likelihood of patients abusing substances on the basis of ethnicity. Individuals with a 'dual diagnosis' of severe mental illness and drug misuse are generally hospitalized for longer periods than those who do not misuse substances (Menezes *et al*, 1996). In a 4-year community survival analysis (Hunt *et al*, 2002), patients with a dual diagnosis were more likely to be rehospitalized, regardless of whether they adhered to their treatment regimen. Non-adherent patients with a dual diagnosis accounted for 57% of all hospitalizations during the study.

The nature of relapse

Many studies use an arbitrary definition of relapse, such as a 40% decrement in score on rating scales, whereas more pragmatic studies tend to identify relapse by re-admission rate. In the real world, however, relapse is not usually measured by rating scales, nor does it inevitably lead to rehospitalization. Relapse can be highly individualized and may often manifest itself as subtle changes in psychosocial functioning, disrupted sleep or apparent vagueness or confusion.

Stressful life events and an increased emotional state can both trigger relapse, and it is not unknown for individuals experiencing early relapse or emotional distress to resort to alcohol or illicit drugs, which can further increase relapse rates (Hunt *et al*, 2002). In addition, a lack of response or poor tolerability to medication can lead to non-adherence – one of the most common causes of relapse, although non-adherence can also be an early manifestation of relapse. It is interesting to note that as many as 25–50% of patients do not respond fully to antipsychotics, thus increasing their likelihood of relapse. The risk of self-harm or injury to others is increased at times of relapse, and social disruption, increased stigmatization and

the secondary morbidity of low self-esteem are also indirect consequences of relapse.

Csernansky *et al* (2002) found that the risk of relapse in patients with schizophrenia was approximately 42% per year. Predictors of more frequent relapse included poor adherence to medication, severe residual psychopathology, poor insight, substance abuse, and poor relationships with family and care providers. Robinson *et al* (1999) examined relapse rates 5 years after initial recovery from a first episode of schizophrenia or schizoaffective disorder and concluded that the cumulative first-relapse rate was 82%. Discontinuing antipsychotic therapy increased the risk of relapse nearly five-fold. Patients with poor pre-morbid adaptation to school and pre-morbid social withdrawal tended to relapse earlier, whereas other baseline measures, including DUP, baseline symptoms, effects during treatment and brain morphology, were not significantly related to time to relapse. Early pre-morbid adjustment was the only variable significantly related to first relapse independent of medication status. Early social isolation and poor adaptation to school were particular characteristics of this pre-morbid state.

Data from the Madras Longitudinal Study (Eaton *et al*, 1998) indicated that age at onset and DUP are variables associated with poor outcomes. It was also found that the use of antipsychotic medications diminished the time to remission after a first episode of schizophrenia, but not after the second episode, while withdrawal from, and non-adherence to, antipsychotic medication were predictive of relapse.

Using a first-episode patient cohort, Wiersma *et al.* (1998) found that 68% of 82 individuals had one relapse during a 15-year follow-up study, while 58% of patients had two relapses, 49% had three relapses and 47% had four relapses. Thus, relapse is usual during the first 5 years following the initial episode.

These observations on outcomes and relapse in schizophrenia confirm that it is a relapsing and remitting condition for the vast majority of individuals, and relapse itself can tend to exacerbate prognosis. Some of the factors mentioned above that are associated with poorer outcome are immutable, for example clinicians cannot alter the fact that a patient is male; single; and has a family history of schizophrenia. However, clinicians can hope to ameliorate psychosocial factors that are linked to relapse or poor outcome such as isolation or lack of employment, as well as comorbid substance misuse. Clinicians should also work with the patient to identify the best particular treatment for them, taking account of both patient preference, previous response to medication, and of course the tolerability and efficacy of the proposed treatment. Similarly, once a response to effective treatment has occurred, it is the clinician's responsibility to promote continuing adherence to that treatment.

This thesis examines the relative effectiveness of the major antipsychotic medications available in Scotland at the time of study, where effectiveness is defined as a 'real world' combination of efficacy; tolerability; and adherence to that treatment. This is an important task as the major randomised controlled (licensing) studies for antipsychotic medications are not always generalisable to heterogeneous clinical populations, such as those in the west of Scotland.

Effectiveness versus efficacy of antipsychotic medication

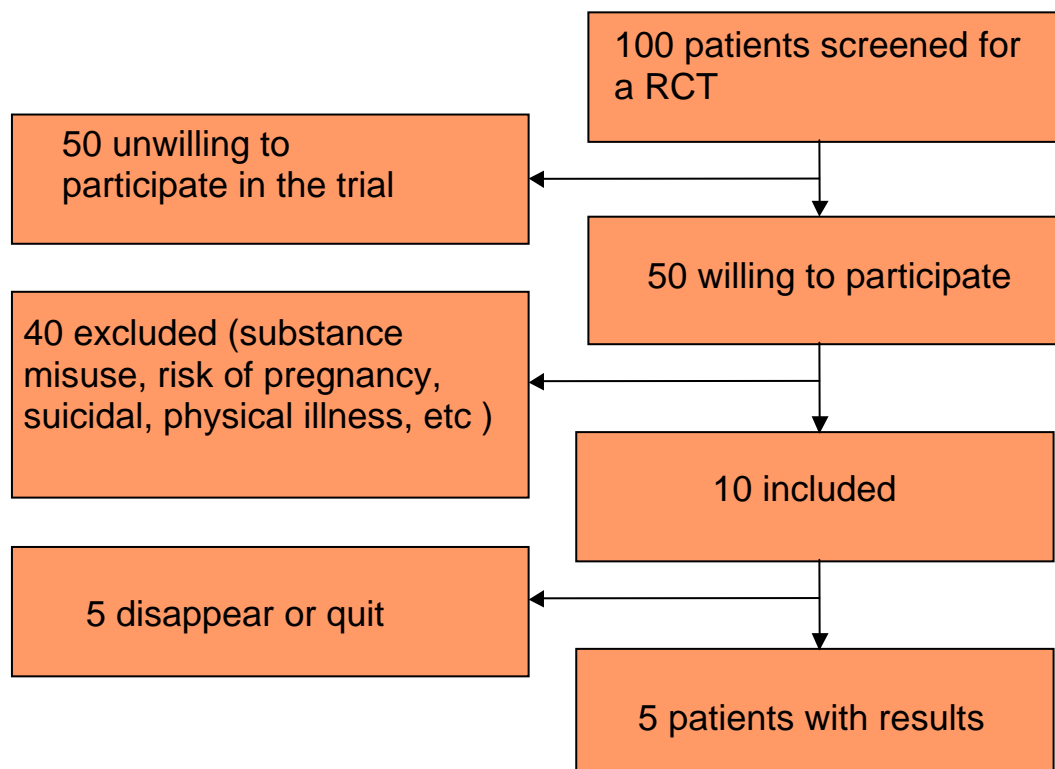
Since the 1940's randomized controlled trials (RCTs) have been the accepted method of establishing the efficacy of medical treatments due to high reliability and low intrinsic bias. Efficacy can be defined as '*does an intervention produce a positive effect in the study variables under ideal conditions*'. In psychiatry, traditionally RCTs usually have a pre-agreed change in score on a relevant rating instrument such as the Positive and Negative Syndrome Scale or PANSS (von Knorring and Linstrom, 1995) as the primary outcome variable. However, many clinicians would have difficulty in equating an arbitrary 20% or 40% change in the PANSS to their everyday practice or deciding on whether a statistically significant change in mean score is clinically relevant. Moreover, RCTs are generally undertaken by the pharmaceutical industry in order to meet regulatory requirements for drug licensing and positive results are generally associated with the study sponsor (Als-Nielsen *et al*, 2003) although this is not invariably the case (Fleishhacker *et al*, 2009) and meta analyses from Leucht *et al* (2009) and Davis *et al* (2008) did not detect a significant sponsor effect.. Lastly, RCT design (Heres *et al*, 2006) may also affect results and negative trial drug results may not be put into the public domain.

RCTs measure efficacy but the controlled environment of a RCT affects the generalisability of the results in the 'real world', especially when high drop out rates, short trial duration, and the selection bias in patient recruitment are considered (Thornley and Adams, 1998; Hodgson *et al*, 2007) The drop out rates of even relatively brief RCTs in medication trials in psychiatry can be up to 70% or even 80% confounding the applicability of the results. In addition, large multicentre

RCTs are expensive to conduct, which militates against undertaking long term or maintenance studies.

In psychiatry the typical exclusion criteria of RCTs means that individuals with co-morbid substance misuse or serious physical illness; or those who are suicidal or only intermittently cooperative will not be enrolled; nor importantly will any woman who cannot guarantee that she will not become pregnant. This problem of recruiting representative 'real world' clinical populations is depicted in Figure 4 which contains hypothetical numbers for illustrative purposes only. Clearly this leads to a potentially unrepresentative RCT study population, which casts doubt on the generalisability of the RCT results.

Figure 4 . Figurative illustration of the difficulties in recruiting into a randomised controlled trial (RCT) with strict inclusion and exclusion criteria.



These limitations of RCTs have resulted in renewed interest in observational studies. Observational studies assess effectiveness, namely whether a treatment or intervention works in the '*real world*' of day-to-day clinical practice. It has been shown (Mallinkrote *et al*, 2003) that well constructed observational studies do not overestimate treatment effects, and statistical methodologies can reduce the impact of non-randomisation. Additionally, the lack of exclusion criteria can reduce selection bias (although this remains a concern) enhancing the utility of the results, particularly in large community based samples. Observational studies are also generally much cheaper than RCTs so can often be undertaken independent of any vested commercial interest.

The concept of treatment effectiveness can be subdivided into the constituents of efficacy, tolerability, and adherence. Clearly, efficacy is a crucial constituent but an efficacious treatment only works if it is acceptable and used on a regular basis by the recipient or patient. Treatment acceptability is usually determined by whether the (subjective) beneficial effects are outweighed by the perception of intolerable treatment-related side effects, including any medically dangerous side effects.

The World Health Organisation has recently suggested that lack of adherence or compliance with maintenance treatment is a key obstacle in the management of long term clinical conditions leading to, for example, initiatives to pay people to adhere to their anti-tuberculous antibiotic therapy in parts of the US. In the management of psychotic illness, the problem of medication adherence has long been known to be problematic, and the effectiveness of maintenance antipsychotic treatment is often undermined by poor medication adherence. Patel and David (2007) estimated an oral medication non-adherence rate in schizophrenia of

between 40-60%, with adherence to long acting injections of (or depot) antipsychotics being between 25-40%.

Another major medication adherence problem that is commonly observed but poorly studied is the issue of partial adherence or compliance (Tacchi and Scott, 2005), where intentional or inadvertent intermittent or erratic medication dosing occurs. In the management of psychosis, partial adherence may lead to poor symptom control irrespective of an increased risk of relapse. Partial adherence to medication is commonly encountered in clinical practice but not extensively studied. Some individuals who adhere poorly with tablets may be offered a long acting injection, but long acting injections are not a panacea for adherence problems nor are they the only strategy by which to improve adherence.

Aren't all antipsychotic medications the same?

Debate over class and intra-class differences in effect between antipsychotic medications was highlighted initially by a controversial meta-analysis from Geddes *et al* (2000). This suggested the then newer (and more expensive) antipsychotic medications did not have superior efficacy to low dose haloperidol. Interestingly, this conclusion was not adopted by NICE guidelines (2002) which suggested atypical or second generation antipsychotics (SGAs) should be chosen in cases of first episode psychosis, after consultation with the patient, although the 2009 NICE guideline retracted from this position, simply advocating 'an antipsychotic medication' for schizophrenia without further specifying type. The debate moved forward after a further independent meta-analysis of the RCT PANSS outcome data, by Davis *et al* (2003), who used a larger data set than Geddes *et al* (2000) and found small but significant and clinically meaningful effect size differences (in

PANSS rated symptom reduction) between individual antipsychotics when compared with haloperidol. Here, clozapine, olanzapine, risperidone and amisulpride were superior to typical or first generation antipsychotics (FGAs) but quetiapine, aripiprazole, ziprasidone and sertindole were not. This study (Davis *et al*, 2003) also challenged the belief that any apparent atypical superiority over FGAs was merely a function of an excessively large haloperidol comparator trial dose.

Leucht *et al* (2009) updated the 2003 Davis *et al* meta-analysis of antipsychotic efficacy, and also concluded there were small but important differences between individual antipsychotic medications. In particular, they found that amisulpride; clozapine; risperidone and olanzapine were more effective than low dose haloperidol in terms of global symptoms and negative symptoms.

However, a smaller but more recent meta-analysis of FGAs versus SGAs in first episode psychosis (Crossley *et al*, 2010) added weight to the original conclusions of Geddes *et al* (2000) finding that SGAs were no different to FGAs for either discontinuation rates (a proxy measure for effectiveness) or symptom efficacy. Crossley *et al* (2010) did show that the side effect profiles of the two groups were different, with FGAs being more likely to cause movement disorders, and SGAs more often associated with weight gain.

Effectiveness studies of antipsychotic medications

Here four of the larger recent effectiveness studies of antipsychotic medication are reviewed:

1) The NIMH funded landmark CATIE studies (Lieberman *et al*, 2005; Stroup *et al*, 2006; McEvoy *et al*, 2006) introduced a paradigm shift in outcome measurement in the treatment of schizophrenia by utilizing medication discontinuation rate as a proxy for effectiveness, arguing that if either the clinician or patient initiated discontinuation then either the medication wasn't working or it wasn't being tolerated. After 18 months of randomized controlled study, olanzapine was found by Lieberman *et al* (2005) to be most effective oral antipsychotic despite inducing significant metabolic problems, although this phase of CATIE did not compare clozapine with olanzapine. A re-analysis of the CATIE data (Citrome *et al*, 2006) produced an impressively low "number needed to treat" (NNT) of between 5.5 and 10 for olanzapine compared to perphenazine, quetiapine, and risperidone. The corresponding "number needed to harm" NNH for olanzapine ranged from -12.4 to -17.7 in terms of discontinuation from adverse metabolic effects. Clozapine (in phase 2 of CATIE) also had low NNT of 3 compared to risperidone and quetiapine, and 6.6 compared to olanzapine.

2) The cost utility of the latest anti psychotic drugs in schizophrenia studies (CUtLASS) (Jones *et al*, 2006; Lewis *et al*, 2006) were sponsored by the UK National Health Services in an attempt to compare the effectiveness of the newer versus older anti psychotic medication. Clinicians who entered patients into this study had to determine whether those individuals previously had a treatment resistant illness or whether a switch of antipsychotic medication was indicated for other clinical reasons. Furthermore these clinicians were free to opt for the individual antipsychotic of their choice from within 2 groups of medications. Quality of life was chosen as the primary outcome measure in the CUtLASS studies, although traditional ratings such as PANSS were also undertaken.

CUtLASS was a one year open label randomised study and 227 people with schizophrenia were included. After 1 year in this study 54 % of patients were still on the 'typical' antipsychotics and 63% were still taking an 'atypical' antipsychotic, although this difference was not statistically significant. There were no other significant differences in other relevant outcomes including the primary outcome of quality of life. However, included within the group of 'typical' or FGAs was sulpiride (although the related amisulpride was viewed as a SGA), and sulpiride was the antipsychotic medication most frequently chosen (49%) by the participating clinicians.

Owens (2008) has observed that sulpiride was originally regarded as an 'atypical' anti psychotic when it was first marketed in the 1970s, and indeed Owens comments that the term "atypical" is no longer helpful in terms of understanding or dichotomising antipsychotic medication. It is also worth observing that CUtLASS failed to meet its predefined recruitment target - this might have been due to clinician preference for SGAs over FGAs (a lack of clinical equipoise). Lastly, as entrance to the CUtLASS study required the need for change in medication, a selection bias of patients who were either non or partial responders or intolerant to the previous medication may have been introduced.

3) The EUFEST study (Kahn *et al*, 2008). This open pragmatic (the treating physicians were not blinded) study included 498 subjects from various centres across Europe (but not Britain), and randomised them to Haloperidol (at a low mean dose of 3mg), amisulpride, olanzapine, quetiapine and ziprasidone, with one year follow-up. Enrolled subjects were described as having a first episode of

psychosis, defined as being symptomatic for 2 years or less. The number of patients who discontinued treatment for any cause within 12 months was (in order of highest discontinuation rate) 63 (Kaplan-Meier estimate 72%) for haloperidol, 51 (53%) for quetiapine, 31 (45%) for ziprasidone 32 (40%) for amisulpride and 30 (33%) for olanzapine. Comparisons with haloperidol showed lower risks for any-cause discontinuation with quetiapine (HR 0.52 [0.35-0.76]), ziprasidone (HR 0.51 [0.32-0.81]), amisulpride (hazard ratio [HR] 0.37, [95% CI 0.24-0.57]), olanzapine (HR 0.28 [0.18-0.43]), However, symptom reductions were virtually the same in all the groups, at around 60%, according to PANSS, although minor but significant improvements on the CGI and GAF favoured amisulpride over haloperidol. Therefore this study indicated that risk for discontinuation was greatest with haloperidol, with incremental benefit for quetiapine, ziprasidone, amisulpride and olanzapine respectively, but that admission rates to hospital (often used as a proxy for relapse) were not significantly different between the five medications studied. EPSE were worst with haloperidol, whereas olanzapine (13.9 kg) and then quetiapine (10.5 kg) produced the most weight gain over the 12 month follow up period. EUFEST, which was described as independent but had sponsorship from three pharmaceutical companies, concluded that discontinuation rates were not the same as symptomatic improvement and hence they could not demonstrate any superior efficacy for SGAs over haloperidol.

4). The Treatment of Early Onset Schizophrenia Spectrum Disorders or TEOSS study was an RCT (Sikich *et al*, 2008; Findling *et al*, 2010) in children and adolescents in the USA aged between 8 and 19 years old. It was a randomised comparison of in 116 individuals of molindone, olanzapine, and risperidone for the treatment of early schizophrenia initially for 8 weeks with a 44 week maintenance

study phase for responders. The results after 8 weeks of treatment did not reveal any differences in symptomatic improvement between the three medications (only 54 / 116 individuals responded in total - 50% to molindone; 46% to risperidone; and 34% to olanzapine) but adverse effects were “frequent” including pathological weight gain in all 3 groups (but particularly olanzapine) and movement disorders in the molindone group. Only 14 individuals were seen to clinically respond by the end of the study.

The results of these studies are in some ways contradictory due in part to their differing designs; differing medications studied; and different study environments. CATIE; EUFEST and TEOSS demonstrate the sobering reality that the majority of individuals do not or cannot continue these medications long term, either due to lack of efficacy or intolerable adverse effects. However, both CATIE and EUFEST seem to indicate that discontinuation rates are lower for some (but not all) of the SGAs, which echoes the findings of the efficacy meta-analyses of Leucht *et al*, 2009, and of Davis *et al*, 2003 (but not Geddes *et al*, 2000). Similarly, both CATIE and CUtLASS 2 suggest that switching to clozapine, when an adequate trial of an initial antipsychotic medication has failed to produce a reasonable response, confers a therapeutic advantage. Again this mirrors the meta-analytic comparative efficacy meta-analytic findings. However, there is enough confusion in the results described above to further stimulate recent debate (Kendall, 2011) over whether there really is a ‘class effect’ vis a vis typical or FGAs versus atypical or SGAs. This thesis examines the comparative effectiveness of the major antipsychotic medications in the west of Scotland populations, along with introducing a new scale for systematically monitoring the tolerability (or adverse effect) profile of antipsychotic medication.

Before original data on antipsychotic effectiveness is presented, there is a description and analysis of the use of medication for schizophrenia and bipolar disorder in secondary care in Greater Glasgow. This sets the scene, highlighting both the current prescribing practice in the 'real world' and the demographic characteristics of the individuals concerned.

CHAPTER 3

**DESCRIBING THE USE OF ANTIPSYCHOTIC MEDICATION IN GLASGOW
USING A CITY WIDE CASE REGISTER**

MT was responsible for the design; concepts; data analysis and interpretation; and drafting of this chapter. John Park kindly extracted the requested data from the case register.

Study conducted 2010 - 2011

The value of case registers in mental health has been reasserted (Perera *et al*, 2009) and can not only aid research (Stewart *et al*, 2009) but also inform day-to-day clinical practice and service provision by providing practice benchmarks and identifying need. The Psychosis Clinical Information System (PsyCIS) in Glasgow was developed (Park *et al*, 2008) as a clinically useful and accurate method of following up patients with psychotic illness in the Greater Glasgow area, using an electronic case record system. Greater Glasgow, in Scotland, is an urban area of approximately one million inhabitants, with the lowest life expectancy in the UK. The National Health Service (NHS Scotland) provides government funded healthcare for all individuals across primary, secondary, and tertiary care, and in Glasgow there is essentially no alternative care provider to the NHS for individuals suffering from serious mental illness. PsyCIS commenced in 2002, with a back-trawl of defined cases in each of the sixteen community mental health teams (general adult psychiatry for adults 16 – 65 years), and was later matched to local primary care (or family doctor) case lists of severe mental illness. Since 2002, all incident cases of psychosis presenting to community mental health services in Glasgow have been captured by PsyCIS, and senior psychiatrists in Glasgow complete standardised annual reviews on identified PsyCIS cases year on year.

This chapter describes the socio-demographic characteristics of PsyCIS cohort, and reviews the main pharmacological treatments for selected diagnostic groups. This overview may allow comparison and benchmarking by mental health services elsewhere.

Aim

To describe the socio-demographic profiles and pharmacotherapy employed in a systematically ascertained large cohort of individuals with psychotic illnesses.

Method

The PsyCIS case register has been fully described elsewhere (Park *et al*, 2008) It contains a record of all adult (16-65 years) patients with a consultant confirmed diagnosis of psychosis who are in contact with any of the 16 city-wide community mental health teams in Greater Glasgow . This chapter focuses on the following ICD 10 diagnoses: schizophrenia; schizoaffective; and delusional disorders (F20-29); manic and bipolar affective disorders (F30-31); and depressive psychosis or severe depression with psychotic features (F32.3 and F33.3). Prior to inclusion on the register, where cases had not been assigned a diagnosis by a consultant psychiatrist or where there was uncertainty over the primary diagnostic coding, case notes were reviewed by the research team in consultation with the local consultant psychiatrist and a clinical consensus diagnostic coding applied. Thereafter, a standardised annual update records current social and legal status; risks including episodes of self harm and violence; and the precise treatments at that time.

Socio-economic deprivation was assessed using Scottish Government originated quintiles (www.scotland.gov.uk/topics/statistics/SIMD), where category 1 represents the highest, and category 5 the lowest socio-economic group. The category 'working' includes students registered part or full time. 'Married' status includes people cohabiting or in de facto marriages; 'single' marital status includes widows and widowers; and 'divorced' marital status includes those couples

separated but not divorced. 'In care / support' indicates that the individual is in long term staff assisted community residence, or long term hospital based accommodation.

Age of onset is defined as first being diagnosed with psychotic symptoms by a psychiatrist, which is usually the first point of contact with mental health services. For the three main diagnostic groupings (schizophrenia; bipolar; and depressive psychosis) the use of medication is reported by early phase (3 years or less) and later (over 3 years illness duration) phase, to differentiate between those with first episode psychosis and those with chronic or refractory psychotic illness. High dose antipsychotic medication is defined as exceeding the BNF recommended maximum dose, either as a single drug or as a combination. First generation antipsychotics (FGA) is the preferred group name for 'typical' or older antipsychotic medications, and second generation antipsychotics (SGA) is the preferred label for 'atypical' or newer antipsychotic medications.

Simple descriptive statistics were used for analysis. All data contained on the PsyCIS system is kept confidential via secure protected electronic systems and anonymised prior to analysis.

Results

5073 individuals were included from the 2010 PsyCIS register, including all individuals diagnosed with schizophrenia; bipolar disorder; and depressive psychosis in secondary mental health care in Greater Glasgow. Specifically, there were a total of 2537 people with an ICD 10 F20 coding of schizophrenia; 986

people within the ICD 10 F21-29 diagnostic code range (diagnostic breakdown illustrated in table 2); 1242 individuals with a bipolar diagnosis (ICD 10, F30-31); and 308 people with a ICD 10, F32.3 diagnosis of depressive psychosis.

Table 2. Diagnostic mix of the ICD 10 F21-F29 group in the PsyCIS case register

Diagnosis (ICD 10 code)	Number of individuals and % of total (n=986)
Schizotypal disorder F21	29; 3%
Persistent delusional disorders F22	208; 21%
Acute and transient psychotic disorders F23	175; 18%
Schizoaffective disorders F25	301; 30%
Other / Unspecified non-organic psychosis	273; 28%

57% of the whole PsyCIS cohort is male. The median age of onset for the whole cohort was 31 years (range = 18-64 years).

Table 3. Socioeconomic group (SEG) status of the PsyCIS population expressed as a percentage of the whole (%).

Quintile 1 is most affluent group, and quintile 5 is most deprived.

SEG quintile	Schizophrenia n=2537	F21-29 group n=986	Bipolar n=1242	Depressive psychosis, n=308
1	6	8	13	8
2	11	13	17	12
3	19	16	20	18
4	25	25	22	25
5	39	38	28	37

Table 4. Social characteristics of the PsyCIS population expressed as a percentage of the whole (%)

	Schizophrenia n=2537	F21-29 n=986	Bipolar N=1242	Depressive psychosis, n=308
Lives alone	53	43	49	45
Lives with others	34	50	47	53
In care / support	11	5	3	1
Homeless	2	2	1	1
Married	12	23	33	38
Divorced	14	14	21	25
Single	74	62	46	36
Working	14	29	35	31
Unemployed	86	71	65	69

Table 5. Regular pharmacotherapy within the PsyCIS population (%) in 2010

	Schizophrenia n=2537	F21-29 N=986	Bipolar N=1242	Depressive psychosis, n=308
Average number regular meds	1.6	1.6	2.1	2.1
No medication (%)	2	12	5	4
SGA antipsychotic (%)	67	74	39	66
FGA antipsychotic (%)	14	11	15	15
LAI antipsychotic (%)	31	13	7	4
Antidepressant (%)	25	34	42	92
Anti-convulsant (%)	5	11	44	5
Lithium (%)	2	6	41	9

SGA = second generation antipsychotic. FGA = first generation antipsychotic. LAI = long acting injectable (depot) antipsychotic medication. Anti-convulsant comprises of sodium valproate; valproic acid; carbamazepine; and lamotrigine.

With regard to antipsychotic polypharmacy in the schizophrenia group, 2164 individuals were regularly prescribed only one antipsychotic medication; 286 people were on two regular antipsychotics; and 12 individuals were on three regular antipsychotics. Of the 4185 individuals in the whole cohort on regular antipsychotics; 112 people (3%) were on high dose medication; and of the 400 individuals regularly prescribed 2 or more antipsychotics, 51 people (13%) were on high dose medication. The precise breakdown of combination antipsychotic medication within the cohort is listed in Table 6 below.

Table 6. Antipsychotic combinations in the PsyCIS cohort, 2010.

	Number of individuals
Entire PsyCIS cohort	5073
Total on regular antipsychotics	4185
2 or more antipsychotics	400
FGA LAI + FGA oral	111
SGA oral + FGA oral	98
FGA LAI + SGA oral	66
SGA oral + clozapine	56
Two differing SGA	28
FGA oral + clozapine	21
SGA LAI + SGA oral	20

SGA LAIs (ie risperidone consta) comprised 16% of total LAIs. The majority of individuals prescribed an LAI medication were voluntary patients, as depicted below in Table 7.

Table 7. Use of the Mental Health (Scotland) Act, 2003 - 'MHA' - long term treatment orders, and current formulation of prescribed medication (in 2010).

Diagnosis	LAI and subject to MHA (%)	Oral medication and subject to MHA (%)
Schizophrenia	15	8
F21-29	22	11
Bipolar	22	7
Depressive psychosis	0	6

Where a medication was stopped in the previous year, it was overwhelmingly due to intolerable side effects rather than lack of efficacy for all four diagnostic groupings.

Analysis of the most commonly prescribed medications, split according to early or mid-late phase of illness is depicted below, in table 8.

Table 8. Most frequently prescribed medications, by illness duration, within the PsyCIS cohort. Total percentages do not reach 100% due to other medications not shown.

Schizophrenia Illness Length \leq 3 Years			Schizophrenia Illness Length $>$ 3 Years		
Name	Total no. patients	% total	Name	Total no. patients	% total
Olanzapine	55	30	Clozapine	432	18
Risperidone	33	18	Olanzapine	417	18
Quetiapine	19	10	Flupentixol Depot	308	13
Procyclidine	15	8	Risperidone	269	11
Amisulpride	14	8	Procyclidine	236	10

Bipolar Illness Length \leq 3 Years			Bipolar Illness Length $>$ 3 Years		
Name	Total no. patients	% total	Name	Total no. patients	% total
Sodium Valproate	55	34	Lithium	451	42
Lithium	37	23	Sodium Valproate	288	27
Olanzapine	26	16	Olanzapine	192	18
Diazepam	19	12	Carbamazepine	107	10
Lamotrigine	17	11	Citalopram	97	9

Depressive Psychosis, illness \leq 3 Years			Depressive Psychosis, illness $>$ 3 Years		
Name	Total no. patients	% total	Name	Total no. patients	% total
Olanzapine	32	29	Risperidone	43	22
Citalopram	27	24	Olanzapine	40	20
Risperidone	23	21	Venlafaxine	31	16
Venlafaxine	23	21	Chlorpromazine	25	13
Mirtazapine	13	12	Citalopram	24	12

Discussion

Case registers like the PsyCIS register in Greater Glasgow can provide useful benchmarking data on the circumstances, diagnostic patterns, and treatment of individuals from a discrete geographic area. These data can inform public policy and service provision, and facilitate audit and research, although concerns around confidentiality and funding have been noted (Perera *et al*, 2009). PsyCIS regularly feeds back localised data compared to citywide medians to the clinicians who contribute, permitting reflective review of caseload and diagnostic and therapeutic practice. Our results represent a true picture of the status and treatment of people with psychotic illness living in Glasgow, as there is no privately funded care for these conditions available locally, and the match between the PsyCIS register and local primary care General Practitioner registers of those with serious mental illness (via the Quality Outcomes Framework) is known (personal communication, Dr Connolly) to be very high at 90%. Some individuals with psychosis however are probably unknown to both primary and secondary care, but the numbers are likely to be low given the serious impact on health and function of these illnesses.

All people with psychosis on the PsyCIS register suffer more economic and social deprivation than the general population despite the presence of well developed local community mental health and social work services. Those diagnosed with schizophrenia are even less likely to be married, or working than those with bipolar disorder and depressive psychosis. This is a concern as it is likely that this social isolation and economic deprivation contribute to the premature mortality seen in schizophrenia (Bushe *et al*, 2010). Similar findings have been reported in other surveys of psychosis in urban areas (Jablensky *et al*, 2000), and emphasises the

need for targeted mental health care and social work input into the most deprived urban areas.

Polypharmacy was frequently noted across all groups studied, particularly for bipolar disorder and depressive psychosis. This is not necessarily a bad thing as long as it's rational and reviewed (Langan and Shajahan, 2010). A small minority of those with a psychotic illness were not on any regular medication (see Table 5). Interestingly, the majority of commonly prescribed medications identified in this study are generic, implying that direct medication costs are low for this population. Those with schizophrenia and related disorders followed up by PsyCIS are usually prescribed a second generation antipsychotic, and the use of a long acting injection of antipsychotic medication in 31% of those with schizophrenia reflects practice elsewhere in the UK (Barnes *et al*, 2009), reiterating the finding that these formulations are useful in reducing relapse (Tiihonen *et al*, 2011).

Clozapine is the most commonly prescribed single medication for those with over 3 years of schizophrenia, again consistent with good practice (Farooq and Taylor, 2011). Nearly 10% of those on regular antipsychotic medication were routinely prescribed two or more regular concurrent antipsychotic medications, despite the lack of evidence (Barnes, 2011) supporting the practice of antipsychotic polypharmacy, and high dose medication was proportionately more common in this group leading to concerns over an increased side effect burden (Paton C *et al*, 2008).

Those with a bipolar disorder usually have a 'mood stabiliser' such as lithium or sodium valproate as their primary regular medication, concurrently with either an

antipsychotic or antidepressant. Geddes *et al* (2010) found combination therapy to be superior to monotherapy in prevention of bipolar relapse, and prescribers in Glasgow seem to agree. Individuals diagnosed with depressive psychosis usually receive an antipsychotic and antidepressant combination, and the pharmacological treatment of this condition seems poorly reported and researched.

Most individuals in this PsyCIS cohort who are in receipt of regular medication are not detained on long term treatment orders under the Mental Health (Scotland) Act, 2003, including those on long acting injections of antipsychotic medications. This implies that the majority of individuals with psychosis, including bipolar and depressive psychosis, are able to consent and willing to accept long term maintenance medication, although actual levels of medication adherence cannot be determined by this methodology.

Strengths and limitations

Strengths of this analysis include the large representative community based population studied in a prospective manner, allowing the results to be generalised to other urban areas with similar health and social care systems. Also, PsyCIS requires regular checks of data accuracy by the senior medical practitioners actually involved in the day-to-day case management, thus ensuring the validity of diagnosis and social state, as well as an up to date account of treatment provided. These local clinicians have a 2-way relationship with the PsyCIS team, which facilitates the return to consultants of clinically relevant information at individual caseload level. Limitations include the possibility of inaccurate data recording, either by the clinicians or when local returns are centrally uploaded. Clinical diagnosis, albeit by highly experienced psychiatrists, rather than a structured

diagnostic interview was used to establish diagnostic category. Also, PsyCIS excludes those under 16 and over 65 years old, as well as those whose psychotic illness is solely managed in primary care; addictions; old age psychiatry; or learning disability services, and hence this sample does not represent the gamut of psychotic illness.

Implications

Psychiatric case registers can permit accurate descriptions of the clinical populations surveyed, and inform service provision whilst being a tool for audit and research. The establishment and maintenance of clinical registers for long term conditions such as psychosis should also be politically desirable, as they can highlight areas of unmet need and facilitate quality assurance in the care pathway. Individual clinicians can also use registers like PsyCIS to compare their practice and caseload with similar neighbouring areas.

Individuals with a psychotic illness in Glasgow, particularly those with schizophrenia, are not only disadvantaged by the direct signs and symptoms of their mental disorder but also by the attendant negative social and economic consequences of these disorders. This morbid concatenation of medical and social disadvantage has been associated with early death (Hamer *et al*, 2008), and requires targeted interventions by a combination of health and social services that are flexible enough to respond to challenges like comorbidity; homelessness; stigma; and variable help seeking behaviour. The vast majority of prescribing documented by PsyCIS appears rational, guideline-compliant and evidence based. SGA are used in over two thirds of patients with schizophrenia and the most frequently prescribed medications in long term patients were clozapine for

schizophrenia and lithium for bipolar disorder. These findings, plus the relatively low use of long term compulsory treatment orders, should be reassuring to the patients involved and their carers and advocates.

CHAPTER 4

**A SIX MONTH PROSPECTIVE STUDY OF THE EFFECTIVENESS OF FIVE
ORAL ANTIPSYCHOTIC MEDICATIONS**

MT conceived the study; analysed and interpreted the data, and drafted the manuscript. Drs Turner, Brown, and Watt contributed to the data interpretation and reviewed the manuscript. Ms Fraser and Ms Martin helped collect the data.

Study conducted 2003 -2005

There are few long term head-to-head studies comparing the efficacy and safety of 'second generation' antipsychotic (SGAs) medications, and fewer still that are independent of pharmaceutical industry support. Perhaps unsurprisingly commercially supported comparative studies (Conley and Mahmoud, 2001; Tran *et al*, 1997) tend to be outcome-neutral or favour the drug produced by the sponsor.

Demonstrating efficacy in randomised controlled trials (RCTs) is not the same as showing effectiveness in routine clinical practice, where dual diagnosis or comorbidity, and lack of adherence are often the norm. Systematic all inclusive open label studies can complement RCTs, and a local demonstration of effectiveness can help inform local clinicians and formularies. A validated system with a scale based on the Clinical Global Impression (Guy, 1970) had previously been developed (Gilchrist *et al*, 2002) (see appendix 1) and the same methodology was used to compare symptom profiles and outcomes of individuals being newly prescribed five commonly used SGAs throughout the city of Glasgow, UK.

Aims

1. To demonstrate the feasibility of systematic outcome monitoring for antipsychotic medication in routine clinical practice.
2. To compare the clinical outcomes after six months treatment of five differing antipsychotic medications.

Method

Study design

A naturalistic prospective assessment of the clinical response to medication in individuals who were newly started or newly switched to one of the following five antipsychotic medications: amisulpride; clozapine; olanzapine; quetiapine; and risperidone. Consultant psychiatrists in Glasgow were asked to complete a standardised rating (see appendix 1) based on the Clinical Global Impression scale when the new antipsychotic medication was commenced, and then undertake a similar structured standardised review after six months of treatment, or at the point of treatment discontinuation. These standardised clinical reviews were undertaken voluntarily by the consultants.

In order to maximise enrolment by the treating consultant psychiatrist, no formal inclusion or exclusion criteria were stipulated for the patient enrolment. The study recruitment ran for one year, with a further six months for follow-up assessments of individuals enrolled towards the end of the one year study period. As this study was viewed as an extension of usual clinical practice by consultants who agreed to the protocol, ethical approval and informed consent were not sought from the patients enrolled. All personal data was anonymised prior to analysis. Participation in the trial did not affect treatment choice or delivery in any way.

Patients

All patients from secondary care adolescent, adult, and old age psychiatry in the Greater Glasgow urban area with a clinical diagnosis (from a consultant psychiatrist) of schizophrenia or schizophreniform disorder, and who were being newly prescribed either amisulpride, clozapine, olanzapine, quetiapine, or

risperidone were prospectively recruited into the study. The patients included in this study were a combination of medication naïve individuals and those requiring a switch in antipsychotic medication as a consequence of lack of efficacy or tolerability, or both.

Measures

Demographic and clinical information (including one or more of five pre-specified reasons for initiating the anti-psychotic) was documented by the prescribing clinician. A standardised assessment form with five linear analogue scales and referenced anchor points was also completed. The scales comprised the Clinical Global Impression (CGI) scale (score range 0 to 7), as well as an assessment of the positive and the negative symptoms of schizophrenia, drug related adverse effects and impairment of quality of life (all with score range 0 to 4). Both the CGI and the adapted CGI domain specific scales, along with the related anchor points, are detailed in Appendix 1. For all assessments the score increases with severity of symptoms. Where possible, the same clinicians re-assessed the patients still on their medication at six months. Previously ascertained (Gilchrist *et al*, 2002) inter-rater reliability weighted kappa scores for the five outcome scales were 0.60 for the CGI, 0.44 for positive symptoms, 0.39 for negative symptoms, 0.69 for drug-related side effects, and 0.75 for quality-of-life impairment. Kappa scores of 0.44 and 0.39 represent only fair to moderate inter-rater reliability, according to conventional cut-offs, whereas scores higher than this indicate good or excellent reliability. Although the low scores for the positive and negative symptom ratings are a limitation, they are representative of day-to-day clinical practice where both the physical and mental state examination have similar ratings (Mojtabai R *et al*, 1995).

Analysis

Simple descriptive statistics are used for the numbers both started and dropping out of antipsychotic treatment, along with the prescribing clinician's reason for the specific medication choice. Observer rated CGI and the four domain specific variable scores at baseline and six months are compared with the non-parametric Wilcoxon matched-pairs signed-ranks test, as the data were not assumed to be normally distributed, or that the variables under analysis would be independent. Significance level was set at the conventional 0.05. Median scores for the CGI at baseline are presented but subsequently the analysis focuses on mean CGI and specific domain scores for ease of comprehension.

Improvement after six months treatment is presented as a percentage change from the mean baseline rating, along with standard deviations to indicate size of distribution. Change across the five treatment groups was analysed using the Kruskal-Wallis test. Data on patients who dropped out of the study early, ie were not on the specified medication at the six month review point, were not subject to a last observation carried forward analysis as there were only 2 data points, and relies on the assumption that the drop out was related to the treatment in question (discussed further below).

Results

Three hundred and seventy three patients (192 men, 181 women) were enrolled with a mean age of 45.9 years (range = 14 - 99). These were individuals being treated in National Health Service (NHS) in-patient and out-patient settings in the

Greater Glasgow urban area. This enrolment represented an uptake rate of 51% of all possible new medication prescriptions, according to pharmacy returns, by psychiatrists working in adolescent, adult, and old age specialities who were newly prescribing SGA medication within a one year period in Glasgow. This 51% enrolment of subjects was evenly distributed across geographic and specialty areas within Glasgow, and hence was felt to be representative of the whole population.

There was a 64% completion rate of returns at the six month review point (n=157) or at discontinuation (n=81), with the remaining 135 subjects being lost to follow up.

Criteria for patient selection as indicated by clinician (n=373): The clinical indications for specific drug selection allowed were intolerable side effects (including extra-pyramidal symptoms or EPS) from previous antipsychotics (including first generation antipsychotics), minimisation of side effects (SE) from the outset of treatment as a priority, marked negative symptoms, refractory schizophrenia, being a first episode case, and other. Indicating more than one of these criteria was allowed, as denoted in Table 9.

Table 9. Reasons given by treating psychiatrist for patient / medication selection, at the time of switch / initiation.

	<i>Amisulpride</i> N=34	<i>Clozapine</i> N=25	<i>Olanzapine</i> N=161	<i>Quetiapine</i> N=38	<i>Risperidone</i> N=115
Intolerable EPS	15	5	41	9	24
Minimise side-effects from outset	17	3	70	16	45
Marked negative symptoms	8	4	19	6	13
Refractory psychosis	14	22	40	16	20
First episode illness	0	0	16	5	12
Other	4	1	32	7	28

Baseline assessments (n=373). The mean scores for all baseline ratings of impairment or disability are given in Table 10. Mean CGI scores ranged from 4.0 to 5.3, with median scores clustering around 4 - 5 (moderate to markedly ill). There was an anticipated difference in mean CGI based pathology scores between clozapine (the only drug licensed in the UK for treatment resistant schizophrenia) at a mean of 5.3, and the other four medications (4.0 - 4.4) although this was not statistically significant.

The other ratings were: positive symptoms mean scores between 1.9 and 2.8 (2 = moderate and 3 = marked pathology); negative symptoms mean scores were 0.8 to 1.7 (1 = mild to 2 = moderate severity); drug-induced side effects had mean scores between 1.0 and 2.0 (1= mild and 2= moderate disability); impairment in quality of life had mean scores from 2.9 to 3.6 (3 = moderate, 4 = severe).

Table 10. Mean rated levels of pathology at baseline assessment.

	<i>Amisulpride</i> <i>n=34</i>	<i>Clozapine</i> <i>n=25</i>	<i>Olanzapine</i> <i>n=161</i>	<i>Quetiapine</i> <i>n=38</i>	<i>Risperidone</i> <i>n=115</i>
Clinical Global Impression (0-7) Mean score	4.0	5.3	4.3	4.2	4.4
Clinical Global Impression (0-7) Median score	4	5	4	4	4
Positive symptoms (0-4)	1.9	2.8	2.1	2.1	2.1
Negative symptoms (0-4)	1.3	1.7	1.1	1.1	0.8
Side effect profile (0-4)	1.9	1.8	1.3	1.7	1.1
Impaired quality of life (0-4)	2.9	3.6	2.9	3.0	2.9

Dose. The mean daily dose at six month review for amisulpride (n=16) was 487.5mg, for clozapine (n=12) was 429 mg, for olanzapine (n=65) was 13.7 mg, for quetiapine (n=8) was 350 mg, and for risperidone (n=56) was 3.4 mg.

Comparison of baseline and follow-up assessments.

After six months treatment there were 157 (66% of those not lost to follow up) individuals available for re-assessment who were still being prescribed the newly initiated SGA. Six month follow up individual ratings by the treating psychiatrist ranged from deterioration through unchanged to improvement, according to the Clinical Global Impression scores, as depicted in table 11. Mean ratings for each of the five treatment groups were improved at the six month review point, and the comparative mean improvement in the five rating scales for the five treatment groups are presented in Table 11, along with percentage change from baseline.

Table 11. Improvement after six months treatment – mean drop in ratings and percent change from baseline

	<i>Amisulpride</i> n=16	<i>Clozapine</i> N=12	<i>Olanzapine</i> n=65	<i>Quetiapine</i> n=8	<i>Risperidone</i> n=56
CGI, mean (SD)	0.85 (1.8)	1.80 (1.7)	1.18 (1.6)	0.83 (1.3)	1.70 (2.1)
percent change	19%	34%*	33%**	11%	38%**
Positive symps, mean (SD)	0.55 (1.35)	1.50 (1.6)	0.9 (1.2)	0.67 (1.75)	1.28 (1.4)
percent change	30%	54%*	51%**	26%	66%**
Negative symps, mean (SD)	0.40 (0.9)	0.40 (1.1)	0.26 (0.9)	1.00 (1.55)	0.51 (1.0)
percent change	24%	20%	11%*	39%	35%*
Side effects, mean (SD)	0.87 (1.5)	0.10 (1.6)	0.90 (1.6)	1.50 (0.6)	0.74 (1.6)
percent change	54%*	13%	51%**	53%	47%*
Quality of Life, mean (SD)	0.38 (2.0)	1.10 (1.7)	0.96 (1.5)	1.17 (1.2)	1.23 (1.3)
percent change	15%	34%	36%**	31%	40%**

SD = standard deviation

* denotes significance level, $p < 0.05$, by Wilcoxon signed rank pairs

** denotes significance level, $p < 0.005$ by Wilcoxon signed rank pairs

There was no significant difference (by Kruskal-Wallis) between the five groups of medication across the five different rating measures, after six months of treatment. For example, differential improvement in CGI between the five treatments, $p = 0.095$.

Dropouts. 81 patients were documented as discontinuing treatment within six months, constituting 36% of the total cohort available at six month follow-up. More than one reason for discontinuation could be specified by the treating psychiatrist, and the specified reasons for discontinuation are listed in Table 12.

Table 12. Reasons given by treating psychiatrist for discontinuation of medication

	<i>Amisulpride</i> <i>n=6 from 34</i>	<i>Clozapine</i> <i>n=5 from 25</i>	<i>Olanzapine</i> <i>n=32 from 161</i>	<i>Quetiapine</i> <i>n=8 from 38</i>	<i>Risperidone</i> <i>n=30 from 115</i>
Not effective	3	0	11	3	12
Non adherence	2	2	13	4	7
Side effects	3	3	8	3	19
Other	0	1	8	1	4

Discussion

Principal Findings

During a one year time frame over half (51%) of all newly initiated regular antipsychotic prescriptions across the city of Glasgow were followed up in systematic manner. The main reasons (45% of all choices) that one of the five specified antipsychotics were chosen was due to the perception of a favourable side effect profile, or to minimise side effects from the outset. This study was undertaken before there was a significant body of evidence available on the adverse metabolic side effect profile of a number of these SGA medications. Olanzapine and risperidone were the two most popular medication choices by prescribers during this study, and these two medications were the first two SGA medications to receive a license in the UK, in 1996 and 1993 respectively, implying that clinicians might have had sufficient experience in these medications to become confident in their use.

Individuals prescribed clozapine had noticeably higher levels of psychopathology at baseline and less improvement in side effects after six months treatment compared to the four other groups, which is hardly surprising as by definition these

individuals were already treatment resistant before a switch to clozapine was contemplated. Patients being initiated on amisulpride, olanzapine, quetiapine, and risperidone had remarkably similar mean levels of observer rated psychopathology at baseline assessment.

The discontinuation rate (81/238 or 34%) for the antipsychotic medication noted in Table 12 is not dissimilar to dropout rates of 22% to 47% reported by Leucht *et al* (2003), but lower than the CATIE and TEOSS trials (Lieberman *et al* 2005 ; Findler R *et al*, 2010) The reasons for medication discontinuation in everyday practice are usually several and medication non compliance or adherence is not necessarily linked to experience of adverse side-effects, as illustrated in Table 12, but may be due to social factors; lack of efficacy; and forgetfulness.

Some of the mean improvement scores at six month review did not achieve statistical significance, although for amisulpride, clozapine, and quetiapine this could be due to a lack of power secondary to the low numbers of patients still on these treatments at six month review. It is clear that all five antipsychotics studied produced clinically observable improvements in the five global ratings of pathology after six months therapy. These improvements in observer rated disease severity mainly occurred in patients switched to one of the five medications studied, as new prescriptions in a medication naïve individuals were less than 10% of the total, even though the evidence suggests switching between individual antipsychotics appears to confer little or no benefit (Rosenheck *et al*, 2009).

The improvements in the clinical global impression (CGI) at six month review were mirrored by improvements in positive symptoms; side effects (except for clozapine)

and to a lesser extent quality of life. Negative symptoms of schizophrenia are arguably a challenging symptom domain for the clinician to detect in the out-patient clinic, as well as being notoriously difficult to treat. The quality of life assessment involved consideration of time utilisation and activities of daily living, and occupational or social role fulfilment.

Differences, albeit trends, in outcome between the five treatments after six months are evident from table 11, but no statistically significant difference between the drugs for any of the five outcome measures studied was detected. This is most likely due to the relatively low numbers patients retained in the study at the six month point. It is also worth noting again that by definition, clozapine was being used in patients who were already treatment resistant and thus any therapeutic gains documented might have been harder to achieve.

Strengths and limitations of the study

A naturalistic 'real world' design was adopted for this effectiveness study. Data were collected prospectively on a consecutively recruited sample of patients with a clinical diagnosis of schizophrenia or schizophreniform psychosis, and no exclusion criteria were applied as exemplified by the wide age range of subjects noted above. Symptom severity was measured with a simple compound scale based on standardised psychiatric rating scales with proven reliability, and the scale used was considered pragmatic enough to be used by psychiatrists in Glasgow during their routine (busy) work. Levine et al¹¹ have already demonstrated, perhaps surprisingly, that the Clinical Global Impression scale has a robust mathematical (and hence clinical) relationship with more in-depth scales

such as the Brief Psychiatric Rating Scale and the Positive and Negative Syndrome Scale, which reinforces the rationale for its choice as a rating scale in this study.

Importantly, all patients with schizophrenia-type psychosis were included regardless of any additional diagnoses or problems, including those who were subject to the Mental Health Act; liable to pregnancy; or had co-morbidity such as substance misuse. Also, as this study of antipsychotic medication was undertaken without involvement from the pharmaceutical industry, it is less liable to sponsorship bias.

Limitations of this study include the fact that standardised psychiatric interviews were not conducted in all subjects, and thus we cannot be sure that the subjects meet diagnostic criteria for schizophrenia, although the subjects are likely to be representative of patients given that clinical diagnosis by experienced psychiatrists. The improvements in ratings scores noted by the treating psychiatrists cannot automatically be assumed to be purely due to medication, even though the raters were explicitly guided to attempt to isolate the medication related impact on the patient. Also, it cannot be certain that the patients described in this study truly represent the gamut of patients with schizophrenia seen in secondary care in Glasgow, as only 51% of new antipsychotic prescriptions were captured during the one year enrolment study period. Further, the lack of power at six month follow up meant observations were sometimes not statistically significant, and this difficulty in retaining people with schizophrenia in follow up over a long period is mirrored in clinical practice. The analysis of missing data on patients (n=81) who 'dropped out'

before the six month review deserves further comment. On the one hand the exclusion of patients who dropped out might artificially inflate the apparent effectiveness of each medication to differing degrees. The technique of last observation carried forward (or LOCF) for the handling of 'drop outs' does have the advantages of minimising the number of the subjects who are eliminated from the analysis, and allowing examination of trends over time, rather than focusing simply on the endpoint. However LOCF does rely on the assumption that patients on the treatment will get better and that any change in state is related to the treatment in question, which cannot be guaranteed here. Also, LOCF is usually employed in studies with multiple data points over the study period, whereas here the design (and cost) necessitated only data acquisition at study entry and exit, so on balance a LOCF analysis of 'drop outs' was not undertaken. Nevertheless, a bias, particularly a selection bias, could have been introduced in the analysis here.

It has previously been demonstrated (Gilchrist *et al*, 2002) that the scales we used had satisfactory inter-rater reliability at one point in time, but it does not necessarily follow that all the raters used in the study would all have agreed with each other to an acceptable extent. However, our kappa values of 0.4 – 0.75 are similar to the typical values of 0.5 for most of the components of the physical examination in general medical practice (Sackett *et al*, 1991). Indeed, in studies such as this one has to balance what is desirable with what is practical, and the use of potentially different raters for particular patients is analogous to clinical situations where one doctor has to assess the effect of a drug prescribed by another. The use of some form of routine outcome rating is likely to provide more reliable information than a variable standard of case note documentation based on

components of a typical mental state examination, which may itself be even less reliable than a typical physical examination (Mojtabai and Nicholson, 1995). Nevertheless, observer bias cannot be excluded in this study. Finally a drop-out or medication discontinuation rate of 34% within a six month naturalistic study period is not unusual when compared to related studies (eg Lieberman *et al*, 2005), but does raise the possibility that improvements in global pathology documented at the six month review might not be representative of the whole population under review, and the results noted here may only be representative of patients who can continue their antipsychotic medication for at least six months.

Conclusions

In summary, this study demonstrates that it is possible to work with busy psychiatrists to evaluate (relatively) new treatments in a systematic manner. At the time of the study, olanzapine and risperidone were the two most frequently prescribed antipsychotics, with prescribers usually stating that minimising the adverse side effect profile was the main goal of the prescription. Data presented here confirms that switching commonly prescribed antipsychotics may confer some clinical advantage to patients with schizophrenia, despite the dearth of positive data on the benefits of the commonly encountered practice of switching antipsychotics.

CHAPTER 5

**A TWO YEAR RETROSPECTIVE COMPARISON OF FIVE ORAL
ANTIPSYCHOTIC MEDICATIONS**

MT conceived and designed the study; participated in data collection and analysis; interpreted the data; and drafted the manuscript. Dr Shajahan designed the study; participated in data collection, interpretation, and analysis; and helped draft the manuscript. Professor Lawrie helped interpret the data and draft the manuscript.

Study conducted 2006-2007.

Debate over the comparative benefits and risks of second generation antipsychotics (SGAs) has continued (eg Kendall, 2011). While the SGAs command widespread clinician confidence and have previously been recommended by influential guidelines, it is not clear that the SGAs are a homogenous group with a clear class effect (Owens 2008). Coupled with this apparent heterogeneity are the increasing licensed uses for some SGAs that have evolved in recent years from schizophrenia and related psychoses to specific phases of bipolar disorder. Deciding which SGA should be used in a particular circumstance is therefore often a matter of trial and error.

Discontinuation rate of SGAs has been adopted as a measure of effectiveness in the landmark Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) studies (eg Lieberman *et al*, 2005), based on the understanding that people will stop taking medication if it is not beneficial or is producing intolerable side-effects. This study was designed to examine antipsychotic effectiveness using discontinuation rates, as well as describing the varying patterns of use of five of the most commonly used SGAs in a representative community based population.

Aims

1. To compare the clinical effectiveness of five antipsychotic medications.
2. To describe the patterns of antipsychotic medication use in a large representative population.

Method

Study design

The county of Lanarkshire, Scotland, comprises approximately 550,000 people in mixed urban and rural settings, and is ethnically homogenous with comparatively low socio-economic status (www.scotpho.org.uk). Using an electronic patient record (EPR) system covering all mental health care contacts for a large area in Lanarkshire (approximately 400,000 people) the study aimed to describe and compare the patterns of use and discontinuation of SGAs, in all individuals prescribed these medications in a two year period.

The EPR included all typed nursing and medical notes and correspondence for patients aged 16 to 65 from February 2002 to June 2005. The EPR system was searched for information on the most commonly used oral SGAs. Both generic and trade names of medications were used as keywords for the searches. The SGAs most commonly prescribed during the study period between 2002 and 2005 were amisulpride; clozapine; olanzapine; quetiapine; risperidone. Chlorpromazine and haloperidol were not chosen as comparators, as searches indicated these were only rarely used for maintenance treatment.

Measures and Outcomes

After initial identification from the EPR, every medical case record containing information on one or more of the five SGAs under study were manually scrutinised for demographic and clinical information, including all diagnoses; dosage of medication; and co-prescribed psychotropic medication. Cross checking between the EPR and 10% of individual case records was done to ensure accuracy of the EPR. All diagnostic groups were included. Diagnoses were always

made by experienced psychiatrists (with a minimum of 4 years postgraduate medical training) using clinical ICD 10 criteria.

After the initial analysis of the total sample, only those cases with a diagnosis of schizophrenia or related psychoses (F2x category, ICD10) were selected for further analysis to allow valid comparisons between clinically comparable groups. Medical case records were only excluded from analysis if there was insufficient clinical or demographic information available.

In this selected population, discontinuation rates for individual SGAs were calculated in cases where the SGA had been initiated after the EPR commenced (ie not including those on the medication prior to the introduction of the EPR) by dividing the number of individuals remaining on the specific medication during their period of study provided there was definite discontinuation with evidence of a prescription being ceased. The mean number of days till discontinuation for each SGA was also calculated. Discontinuation rate was adjusted for length of exposure (ie length of record) but this did not affect the results. Reasons for the discontinuation noted in the EPR and medical case record were assigned to three groups: discontinuation due to intolerable side-effects; due to inefficacy; or due to other reasons (eg. patient choice).

Hospital admission rates were also calculated for each SGA, but again only in those cases where the SGA was initiated after the EPR commenced.

In order to examine any relationship between mean dosage of SGA and discontinuation rate, the mean maximum dose of SGA used in both cases who continued and those who discontinued a particular SGA was calculated.

Statistical analysis

StatsDirect (issue1.8.9) was used for simple descriptive statistics. Statistical significance was set at two-tailed $p < 0.05$; and 95% confidence intervals were calculated where appropriate. Paired t-test and chi square tests for comparisons between groups were used, where appropriate.

Results

Patient Characteristics

A total of 11,250 case records were searched. 2013 individuals (18% of the total) were prescribed one or more of the five SGAs under scrutiny, but only 1464 individuals (13% of total) had case records of sufficient quality (defined as having two or more independent documents mentioning the SGA in question) to allow thorough analysis. This relative proportion of case records available for analysis is illustrated in Table 13, along with the patterns of use of the five SGAs across broad diagnostic categories.

Table 13. Diagnoses and use of SGA medication

	<i>Amisulpride</i>	<i>Olanzapine</i>	<i>Quetiapine</i>	<i>Risperidone</i>	<i>Clozapine</i>
Total number prescribed SGA	340	893	436	192	152
Number available for analysis	251	632	309	136	136
Schizophrenia / psychosis (%)	159 (63%)	323 (51%)	121 (39%)	74 (54%)	132 (97%)
Bipolar disorder (%)	28 (11%)	101 (16%)	65 (21%)	7 (5%)	4 (3%)
Depression / anxiety (%)	52 (21%)	153 (24%)	106 (34%)	42 (31%)	0
Personality disorder (%)	4 (2%)	10 (2%)	11 (4%)	4 (3%)	0
Other (%)	8 (3%)	45 (7%)	6 (2%)	8 (6%)	0

Diagnostic categories placed in the “other” group include post-traumatic stress disorder and dementia. Unsurprisingly, clozapine is used here almost exclusively for schizophrenia and related psychoses. Quetiapine, in contrast, was used in the majority of cases for mood disorder and anxiety, rather than schizophrenia.

Table 14. Average dose of SGA (rounded to the nearest 0.5mg)

		<i>Amisulpride</i>	<i>Olanzapine</i>	<i>Quetiapine</i>	<i>Risperidone</i>	<i>Clozapine</i>
Number of cases		251	632	309	136	136
Average dose <i>mg. per day</i>	Schizophrenia	589	15.5	441	6	427
	Bipolar	396	14	375	2.5	350
	Other	356	10	240	2.5	-

Table 14 reveals the average dosages of the five SGAs over the entire duration of treatment for all diagnostic categories, ie. schizophrenia and related psychoses; bipolar disorder; and “other” diagnostic categories which includes depression, anxiety, and personality disorder. Table 14 also shows that the average dose for all five medications studied is lower in bipolar disorder than schizophrenia [with average dose reduction between SGAs ranging from 16% (clozapine) to 59% (risperidone)].

For further analyses, only those individuals with a diagnosis of schizophrenia or related psychosis and who had commenced the relevant SGA after the start of the EPR were selected. The numbers of case records meeting these inclusion criteria are given in table 15, along with related demographic and clinical characteristics.

Table 15. Characteristics of individuals with schizophrenia newly started on a SGA

	<i>Amisulpride</i>	<i>Olanzapine</i>	<i>Quetiapine</i>	<i>Risperidone</i>	<i>Clozapine</i>	Significance
Total number	95	148	78	39	40	
Mean Age (years) [95% C.I.]	41 [38-43]	40 [39-42]	41 [38-44]	43 [39-47]	37 [33-40]	NS
Percent male	63% (n=60)	64% (n=95)	38% (n=30)	62% (n=24)	65%(n=26)	p=0.0006 ^a
History of alcohol misuse*	36% (n=34)	34% (n=51)	23% (n=18)	28% (n=11)	38% (n=15)	NS
History of illicit substance use**	22% (n=21)	23% (n=34)	27% (n=21)	10% (n=4)	28% (n=11)	NS
Co-prescription (antidepressant)	46% (n=44)	55% (n=81)	62% (n=48)	46% (n=18)	43% (n=17)	NS
Co-prescription (mood stabiliser)	18% (n=17)	8% (n=12)	14% (n=11)	15% (n=6)	13% (n=5)	NS
Co-prescription (antipsychotic)	37% (n=35)	27% (n=40)	26% (n=20)	31% (n=12)	8% (n=3)	NS

NS = not significant

^a $\chi^2=19.4$, d.f.=4, p=0.0006

* Any record of lifetime history of alcohol consumption greater than recommended safe limits (>21 units or standard drinks per week for men, >14 units for women), or any diagnostic record of misuse or dependency.

** Any record of lifetime history of regular illicit substance use.

Table 15 indicates there were no significant differences in age between the five groups, with this being a middle aged population. Quetiapine was preferred in female patients (p=0.0006) but no other gender differences exist. The rate of drug and alcohol misuse for the entire population, as recorded in the patients' clinical records, is relatively high, but no inter-group differences exist in substance co-morbidity. The most common drug of misuse was cannabis.

A high rate of psychotropic co-prescription is also documented in Table 15, with co-prescribed anti-depressants and perhaps surprisingly a second anti-psychotic medication being common. Clozapine is the SGA least likely to be combined with

another antipsychotic, ($\chi^2=5.9$, d.f.=1, $p=0.015$), No significant differences between the rate of co-prescription of antipsychotics among the other SGAs were observed.

Table 16. Discontinuation and hospital admission rates, as well as duration of treatment.

	<i>Amisulpride</i>	<i>Olanzapine</i>	<i>Quetiapine</i>	<i>Risperidone</i>	<i>Clozapine</i>	Significance
Total number	95	148	78	39	40	
Mean duration of record, days [95% CI] =A	716 [655-778]	644 [594-694]	670 [608-733]	530 [430-629]	705 [613-797]	$p=0.016^a$
Discontinuation rate (%) =B	51% (n=48)	41%(n=60)	36%(n=28)	28% (n=11)	18% (n=7)	$p=0.02^b$
Discontinuation reasons	Side effects	35% (n=17)	32%(n=19)	46%(n=13)	0%	$p=0.03^c$
	Inefficacy	33% (n=16)	28%(n=17)	36%(n=10)	73% (n=8)	
	Other	32% (n=15)	40%(n=24)	18% (n=4)	27% (n=3)	86% (n=6)
Mean number days to discontinuation [95% CI]	232 [165-299]	256 [194-318]	191 [113-231]	152 [74-231]	427 [108-746]	NS
Hospital admission during time of record	24% (n=23)	25%(n=37)	29%(n=23)	13% (n=5)	35%(n=14)	NS

NS=Not significant

a - $F(4,399)=3.1$, $p=0.016$

b - $\chi^2=4.3$, d.f.=1, $p=0.02$ (Clozapine versus other 4 SGAs), but no significant difference between the 4 SGAs excluding clozapine.

c - $\chi^2=10.8$, d.f.=4, $p=0.03$

There were significant differences in the length of case record available in this selected population, as illustrated in Table 16, with the longest mean duration of record being for amisulpride (approximately 2 years) and the shortest mean duration being for risperidone (approximately 17 months). Overall medication discontinuation rate was significantly lower for clozapine than the other four SGAs studied, and this remained the case after adjusting for the length of psychiatric case record available. Removing clozapine from the analysis revealed that there

was no significant difference in medication discontinuation rate between amisulpride, olanzapine, quetiapine, and risperidone.

Table 16 indicates that discontinuation due to side effects was lower for risperidone and clozapine compared to the other three SGAs although the numbers are low. Discontinuation with clozapine was associated with non-adherence rather than lack of efficacy, and a weak trend ($p=0.12$) towards a higher mean number of days to discontinuation was also observed with clozapine. "Other" reasons for discontinuation were firstly non-adherence with medication, followed by improvement in clinical state, followed by unidentified reasons. Further analysis showed that those who continued treatment with risperidone were on significantly higher maximum dose (5.4 mg versus 3.2 mg [$t=1.9$, $df=36$, $p=0.03$]) than those discontinuing treatment. There was no significant relationship between mean dosage and discontinuation as opposed to continuation of treatment for the other four SGAs under examination.

No significant differences in hospital admission rates between the five SGAs were evident, with lowest hospitalization rate being evident for risperidone (13%), although this was only five subjects, and the highest rate of hospitalization being seen in those on clozapine (35%).

Discussion

Principal findings

Here the comparative patterns of use and discontinuation of five of the most commonly used oral antipsychotic medications in a large representative community based population are reported. Rate of medication discontinuation was adopted as the primary outcome measure in this large independent observational study. The study period ranged between 530 and 716 days, and as such this study represents one of the longer comparative analyses of antipsychotic medications.

Approximately 18% of all individuals in contact with mental health services were prescribed SGAs. During the study period olanzapine was the most commonly prescribed antipsychotic, followed by quetiapine. Across Scotland according to government figures, 0.84% of the adult population are in receipt of daily antipsychotic prescriptions and by volume olanzapine, quetiapine, and risperidone are most frequently used nationally along with chlorpromazine (which is mostly used by general practitioners or on an 'as required' basis) – see chapter one.

Clozapine had a significantly lower discontinuation rate than amisulpride, olanzapine, quetiapine, and risperidone in this study, and a (non-significant) lower age of initiation. The superior effectiveness of clozapine has been noted elsewhere (eg Farooq and Taylor, 2011) and a large industry sponsored observational study (Haro *et al*, 2006) found both clozapine and olanzapine to have lower discontinuation rates than the other three SGAs we studied. Clozapine was also significantly less likely to be combined with another antipsychotic medication, which is arguably a measure of individual medication effectiveness. It is worth noting that clozapine requires regular contact with health professionals due to

blood monitoring and is licensed only for treatment resistant schizophrenia due to its adverse side-effect profile. As such, prescribers may be less willing to discontinue or switch away from clozapine, as it may be felt to represent the 'last best hope' for the patient.

In this study there was no association between our measures of effectiveness and average dose as a proportion of the maximum recommended dose in any of the antipsychotics studied, suggesting that effectiveness was not confounded by sub-optimal dosing, although the dose - response relationship with antipsychotics is complex (Davis and Chen, 2004).

Once clozapine was excluded from analysis, no significant difference in discontinuation rate between amisulpride, quetiapine, olanzapine, and risperidone was observed. This is in contrast to some data discussed elsewhere in this thesis, although others (eg. Crossley *et al*, 2010) have put forward analyses suggesting SGAs may be differentiated only by side-effect profile and not efficacy. One of the major if somewhat surprising findings to some observers of the CATIE studies was the high antipsychotic discontinuation rate (Lieberman *et al*, 2005). The discontinuation rates here are lower and possibly more representative of normal clinical practice although our lower discontinuation rates could also be attributable to differences in community based health care delivery between the UK and US, as well as differences arising from the demands of conducting RCTs, such as CATIE, in this population. This reinforces the value of routinely collected observational data. Additionally, the reasons given here for discontinuation need to be taken cautiously in view of the low numbers involved.

The patterns of use of SGAs described here for the period 2002-2005 demonstrate that off–license prescribing and polypharmacy were common. One survey (Lowe-Ponsford and Baldwin, 2000) found that 65% of UK psychiatrists ‘admitted’ to prescribing off-license in the preceding month. This study found that quetiapine (especially for women) and then olanzapine were the preferred choices for mood disorder, with quetiapine being used as an antipsychotic only in a minority of cases. This reflects other evidence suggesting these medications are useful in bipolar disorder (Taylor *et al*, 2009). The dose range of all five medications studied was lower in bipolar disorder than in schizophrenia, and this may be a consequence of antipsychotic medication in bipolar disorder often being employed as an adjunct to a mood stabiliser such as lithium or valproate as opposed to antipsychotic monotherapy in schizophrenia.

For individuals with schizophrenia or related psychosis prescribed an SGA after the electronic record commenced, quetiapine was used significantly more frequently in women than the other four SGAs (which were used in men usually). Also the relatively high documented rates (up to 38%) of alcohol and drug misuse in this population reflects the ‘real world’ nature of the study. Psychotropic co-prescription was common and except for clozapine, over a quarter of the patients studied were also prescribed a second antipsychotic medication. A survey (Paton *et al*, 2003) of over 4000 psychiatry inpatients in the UK found nearly a half were prescribed two or more antipsychotics, whilst other authors (Centorrino *et al*, 2004) have highlighted an association between antipsychotic polypharmacy and increased mortality or adverse events. On the other hand, Tiihonen *et al* (2006) demonstrated an increase in mortality in those individuals not using any antipsychotic medication after an initial hospitalisation.

Strengths and limitations of the study

Mention must be made of the particular strengths and limitations of this study. This was essentially a retrospective case note review, with all the limitations that come with unstructured assessment and recording but it was a large, comprehensive, and inclusive electronic survey covering a representative community sample of all secondary mental health care contacts. It is possible that human error occurred during the manual counting of the various clinical measures, although it is highly unlikely that this could have occurred in a systematic manner. The use of a representative naturalistic population, should have reduced the possibility of selection bias and enhanced the generalizability of the findings, and sponsorship bias for this particular study has also been avoided.

CHAPTER 6

**A RETROSPECTIVE LONG TERM FOLLOW UP OF THE
EFFECTIVENESS OF LONG ACTING (DEPOT) INJECTIONS OF
ANTIPSYCHOTIC MEDICATION**

MT conceived and designed the study; helped analyse and interpret the data, and drafted the manuscript. Dr Shajahan designed the study; collected, analysed, and interpreted the data; and drafted the manuscript. Drs Spence and Daniel collected the data; and contributed to the manuscript. Professor Pelosi designed the study; and helped draft the manuscript.

Study conducted 2007-2008

Adherence to antipsychotic medication has been shown to be the single most important determinant of relapse in schizophrenia (Robinson *et al*, 2002). Compared with oral antipsychotics, long acting injections are associated with better global outcome, reduced risk of hospitalisation and longer times to discontinuation (eg Tiihonen *et al*, 2011). Risperidone long-acting injection was the first of the second generation antipsychotics to be available in depot or long-acting formulation and has been used in routine UK clinical practice since 2002. There is little research to inform prescribing decisions in the clinic between the various long-acting injections. Meta-analytic review of first-generation depots found little difference between individual medications (Adams *et al*, 2001; Haddad *et al*, 2009). No direct comparisons of risperidone long-acting injection with the first-generation depots are available except for one open, 6-month randomised study that showed favourable outcome for risperidone long-acting injection compared with zuclopenthixol decanoate for individuals with comorbid substance misuse (Rubio *et al*, 2006).

Due to the growing trend towards the use of second-generation antipsychotics in general, including risperidone long-acting injection, despite the lack of head-to-head evidence noted above, we aimed to retrospectively identify and measure the outcome of patients started on: risperidone long-acting injection, zuclopenthixol decanoate, flupentixol decanoate, fluphenazine decanoate, pipothiazine palmitate and haloperidol decanoate. To assess effectiveness we applied the Clinical Global Impression (CGI) scale (Guy, 1970) and measured discontinuation rates and time to hospitalisation after the long-acting injection was started.

Aims

1. To describe the patterns of use of long acting (depot) injections of antipsychotic medication in a large representative population.
2. To compare the clinical effectiveness of the most commonly prescribed long acting antipsychotic injections.

Method

The electronic patient records covering all secondary care contacts for psychiatry in a discrete geographic area (the county of Lanarkshire, Scotland, population 550,000) were examined up until the end of 2008. The electronic records were phased into NHS Lanarkshire's mental health service over the period 2002 to 2005 into general, rehabilitation, liaison, addiction and forensic psychiatry services.

There are no private or independent secondary mental health care facilities in Lanarkshire, and no intensive home based alternatives to hospitalisation existed during this period. All individuals in mental health care follow up have a patient record. A total of ~35,000 individual records were available, and these were electronically searched using the data management system (Genesys) for the keywords relating to the generic and UK trade names of the following depot antipsychotic injections:

- flupentixol decanoate
- fluphenazine decanoate
- haloperidol decanoate

- pipothiazine palmitate
- risperidone long acting injection (risperidone consta), and
- zuclopenthixol decanoate

Inclusion criteria: Patient records were included if they contained the following ICD-10 diagnoses included in this study were schizophrenia (F20), persistent delusional disorders (F22), and schizoaffective disorders (F25). Exclusion criteria: All other ICD-10 diagnoses were excluded, Patient records resulting from this search which were considered inadequate for analysis, i.e. those where the drug was started before the electronic record became available, or those with only a single mental health contact were excluded. No other exclusion criteria were applied in order to maximise the 'real world' applicability of the findings.

To assess effectiveness, the Clinical Global Impression (CGI) scale was applied (see appendix one) and discontinuation rates and time to hospitalisation measured after commencement of the depot.

Demographic and clinical variables

These were extracted from the records. These included age and gender; duration of contact with mental health services; compulsory treatment; lifetime history of drug or alcohol misuse; ICD 10 diagnosis; previous antipsychotic and reason for discontinuation; maximum doses of medication used; concurrent antipsychotic, antidepressant and mood stabilising medication; previous or subsequent clozapine treatment or consideration thereof. Additional concurrent antipsychotics were defined as being another regular (not 'as required') antipsychotic drug prescribed at least 50% of the time that patients were on the depots. This was quantified by

converting doses to percentage of British National Formulary (BNF, 2011) defined maximum dosage. For example, 100 mg per day of chlorpromazine = 10% of maximum BNF daily dose. This measure is important in clinical practice where BNF defined maximum dosages are linked to high dose antipsychotic protocols.

Clinical Global Impression – see appendix one

The clinical status of subjects was assessed using the Clinical Global Impression (CGI) Severity (S) and Improvement (I) scales. The proportion who improved as defined by CGI I scores 1-4 (very much improved through to minimally improved) was the primary outcome measure. The rationale for this broad definition was that in clinical practice, any degree of improvement is of potential value as opposed to clinical trials where more stringent criteria tend to be employed. The CGI scores were based on the details in the patient records and assigned retrospectively. Severity rating was assigned at the start of treatment, at approximately 3-5 months after onset of treatment and, at the end of treatment if the drug was discontinued, or at the end of the medical record. The reason for examining severity at 3-5 months post depot initiation was that there were anecdotal reports of risperidone long acting injection (RLAI – otherwise known as risperidone consta) taking a longer time to show clinical benefit compared with other depots, and requiring longer oral antipsychotic supplementation during initiation compared to other depots. Improvement scores were assigned due to the perceived effects of the commenced medication and therefore took into account baseline severity of illness. Such retrospective CGI assignment has been used elsewhere for examining clinical response to antipsychotics (Shajahan *et al*, 2009).

Discontinuation and hospitalisation

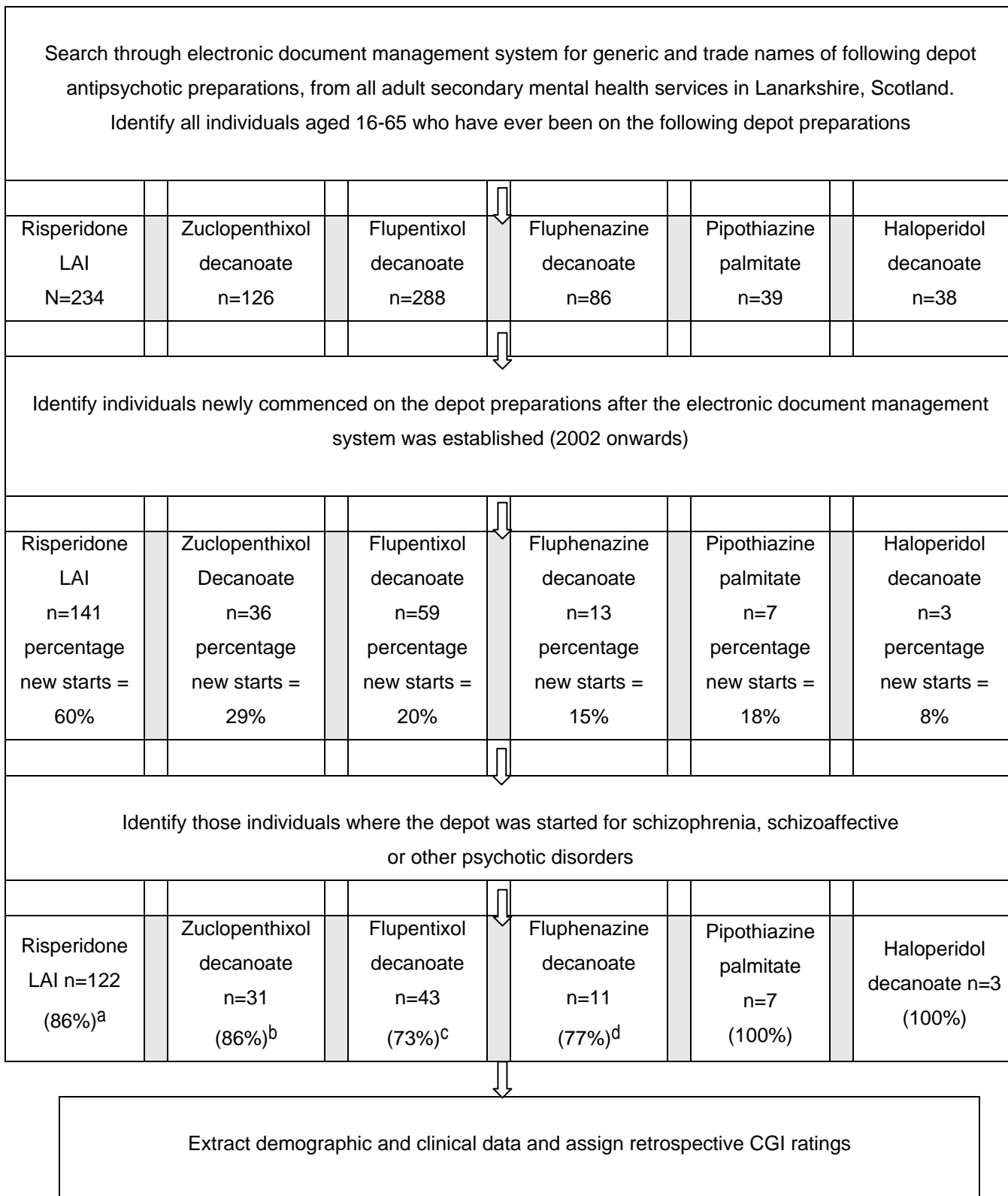
Time to discontinuation was examined for any cause and sub-categorised into time to discontinuation due to inefficacy or adverse effects. When investigators noted more than one reason for discontinuation, we used the clinically most important reason identified after reviewing the record, for the statistical analyses. Time to admission to hospital (mental health admission unit) was recorded as a further measure of effectiveness and can be considered a marker of antipsychotic treatment failure (Essock *et al*, 1996).

Statistical analysis

StatsDirect (issue 1.8.9) was used to perform for the analyses. Continuous data were reported as means with 95% confidence intervals and compared using analysis of variance and t-tests. Categorical and non-parametric data were analysed using χ^2 tests and were log-transformed as appropriate. Significance levels required two-tailed p values <0.05. Kaplan-Meier survival curves were used to illustrate the probability of treatment discontinuation or hospitalisation over time. Hazard ratios [HR] were calculated for survival analyses, and survival curves were compared using nonparametric methods with no assumptions about the distributions of survival estimates. As prior or subsequent treatment with clozapine (a marker of treatment resistance) and affective symptoms were viewed as having an effect on proportional CGI improvement (less improvement with clozapine, more with schizoaffective disorder), analyses were performed on all subjects and separately after excluding patients with treatment resistance and schizoaffective disorder. The null hypothesis was that the risk of medication discontinuation or hospitalisation was the same for all depots.

Results

Figure 6: Study profile for retrospective analysis of depot medication



^a(bipolar affective disorder n=14, emotionally unstable personality disorder borderline type n=4, depressive disorder n=1)

^b(bipolar affective disorder n=3, emotionally unstable personality disorder borderline type n=2)

^c(bipolar affective disorder n=4, emotionally unstable personality disorder borderline type n=9, depressive disorder n=3)

^d(emotionally unstable personality disorder borderline type n=2)

Figure 6 shows the study profile. 811 individuals were identified as having records mentioning that they had ever been on the depots being studied. Of these 811 patients, 259 had been commenced on depots after the electronic document management system had become available. Of the 259 patients commenced on the six depot antipsychotics, 84% (n=217) had a diagnosis of schizophrenia, schizoaffective disorder or related psychosis (see Table 17 for further details of diagnosis).

The proportion of patients commenced on RLAI exceeded the cumulative total of those started on the other depots, illustrating its prescriber preference over FGA depot antipsychotics during 2002 to 2008. As the numbers of patients commenced on fluphenazine decanoate, pipothiazine palmitate and haloperidol decanoate were small they were not included in further analyses.

Table 17. Clinical profile of patients started on depot antipsychotics

	^a Risperidone long acting injection n=122	^b Zuclopenthixol decanoate n=31	^c Flupentixol decanoate n=43	p value (a v b v c)
Mean Age (Years) [95% C.I.]	39.0 [36.9-41.0]	39.0 [34.3-43.6]	40.1 [37.1-44.5]	NS
Duration contact with mental health services prior to depot	0-1 yr 5 1-3 yrs 8 >3 yrs 109 (89%)	4 3 24 (77%)	1 2 40 (93%)	NS
Percent male	62%	52%	58%	NS
Compulsory treatment	23% (n=28)	32% (n=10)	14% (n=6)	NS
History of alcohol misuse	47% (n=57)	42% (n=13)	44% (n=19)	NS
History of substance misuse	34% (n=41)	39% (n=12)	30% (n=13)	NS
Diagnosis of schizoaffective disorder	19% (n=23)	26% (n=8)	16% (n=7)	NS
Previously on oral or intramuscular antipsychotics (i.e. 'switching' medications)	92% (n=112)	81% (n=25)	86% (n=37)	NS
Previously on another depot antipsychotic	23% (n=28) ¹	19% (n=6)	26% (n=11)	NS
Reason for discontinuing previous antipsychotic	inefficacy 39% (n=48) side- effects 11% (n=14) Non- adherence 39% (n=48)	61% (n=19) 6% (n=2) 16% (n=5)	49% (n=21) 9% (n=4) 21% (n=9)	NS
	^a Risperidone	^b Zuclopenthixol	^c Flupentixol	p value (a v b)

	long acting injection n=122	decanoate n=31	decanoate n=43	v c)
Regular additional oral antipsychotic	25% (n=30)	29% (n=9)	40% (n=17)	NS
Co-prescription, antidepressant	38% (n=46)	42%(n=13)	51% (n=22)	NS
Co-prescription, mood stabiliser	11% (n=14)	16% (n=5)	7% (n=3)	NS
Clozapine considered or tried (before/after depot)	25% (n=30)	10% (n=3)	19% (n=8)	NS
Total patient years of depot treatment	166.4	44.2	48.8	
Median duration of electronic record before depot started, months [range]	12.8 [0-58.6]	15.4 [0.5-55.9]	12.3 [0-51.7]	NS

BNF = British National Formulary

1(flupentixol dec n=17, zuclopenthixol dec n=8, fluphenazine dec n=1, pipothiazine palmitate n=1, haloperidol dec n=1),

Table 17 shows the inclusive nature of the study population with significant proportion of the whole sample being women (38%), requiring compulsory treatment (24%), having a lifetime history of alcohol or substance misuse (29-47%), concomitant antidepressant and mood stabilising medications (9-42%), antipsychotic polypharmacy (defined as above - 30%) and treatment resistance – as defined by prior clozapine use or consideration of clozapine use (23%). The majority of patients (89%) were switching from another antipsychotic. There was trend for zuclopenthixol to be commenced after the previous antipsychotic was discontinued due to inefficacy. There was a mean period of 15.6-18.5 months before the 3 main depot antipsychotic were introduced, reflecting the duration of

history and contacts prior to the depot being started, as noted in the e-record. The proportion of patients per treating psychiatrist, ie rate of prescription, varied between RLAI (4.1), zuclopenthixol decanoate (2.1) and flupentixol decanoate (1.7), as reflected in the 'popularity' of prescribing choice noted above. There were also differences in the mean total duration of record between the three main depots studied with zuclopenthixol decanoate records being around 8 months less than RLAI or flupentixol decanoate records. In total, the study incorporated 283 patient years of depot antipsychotic experience.

Table 18. Proportion of patients in depot medication study who improved according to CGI-I (<5)

	Risperidone long acting injection		Zuclopenthixol decanoate		Flupentixol decanoate		p value
All patients	74% (n=90/122)		74% (n=23/31)		72% (n=31/43)		NS
Age less than 30	71% (n=21/31)		75% (n=6/8)		67% (n=6/9)		NS
Age greater than 30	76% (n=69/91)		74% (n=17/23)		74% (n=25/34)		NS
Male	72% (n=55/76)		81% (n=13/16)		72% (n=18/25)		NS
Female	76% (n=35/46)		67% (n=10/15)		72% (n=13/18)		NS
Service contact less than 3 years	62% (n=8/13)		71% (n=5/7)		67% (n=2/3)		NS
Service contact over 3 years	74% (n=81/109)		75% (n=18/24)		73% (n=29/40)		NS
Schizoaffective disorder	86% (n=19/22)		50% (n=4/8)		57% (n=4/7)		0.08 ^a
Schizophrenia /other psychoses	71% (n=71/100)		83% (n=19/23)		75% (n=27/36)		NS
*Treatment resistance	53% (n=16/30)		67% (n=2/3)		38% (n=3/8)		0.07 ^b
No treatment resistance	80% (n=74/92)		75% (n=21/28)		80% (n=28/35)		NS
Switching from another depot	64% (n=18/28)		67% (n=4/6)		64% (n=7/11)		NS
Not switching from another depot	77% (n=72/94)		76% (n=19/25)		75% (n=24/32)		NS
	25mg	73%	100-350mg	73%	20-50mg	75%	
Equivalent fortnightly dose	37.5mg	75%	400-600mg	77%	60-120mg	67%	
	50mg	69%	800-1200mg	67%	150-250mg	100%	

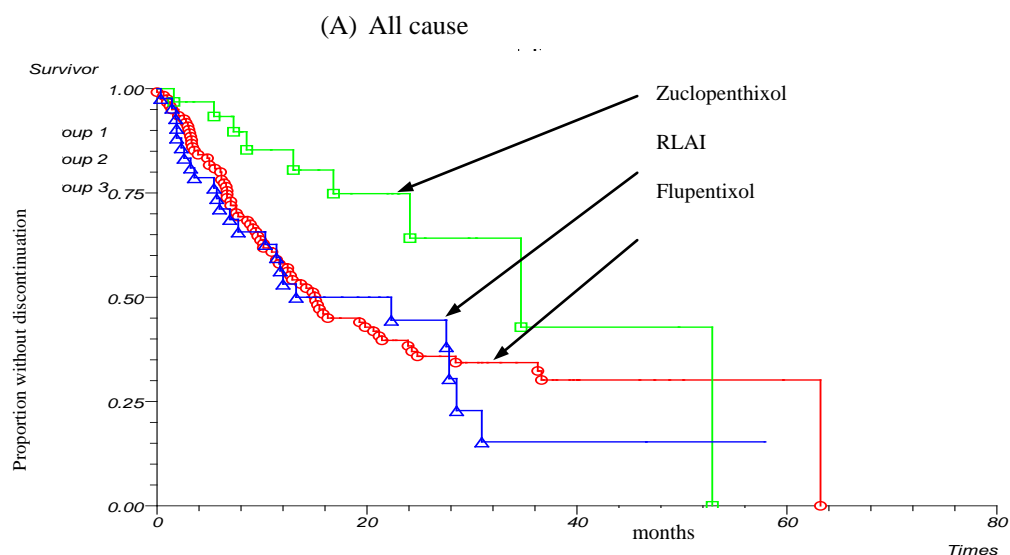
*clozapine considered or prescribed before or after depot was commenced

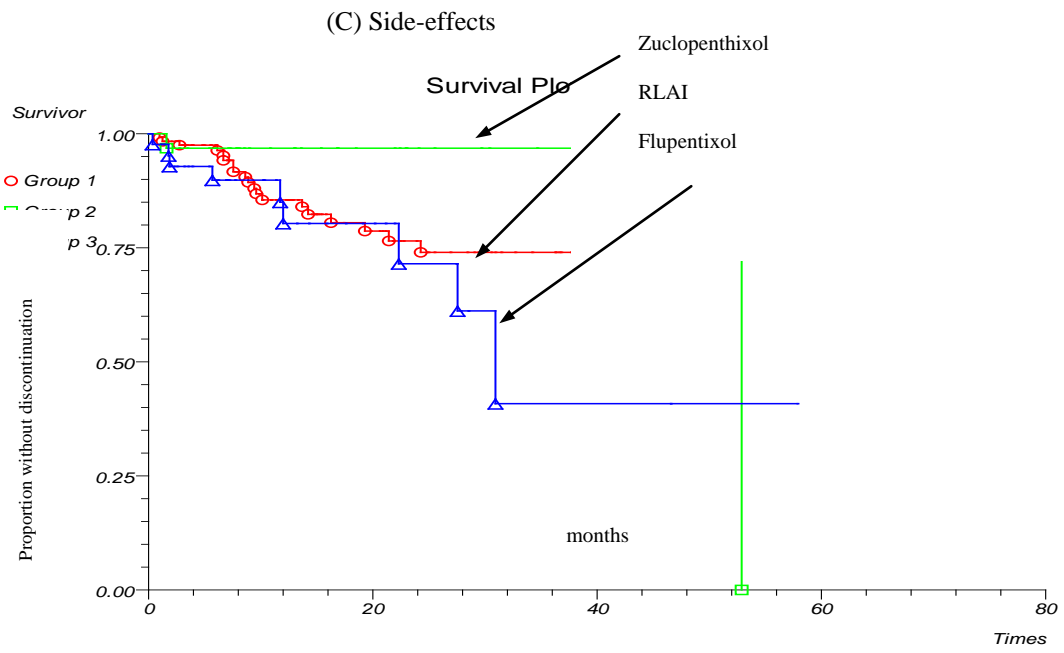
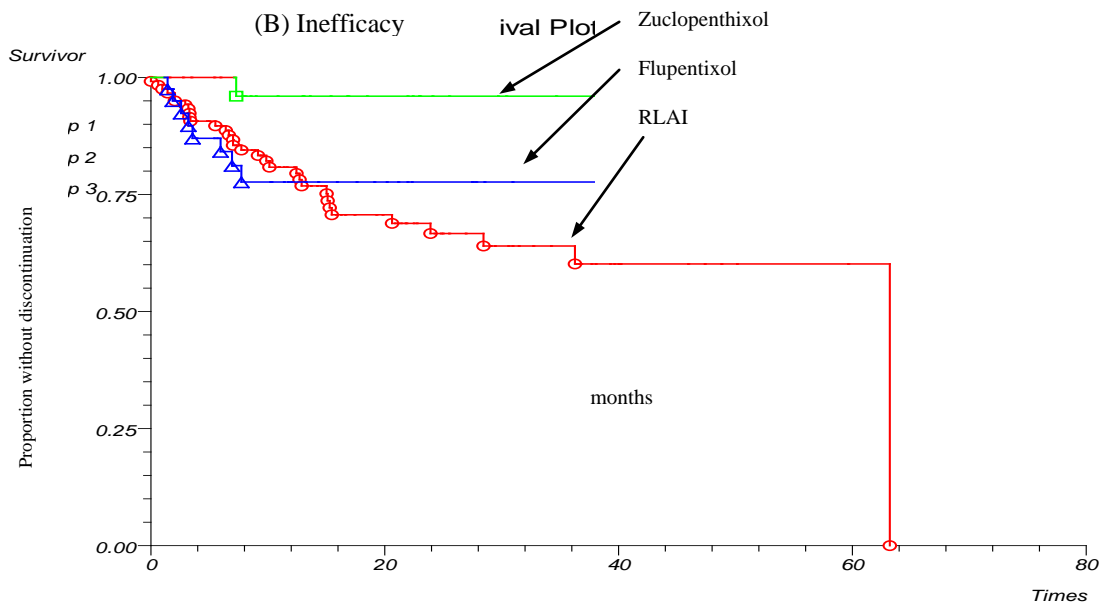
^a $\chi^2 = 5.0$, d.f.=2, p=0.08; ^b $\chi^2 = 3.2$, d.f.=1, p=0.07

Table 18 shows CGI severity and improvement scores. Adjusted results after excluding schizoaffective and treatment resistant patients showed similar patterns with statistical significance remaining. Flupentixol decanoate was started on

patients with a lower severity of illness score compared with zuclopenthixol decanoate ($p=0.003$) or RLAI ($p=0.018$). After 3 to 5 months CGI severity scores were lower with flupentixol compared to RLAI ($p=0.038$). Around 80% of patients made some degree of clinical improvement following the commencement of RLAI, zuclopenthixol decanoate or flupentixol decanoate. Within the CGI improvement categories (1-8) fewer patients had 'very much improved' or 'much improved' (CGI I=1 or 2) after commencing zuclopenthixol decanoate compared with RLAI or flupentixol decanoate ($p=0.0007$).

Figure 7. Survival curves in depot medication study - Time to treatment discontinuation due to all causes (A), inefficacy (B), and side-effects (C) and time to hospitalisation (D).





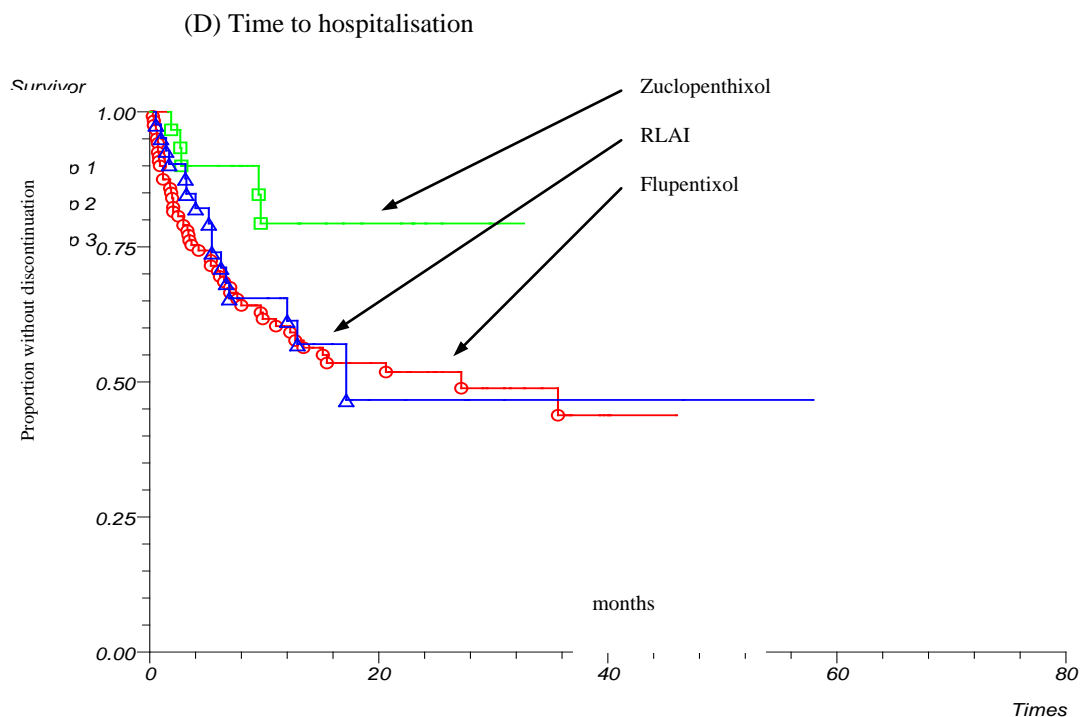


Figure 7 depicts survival curves illustrating time to discontinuation for any cause, inefficacy, side effects and time to hospital admission. Survival curves after excluding treatment resistant and schizoaffective patients showed similar results.

Any cause discontinuation differed significantly between zuclopendixol decanoate and RLAI, (HR 0.46 [95% CI=0.27-0.77]) and flupentixol decanoate (HR 0.41 [0.22-0.78]). Discontinuation due to inefficacy differed between zuclopendixol decanoate and RLAI, (HR 0.12 [0.05-0.27]) and flupentixol decanoate (HR 0.14 [0.05-0.39]). The likelihood of hospitalisation differed between zuclopendixol decanoate and RLAI, (HR 0.32 [0.17-0.59]) and flupentixol decanoate (HR 0.34 [0.16-0.71]). Despite the trends evident in these results, none were statistically significant.

Table 19: Clinical Global Impression scores and duration of treatment
(unadjusted)

	Risperidone long acting injection n=122	Zuclopenthixol decanoate n=31	Flupentixol decanoate n=43	p value
CGI-S (severity) at onset of treatment, mean [95% C.I.]	4.5 [4.3-4.7]	4.8 [4.5-5.0]	4.1 [3.8-4.4]	0.0026 ^a
CGI-S (severity) at 3-5 months after starting depot, mean [95% C.I.]	3.3 [3.0-3.5]	3.1 [2.9-3.4]	2.6 [2.1-3.1]	0.038 ^b
CGI-S (severity) percentage improvement after 3-5 months of treatment, mean [95% C.I.]	24.7 [19.7-29.8]	32.6 [25.6-39.5]	36.4 [26.6-46.3]	NS
CGI-S (severity) at end of treatment or record, mean [95% C.I.]	3.3 [3.1-3.5]	3.1 [2.8-3.4]	2.9 [2.6-3.3]	NS
CGI-S (severity) percentage improvement from onset of treatment, mean [95% C.I.]	24.7 [19.7-29.8]	33.0 [25.3-40.6]	27.8 [19.9-35.8]	NS
CGI-I (improvement), mean [95% C.I.]	3.5 [3.2-3.7]	3.4 [3.0-3.8]	3.3 [2.9-3.7]	NS
Percent improved [CGI-I <5] -all patients	74% (n=90)	74% (n=23)	72% (n=31)	NS
CGI-I, Improvement category, percentage of patients	1. Very much improved	11% (n=13)	0% (n=0)	7% (n=3)
	2. Much improved	18% (n=22)	16% (n=5)	30% (n=13)
	3. Moderately improved	21% (n=26)	55% (n=17)	21% (n=9)
	4. Minimally improved	24% (n=29)	3% (n=1)	14% (n=6)
	5. No change	20% (n=24)	26% (n=8)	23% (n=10)
	6. Minimally worse	4% (n=5)	0% (n=0)	5% (n=2)
	7. Moderately worse	2% (n=3)	0% (n=0)	0% (n=0)
	8. Much worse	0% (n=0)	0% (n=0)	0% (n=0)
Duration of treatment with depot, mean months [95% CI]	16.4 [13.9-18.9]	17.1 [12.5-21.7]	13.6 [9.8-17.5]	NS

a $F_{(2,195)} = 9.2$, $p = 0.0026$ (difference between zuclopenthixol dec v flupentixol ($p = 0.003$) and RLAI v flupentixol dec ($p = 0.018$); no difference between RLAI v zuclopenthixol dec)
b $F_{(2,145)} = 3.3$, $p = 0.038$ (difference between RLAI v flupentixol dec)

Discussion

Principal findings

Over the period 2002-2008, a trend towards the increasing use of long-acting risperidone over first-generation long-acting antipsychotic injections was observed here. This is consistent with the trend seen in the increasing use of SGA antipsychotics generally in Scotland (see Figure 1). Most (76%) of the sample on long-acting injections were not detained and hence were receiving the injections on a voluntary basis. Co-prescription of antidepressants occurred in up to 51% of this group of people with chronic schizophrenia and additional oral antipsychotics were required in up to 40%. In terms of percentage of individuals showing any degree of CGI improvement, there was no difference between the three main depots (72-74% improved) although there were fewer people in the 'very much improved' or 'much improved' groups with zuclopenthixol decanoate compared with risperidone long-acting injection and flupentixol decanoate. Those started on risperidone long-acting injection who achieved 'very much improved' on the CGI had a higher initial illness severity to start with (two-tailed t-test $P < 0.001$) and were less likely to have been tried on clozapine. Time to discontinuation as a result of inefficacy and time to hospitalisation (non-significantly) favoured zuclopenthixol decanoate over risperidone long-acting injection and flupentixol decanoate. Time to discontinuation as a result of side-effects did not differ between the three depots. Second-generation antipsychotics were marketed on their superior side-effect profile and although we were unable to examine side-effects during treatment, discontinuation

because of side-effects did not differ significantly with risperidone long-acting injection compared with zuclopenthixol decanoate or flupentixol decanoate.

Methodological issues

All typed correspondence from clinicians was uploaded into the electronic document management system in NHS Lanarkshire mental health services and the record is considered an effective duplication of the correspondence section of paper-based case records. As individuals on depot medication are usually within secondary care services and have repeated, usually multidisciplinary contacts, confidence can be expressed that the electronic records (which include medical, nursing and occupational therapy documents) captured a comprehensive and accurate picture of clinical contacts for all patients on the depot antipsychotics studied.

The possibility that the treatment practice or recommendations of a minority of psychiatrists, or the different lengths of the electronic records may be responsible for the results seen also requires consideration. Records for zuclopenthixol decanoate were shorter in duration than for risperidone long-acting injection or flupentixol by approximately 8 months on average. Theoretically, this allows less time for discontinuation events; however, using Kaplan-Meier derived survival curves and mean times to discontinuation or hospitalisation takes this into account. In addition, the mean duration of treatment was similar for the three main depots studied. Therefore, it is unlikely that different duration of records explains the different discontinuation rates seen.

The lower discontinuation rates for zuclopenthixol decanoate may have reflected its use in more individuals with treatment resistant illness, similar to the situation

with clozapine where clinicians feel they are limited by subsequent choices after treatment failure and are reluctant to discontinue. There was some evidence to support this in that more individuals were started on zuclopenthixol decanoate as a result of inefficacy (61%) compared with risperidone long-acting injection (39%) or flupentixol decanoate (49%), although this just failed to achieve statistical significance. Similarly, a greater proportion of people started on zuclopenthixol decanoate were treated compulsorily, although again, this was not statistically significant. However, there was evidence to refute that zuclopenthixol decanoate was reserved for more treatment-resistant individuals in that these patients were less likely to have been tried on clozapine and there was no difference in the duration of contact with psychiatric services. Overall, these data do not support that zuclopenthixol was being used as a 'last resort' medication that clinicians were reluctant to discontinue.

Strengths and limitations of the study

The electronic record system allowed study of all patients who were started on the most commonly prescribed depot antipsychotics in secondary care mental health services in a discrete geographical region within a defined period. This meant that individuals with co-prescription of other psychotropic agents, with comorbid conditions such as alcohol and substance misuse, and those who would be unable to consent to clinical trials (e.g. high illness severity and detained patients) were all included, representing routine clinical practice. Such inclusiveness also permits follow-up of individuals over a relatively long period (in some cases over 5 years) thereby offering outcome information beyond the acute illness phase. This study is thus generalisable everyday clinical practice, in keeping with the views of Adams *et*

al (2001) that study populations of long acting injections of antipsychotics need to be as representative and long term as possible. The downside of this inclusiveness is that the 'noise' generated by many confounding variables (which would lead to exclusion from some clinical trials) may mask the efficacy signal from one particular compound. The selection of patients was not from strict *a priori* criteria but a reflection of clinician and patient choice in the decision to start a depot during a particular psychotic illness episode. The study population is predominantly white and middle-aged and so may not be necessarily generalisable to other specific populations, for example, young adults with first-episode psychosis.

The effectiveness measure employed (proportion improved according to CGI) is a clinically relevant one, reflecting everyday clinical review of patients and their response to treatment. The CGI scale was originally designed to be used prospectively and is undoubtedly a less sophisticated instrument than specific symptom rating scales, but has been used elsewhere (eg Shajahan *et al*, 2009) to identify clinical response retrospectively.

Time to discontinuation has been increasingly used as a primary outcome measure in antipsychotic effectiveness research (Lieberman *et al*, 2005, Kahn *et al*, 2008). It is a relatively unbiased measure and usually, although not always, signals treatment failure because of inefficacy, adverse effects, non-adherence or combinations of these. Both time to and rate of hospitalisation (Hodgson *et al*, 2007; Kahn *et al*, 2008) may also be considered as markers of treatment failure. However, experience of clinical practice informs that the reasons for hospitalisation are varied and usually include risks of self-harm, risk of harm to others and

adverse social circumstances. During this study, non-hospital options (e.g. home treatment teams) were not available during the study period.

Conclusions

When considering the study outcomes that were less subject to potential bias (i.e. time to discontinuation and hospitalisation) there was a trend for zuclopenthixol decanoate to be superior to risperidone long-acting injection and flupentixol. These findings are consistent with the meta-analytic review by Adams *et al* (2001) that showed a modest advantage for zuclopenthixol decanoate over other first-generation depots in terms of discontinuation. However, when considering the CGI, which was arguably more prone to potential bias, zuclopenthixol was associated with fewer individuals in the 'very much improved' and 'much improved' categories compared with risperidone long-acting injection and flupentixol. Of interest was the use of zuclopenthixol decanoate in people with probably greater illness severity, suggesting clinician preference in its use when individuals were more severely unwell.

CHAPTER 7

**DEVELOPING AND VALIDATING A NEW SIDE-EFFECT SCALE FOR
ANTIPSYCHOTIC MEDICATION**

MT conceived and designed the study; collected, analysed, and interpreted the data, and helped draft the manuscript. Dr Waddell obtained ethical approval for the study; collected, analysed, and interpreted the data; and drafted the manuscript.

Study conducted 2006-2008.

Lack of or partial adherence with antipsychotic medication is perhaps the main determinant of relapse in schizophrenia (Tacchi and Scott, 2005). The tolerability or experience of side effects of a particular antipsychotic medication has been regarded as one of the key factors predicting continued adherence (Lambert *et al*, 2004) and crucially the experience of adverse antipsychotic side effects is commonly stated by patients as an important reason for non adherence. This highlights the importance of an open and systematic discussion regarding medication related side effects. An open acknowledgement of the risks and benefits of a particular treatment helps establish a collaborative approach between clinicians and patients, and can contribute to a therapeutic rapport.

Antipsychotic side effect rating scales have been used in research studies since at least 1970. They include traditional observer rated side effect scales such as the Simpson-Angus (1970) and the Barnes Akathisia scale (1989). These more often were found in research settings than routine clinical practice, and arguably side effect scales focusing only on movement disorder or extra-pyramidal symptoms have now become less relevant as the widely used second generation antipsychotics (SGAs) have a lower incidence of extra-pyramidal side-effects (eg Crossley *et al*, 2010).

Additionally, although observer rated scales may avoid over-reporting bias they can be more time consuming than self report scales, and less likely to identify potentially embarrassing concerns such as sexual dysfunction. The Liverpool University Neuroleptic Side Effect Rating Scale (LUNSERS) (Day *et al*, 1995) is a commonly used self report scale which concentrates on one word symptoms but again is over a decade old. The LUNSERS also takes time to complete as it is

three pages long, and an audit (Negi, 2007; only presented in abstract form) found that use of the LUNSERS did not improve case record documentation of side effects. Lastly experience with the LUNSERS found that patients commonly have to ask for help in understanding terms such as “chilblains”, emphasising that the use of simple plain English is vital in self report scales.

In view of this, it was felt that an easy to understand self-report side-effect scale that was brief, valid, practical and informative would be clinically useful. It was envisaged that a short self-report scale could facilitate further discussion in the clinic regarding the tolerability of antipsychotic medication.

Aims

1. To develop a new pragmatic scale for monitoring antipsychotic medication adverse side-effects.
2. To test the validity and reliability of the new scale against the existing ‘gold-standard’ scale, in individuals taking antipsychotic medication and healthy comparison subjects.

Method

Ethical approval for the study was granted by the local Greater Glasgow Primary Care Division Research and Ethics Committee (chair – Dr Paul Fleming) – see appendix two.

Constructing the scale

A literature review was undertaken using Medline and other internet search engines with various keywords including *neuroleptic; adverse effects; side effects; antipsychotic; rating scale; and schizophrenia*. Also, medical, pharmacy, and nursing staff were questioned about their experience of identifying antipsychotic side-effects. All nine currently widely available antipsychotic side-effect rating scales were identified and reviewed to identify their strengths and weaknesses (see Table 20).

Table 20. Existing side-effect rating scales

Scale	Number questions	Rating	Advantages	Disadvantages
Simpson Angus Scale (SAS) (Simpson & Angus, 1970)	10	Clinician rated	Objective rating of EPSE, quick & easy to perform	Focus on extrapyramidal side effects (EPSE) only
Abnormal Involuntary Movement Scale (AIMS) (Guy, 1976)	12	Clinician rated	Objectively records presence & severity of involuntary movements; quick to perform	Focus on abnormal movements only
Extrapyramidal Side Effect Rating Scale (ESRS) (Chouinard et al, 1980)	12	Clinician rated	Quick to perform, objective documenting of EPSE.	EPSE only. No differentiation between dyskinesia & dystonia.
Drug Attitude Inventory (Hogan et al, 1983)	30	Self rated	Simple to understand questions & true / false answers. Assesses attitude	Not specifically aimed at detecting antipsychotic side-effects
Side Effects Rating Scale for the Registration of Unwanted Effects of Psychotropics (Lingjaerde et al, 1987)	47	Clinician rated	Covers an extensive range of side effects from antipsychotic medication	Requires a lengthy semi structured interview and clinical observation
Barnes Akathisia Rating Scale (Barnes, 1989)	4	Clinician & self rated	Both subjective & objective rating of akathisia; quick	Focuses on akathisia only
Hillside Akathisia Scale (HAS) (Fleischhaker et al, 1989)	5	Clinician & self rated	Both subjective & objective rating of akathisia; quick	Focuses on akathisia only
Liverpool University Neuroleptic Side Effect Rating Scale (LUNSERS) (Day et al, 1995)	51	Self rated	Assesses wide range of side effects; red herring questions for over-reporting of side-effects	One word symptoms that can be difficult to understand.
Antipsychotic Non-Neurological Side Effect Rating Scale (ANNSERS) (Yusufi et al, 2005)	35	Clinician & self rated	Covers wide range of side effects for 1st & 2nd generation antipsychotics	Lengthy & time consuming.

After referring to existing scales, important antipsychotic side effects were listed using information from the British National Formulary and the pharmaceutical industry. Consistent with NICE guidelines (2010) these side effects were then ranked in importance by the author in terms of the gravity of the medical consequences. In addition, a focus group of patients already taking antipsychotic medication ranked the list of side effects in terms of acceptability. This focus group comprised six individuals on antipsychotic medication who were recruited on a voluntary basis from one community mental health team in north Glasgow, thought (by the author) to be representative of patients with psychotic illness on maintenance antipsychotic medication. Twenty two questions were arrived at which summarised the prioritised side effects with priority given to long term adverse medical consequences. These were then grouped into classical medical systems such as cardiovascular; and central nervous system (see 'staff information' section in Table 21).

The majority of side effects addressed by the new scale are already contained in LUNTERS but the twenty two questions were converted into unambiguous plain English by consulting with non-health care staff. The new scale, termed the Glasgow Antipsychotic Side-effect Scale or GASS was scored 0, 1, 2, and 3 for questions one to twenty, with higher scores reflecting more frequent experience of side-effects. Questions twenty one and twenty two scored 0 for "no" and 3 for "yes". Total GASS scores were arbitrarily divided into suggested ranges for categorical severity, i.e. 0-12 = absent / mild side effects; 13- 26 = moderate side-effects; and 27-63 = severe side effects. A separate (un-scored) column was

added to allow people completing the GASS to note if the side effect experienced was distressing.

Participants

Fifty outpatients aged 18 to 65 who were currently prescribed and taking a second generation antipsychotic (regardless of diagnosis or other medication prescribed) consented to participate. These individuals were recruited from outpatient and clozapine clinics in the three North Glasgow resource centres, covering an area of significant socio-economic deprivation (see related information in chapter three). Adherence with prescribed medication by the outpatients was confirmed at clinical interview with the author. Fifty comparison subjects within the same age range also agreed to participate after excluding individuals on prescribed medication and those working in mental health care. These individuals were recruited by directly approaching consecutive members of the public encountered on the streets of central Glasgow, after explaining the nature and purpose of the study and confirming that confidentiality was assured. Individuals unable to read English were also excluded.

Assessment of the new scale

Outpatients completed both the LUNSERS and the GASS at the same time, with the choice of which scale was completed first being randomly assigned via coin tossing. The out-patients were also asked to complete a copy of the GASS again a week later to assess test-retest reliability. Comparison subjects completed the

GASS, to demonstrate that the GASS could differentiate between those taking and those not taking second generation antipsychotics.

Statistical analyses were performed using MedCalc for Windows, version 9.2.0.1 (*MedCalc Software*). Categorical differences were determined using the Mann Whitney test, with significance set at $p < 0.05$. Level of agreement between the scales was assessed using the weighted kappa and Spearman correlation coefficient. No analysis of internal consistency or factor variance eg via principal components analysis, was undertaken.

Results

The GASS is illustrated below (see Table 21). Table 22 shows the mean ages and the mean GASS score for the two groups.

There was no significant difference in age between the two groups ($U=1410$, $p=0.27$). The GASS scores for the two groups differed significantly (Mann Whitney U test, $U= 2336$, $p<0.0001$) with a mean of 14.3 for those on antipsychotic medication, and 3.6 for those not on medication. This confirms the construct validity of the GASS.

Figure 8 shows the spread of the GASS scores within each of the proposed categorical cut off points, for both cases and normal comparisons. Cases prescribed polypharmacy or monotherapy are also shown separately. As expected all controls scored within the absent to mild category.

29 of the outpatient group were prescribed clozapine, 9 risperidone (7 oral, 2 depot), 8 olanzapine, and 4 amisulpride. All doses were prescribed within BNF limits. 36 outpatients were prescribed only a second generation antipsychotics whilst the remaining 14 were on other regular medications (8 on antidepressants, 5 on mood stabilisers, 1 procyclidine, 1 methadone and 1 oral hypoglycaemics).

Repeating the analysis of GASS scores excluding the results of the 14 polypharmacy outpatients still revealed that outpatients had a significantly higher mean GASS score of 11.5 (SD=7.9) and they differed significantly from the normal comparisons (U score 1681, $p < 0.0001$).

When the GASS was compared to the LUNSERS in the fifty outpatients, the kappa score = 0.73, with spearman rank correlation coefficient = 0.93 (sum of squared differences = 1548; ie 93% level agreement). This indicates a strong level of agreement between the GASS and LUNSERS, according to convention for the interpretation of kappa.

Only 17 of the 50 outpatients returned (by post) the second GASS questionnaire adequately filled out a week later. Test- retest reliability was good, with kappa = 0.72. The Mann Whitney U test failed to identify any significant difference in the GASS score of those that returned the second GASS questionnaire and those that did not (U=308, $p = 0.57$) or their age (U=284, $p = 0.94$). There were 10 males and 7 females in the group that returned the second GASS, compared to 16 males and 17 females in the group that did not.

Table 21. **Glasgow Antipsychotic Side-effect Scale (GASS)**

Name:

Age:

Sex: M / F

Please list current medication and total daily doses below:

This questionnaire is about how you have been recently. It is being used to determine if you are suffering from excessive side effects from your antipsychotic medication. Please place a tick in the column which best indicates the degree to which you have experienced the following side effects. Tick the **end** box if you found that the side effect distressed you.

<i>Over the past week:</i>	<i>Never</i>	<i>Once</i>	<i>A few times</i>	<i>Everyday</i>	<i>Tick this box if distressing</i>
1. I felt sleepy during the day					
2. I felt drugged or like a zombie					
3. I felt dizzy when I stood up and/or have fainted					
4. I have felt my heart beating irregularly or unusually fast					
5. My muscles have been tense or jerky					
6. My hands or arms have been shaky					
7. My legs have felt restless and/or I couldn't sit still					
8. I have been drooling					
9. My movements or walking have been slower than usual					
10. I have had, or people have noticed uncontrollable movements of my face or body					
11. My vision has been blurry					
12. My mouth has been dry					
13. I have had difficulty passing urine					
14. I have felt like I am going to be sick or have vomited					
15. I have wet the bed					
16. I have been very thirsty and/or passing urine frequently					
17. The areas around my nipples have been sore and swollen					
18. I have noticed fluid coming from my nipples					
19. I have had problems enjoying sex					
20. <u>Men only</u> : I have had problems getting an erection					

Tick yes or no for the following questions about the last three months	<i>No</i>	<i>Yes</i>	<i>Tick this box if distressing</i>
21. <u>Women only</u> : I have noticed a change in my periods			
22. <u>Men and women</u> : I have been gaining weight			

Staff Information

1. Allow the patient to fill in the questionnaire themselves. Questions 1-20 relate to the previous week and questions 21-22 to the last three months.

2. Scoring

For questions 1-20 award 1 point for the answer "once", 2 points for the answer "a few times" and 3 points for the answer "everyday".
Please note zero points are awarded for an answer of "never".

For questions 21 and 22 award 3 points for a "yes" answer and 0 points for a "no".

Total for all questions=

3. For male and female patients a *total score* of:

0-12 = absent/mild side effects

13-26 = moderate side effects

over 26 = severe side effects

4. Side effects covered by questions
 - 1-2 sedation and CNS side effects
 - 3-4 cardiovascular side effects
 - 5-10 extra-pyramidal side effects
 - 11-13 anticholinergic side effects
 - 14 gastro-intestinal side effects
 - 15 genitourinary side effects
 - 16 screening for diabetes mellitus
 - 17-21 prolactinaemic side effects
 - 22 weight gain

The column relating to the distress experienced with a particular side effect is not scored, but is intended to inform the clinician of the service user's views and condition.

Figure 8. Spread of GASS scores in patients and normal comparisons

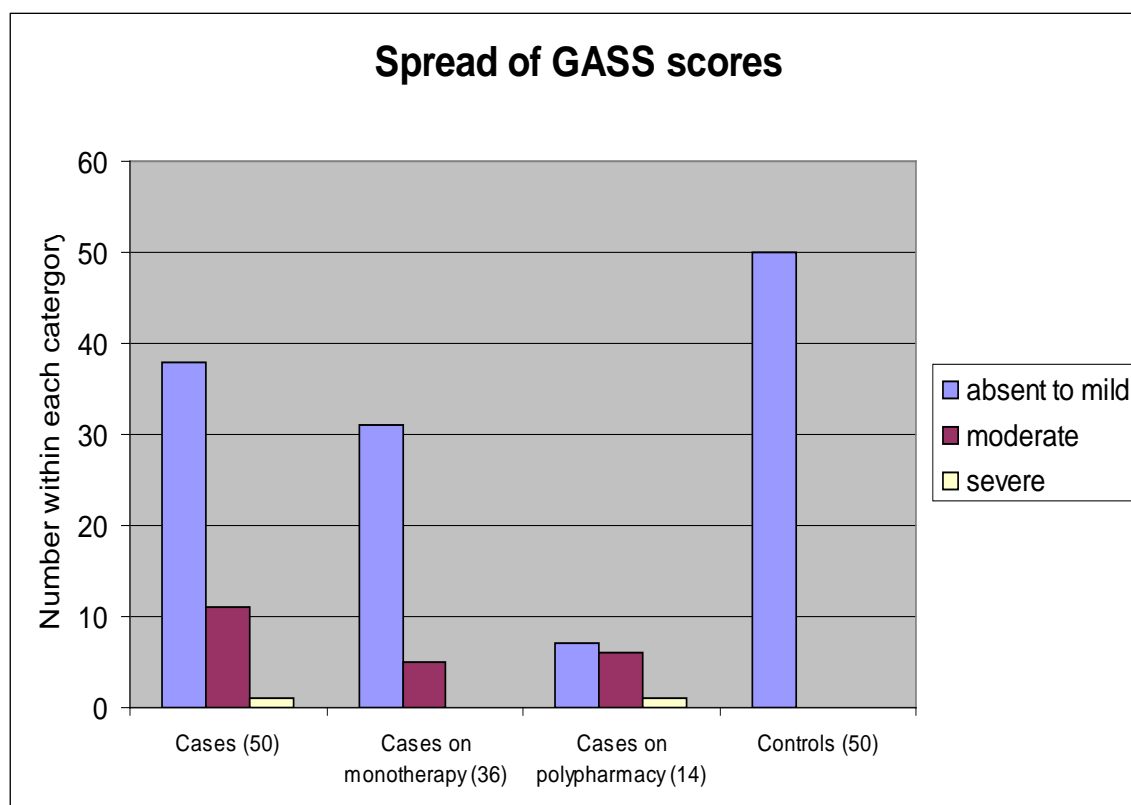


Table 22. Mean ages and GASS scores of participants

Statistic	Cases (n=50)	Comparisons (n=50)
Mean Age (years) [SD]	41.4 [9.1]	39.9 [14.1]
Age Range (years)	24 to 65	19 to 65
No. Males	26	21
Mean GASS [SD]	14.3 [10.5]	3.6 [4.1]

SD = standard deviation

Discussion

A new self-report rating scale assessing SGA side effects that is easy to use was constructed. The GASS takes five minutes to complete and contains self-explanatory questions in everyday plain English whilst providing a structured systematic method of reviewing antipsychotic side effects. In the waiting room of a busy community mental health team, or on the in-patient unit, the use of simple, jargon-free language will enhance understanding and accurate completion of a self-report scale, particularly if that scale is seen as brief. Furthermore, recognising that the experience of a side-effect may not necessarily be adverse even if it is common or may not cause distress or functional impairment when present, a column to the GASS allowing the subject to rate whether the experienced side-effect was in fact distressing (or not) was added. This was left as a simple global 'yes / no' response in view of the complexity of this judgement. Thus the GASS allows a grading not only of the frequency of an experienced side-effect but also a subjective judgement of the distress associated with a particular side-effect.

The widespread use of SGAs is in large part due to a perception of increased tolerability, although later independent studies (eg Lieberman *et al*, 2005) have confirmed SGAs have important adverse side-effects with associated long term health implications. Numerous studies have demonstrated that adherence with prescribed medication is a key determinant of relapse prevention (eg Robinson *et al*, 1999), and medication side-effects are commonly cited by patients as a main reason for non-adherence (Tacchi and Scott, 2005) perhaps because clinicians consistently underestimate the severity and frequency of side effects. The routine use of rating scales or systematised evaluation in psychiatry is not widespread, but arguably will increase and can be used to enhance the clinician-patient interaction.

Self-report scales generally are less onerous for the busy clinician and arguably permit a more complete and considered responses as well as minimising potential embarrassment on subjects such as sexual dysfunction.

The older side effect rating scales (see Table 20) such as the AIMS; Simpson Angus; Barnes Akathisia all focussed exclusively on movement disorder and extrapyramidal symptoms and are usually observer rated. The more recent scales such as LUNSERS and ANNSERS are more comprehensive and suitable for SGAs but are lengthy and time-consuming. The LUNSERS is regularly used in the UK, despite its size, age, and occasionally confusing language, illustrating that a systematic appraisal of medication side effects is considered important. Both the weighted kappa score and Spearman's rank correlation score demonstrated a very good level of agreement between the LUNSERS and the GASS in a representative psychiatric out-patient population. The test-retest results also indicate that the GASS is reliable and stable over time (test-retest time here was one week) although the fact that only 17 of the 50 patients asked to re-complete the GASS actually did so diminishes the validity of this finding. Ideally replication of these findings - the comparison with the LUNSERS; validation against non-medication using comparison subjects; and test-re-test reliability should occur in another centre.

The results demonstrate that individuals taking SGAs had significantly higher GASS scores than matched normal comparison subjects, as hypothesised, and that this difference was not confounded by polypharmacy.

The use of medical and consumer opinion as well as the literature review may well have enhanced the face validity of the GASS, and as the GASS combines brevity with validity it is suitable for busy clinical environments and as part of routine clinical monitoring e.g. during ward round or out-patient review. The GASS can also be completed outside the actual clinical interview, and can thus open up discussion between clinician and service user on medication tolerability in a systematic and structured manner, rather than relying on an *ad hoc* approach.

Given these results, the GASS is proposed as a valid reliable tool which could aid systematic clinical assessment, particularly in view of its brevity and user-friendly language.

Strengths and limitations

The GASS was only assessed in outpatients taking SGAs, so the results may not be applicable to those on typical or first generation antipsychotics or acute inpatients. It may not be possible to generalise the results of this study beyond a white middle aged population in view of the age range and ethnicity of the two study groups. Furthermore, only one patient in this study was rated as having 'severe' side-effects using the suggested categorical cut-offs which could cast doubt on the validity of this category. Ideally this validation study should be repeated with a larger sample in a different setting. Although the GASS appears to be as discriminating as the LUNSERS in terms of identifying emergent medication related side-effects, this study does not necessarily definitively measure what it purports to measure, as there has not been any external validation with objective measures, eg weight gain. The subjective rating of distress caused by each side effect also requires further study.

CHAPTER 8

DISCUSSION AND CONTEXT OF THE RESULTS

This concluding chapter deals with the differences and similarities between the antipsychotics studied in chapters 3 to 6 with a view to informing prescribing choice. There will be specific comment on the commonly occurring polypharmacy as noted in chapters 3 and 5; with a subsequent specific focus on clozapine and depot or long acting injectable antipsychotics, in view of the findings in chapters 5 and 6. This chapter will also attempt to highlight how routine monitoring of medication related outcomes, including the Glasgow Antipsychotic Side-effect Scale (GASS – see chapter 7), is informative for day-to-day clinical practice.

Choice of antipsychotic medication

A diverse range of factors influence a prescription choice and include not only the scientific evidence base of randomised controlled trials (RCTs); meta-analyses; and clinical guidelines (evidence or consensus based); but also less rational factors such as personal experience; peer opinion; and marketing influence. This section will solely focus on the scientific evidence base when discussing the context of the results in chapters 3, 4, 5 and 6.

The National Institute for Health and Clinical Excellence (NICE, 2010) guideline suggests that there is little to differentiate between any oral antipsychotic for the acute treatment of schizophrenia in terms of clinical efficacy, with the main differences relating to side effect profiles. However, the meta-analysis by Leucht

and colleagues (2009) which compared SGAs with low dose haloperidol concluded that four of the SGAs, namely amisulpride, clozapine, olanzapine and risperidone were better than the other antipsychotics studied in terms of overall efficacy – with small to moderate effect sizes. The symptom reduction effect size (Hedges' g) for clozapine was -0.52 compared to amisulpride ($g=-0.31$); olanzapine ($g=-0.28$); and risperidone (-0.13). The results in Chapter 5 also highlight the superior effectiveness of clozapine, and this will be discussed further below. It is notable that other SGAs such as aripiprazole and quetiapine were not more efficacious than low dose haloperidol, even for negative symptoms, in the meta-analytic review of Leucht *et al* (2009). The small to moderate efficacy differences noted above need to be balanced with the large differences in side effect profiles for individual patients. Furthermore, the large meta-analyses of the comparative efficacy and tolerability of antipsychotic drugs are largely based upon short-term (eg 12 weeks) RCTs of antipsychotic drugs for acute relapses of schizophrenia. This is in contrast to the six month prospective study (chapter 4) and 2 year retrospective study (chapter 5) noted here, which arguably makes generalisation of the findings difficult, and hence studies examining longer term relapse need to be reviewed. In particular, rates of relapse and psychiatric hospitalisation are directly relevant to the data in chapters 4 and 5.

Early RCTs showed that individuals who are well stabilised on antipsychotic drugs have high rates of relapse when their medication is discontinued or switched to placebo (Kane, 1996). Relapse risk is especially increased if medication is stopped abruptly, but about one-half will relapse within six months even if medication is withdrawn gradually. Continuing antipsychotic medication treatment over several years can reduce relapse rates by approximately two thirds (Leucht *et*

al, 2011) although various studies (eg Shepherd *et al*, 1989) suggest that about 20% of patients will have a single episode implying that maintenance treatment is not required for all patients. Another RCT (Marder *et al*, 2003) showed that active treatment relapse rates were one third of those on placebo, with relapse predictors also including persistent symptoms, poor adherence, lack of insight, and substance misuse. The industry sponsored SOHO observational study (Haro *et al*, 2007) had a similar naturalistic design to the study described in chapter 4, and found a relatively constant relapse rate over the 3 years, with 25% relapsing in total.

An early meta-analysis (Davis *et al*, 1993a) of 35 double-blind studies (not all of which were RCTs), comparing maintenance treatment with FGAs versus placebo in over 3,500 service users found that relapse was reported in 55% of those who received placebo, compared to 21% of those receiving active drugs. Davis *et al*, (1993b) suggested that the number of people who survive without relapse after discontinuing drug treatment declines exponentially by around 10% a month; but approximately 20-30% of patients will not relapse after their initial episode(s). Gilbert and colleagues (1995) reviewed 66 antipsychotic withdrawal studies, published between 1958 and 1993, involving over 4,000 patients, and found a mean cumulative rate of relapse in the medication withdrawal groups of 53% compared with 16% (follow-up of approximately 8 months on average) in the antipsychotic maintenance groups. Similarly, a meta-analysis by Leucht *et al* (2003) concluded that SGAs as a whole reduced relapse rate by 23% as compared to 15% for FGAs as a group, suggesting that antipsychotics perhaps do not all have comparable effectiveness

.

Of relevance to the choice of antipsychotic treatment for adults in terms of effectiveness over the medium to longer term are the findings of three pragmatic trials of antipsychotic treatment (EUFEST, CATIE and CUtLASS1). In the EUFEST study (Kahn *et al*, 2008) 500 participants with first-episode schizophrenia or schizophreniform disorder were assigned to low-dose haloperidol or one of four SGAs. The main finding was that treatment discontinuation over 12 months was significantly more common in patients assigned to low-dose haloperidol than in those treated with the SGAs, and the lowest discontinuation occurred with olanzapine. There were however no significant differences in therapeutic efficacy between the different treatment groups in terms of symptom severity. The CATIE studies (Lieberman *et al*, 2005; Stroup *et al*, 2006; McEvoy *et al*, 2006) also used all-cause discontinuation as the primary outcome measure, and of the 1493 participants, antipsychotics were discontinued in 60–80% of cases within the 18-month follow-up period. There was a significantly lower chance of discontinuation of olanzapine overall, compared to perphenazine, quetiapine, and risperidone but olanzapine was also associated with more discontinuation due to weight gain or metabolic effects. The Cost Utility of the Latest Antipsychotic Drugs in Schizophrenia Study (CUtLASS1 – Jones *et al*, 2006) was a smaller UK trial which compared allocation to an FGA or an SGA (excluding clozapine) in 227 participants with established schizophrenia for whom a change in antipsychotic medication was considered by their psychiatrist to be clinically indicated due to inadequate clinical response or intolerance. For each participant in the study, the choice of individual drug within the assigned FGA or SGA group was the choice of the prescribing clinician. Over the 1-year follow-up, there was no apparent disadvantage in using FGAs compared to SGAs in terms of quality of life, symptoms or the associated costs of care. It is scientifically reasonable and

relevant to compare these pragmatic randomised effectiveness studies with the results in chapter 4 and particularly chapter 5, where little difference was found in the measures of antipsychotic effectiveness between amisulpride; olanzapine; quetiapine; and risperidone.

In clinical practice, the choice of maintenance treatment for a particular patient is probably best made on the correct drug, dose and formulation for that individual, bearing in mind patient preferences, illness severity, likely adherence, known previous drug response(s), any substance misuse, levels of depression, cognitive function and adverse effect profile. Generally, patients with schizophrenia will benefit from reduced relapse rates if they remain on antipsychotic medication. No particular drug or class is conclusively better in terms of efficacy (leaving aside clozapine – see below), or at reducing relapse rates than any other, despite the findings of Leucht and colleagues (2003, 2009). The available RCTs tend to favour SGAs (especially amisulpride, risperidone and olanzapine) but numerous methodological factors (e.g. comparator drug and dose, drop out rates) could account for any such differences. This benefit of maintenance antipsychotic medication may also only apply to one-third to two-thirds of patients however and there is as yet no reliable method of predicting who will benefit compared to those who will relapse on an individual basis. The factors which tend to be associated with an increased chance of relapse clinically – such as illness severity and substance misuse - are also those which predict poor adherence with medication.

Tolerability of antipsychotic medication

Most RCTs of SGAs and FGAs are of relatively short duration and not designed to prospectively examine side effects, so these trials provide little insight into the

longer-term adverse effects of treatment or whether there are clinically significant differences between antipsychotic drugs. The overall drop out (leaving the study early) specifically due to adverse effects in these studies is approximately 5-10%, in the short term, with no apparent difference between drugs. A clear advantage for SGAs was fewer episodes of tardive dyskinesia according to a review by Correll and Schenk (2008), which occurred with an annual incidence of 3.0% in SGAs vs. 7.7% with FGAs.

Adherence with anti-psychotic medication generally runs at approximately 50% in the medium to longer term (Patel *et al*, 2009), and results in chapter 5 demonstrate that a major reason for non-adherence is the experience of intolerable side-effects. This is why systematic review of antipsychotic side-effects using a valid instrument such as the GASS (as described in chapter 7) is so important, both in terms of good clinical practice and maintaining rapport through inclusive discussion. The three pragmatic trials of antipsychotic treatment (EUFEST, CATIE and CUtLASS1) described in detail above reached essentially the same conclusions in terms of medication discontinuation. In the EUFEST study (Kahn *et al*, 2008), all cause treatment discontinuation over 12 months ranged from 33% to 72%. The CATIE studies (Lieberman *et al*, 2005; Stroup *et al*, 2006; McEvoy *et al*, 2006) funded by the National Institute of Mental Health, also used all-cause discontinuation as the primary outcome measure and found that antipsychotics were discontinued in 60–80% of the 1493 participants within the 18-month follow-up period. Both studies favoured SGAs. The Cost Utility of the Latest Antipsychotic Drugs in Schizophrenia Study (CUtLASS1, Jones *et al*, 2006) funded by the NHS Research and Development Health Technology Assessment Programme in England, found that more patients randomized to receive an SGA than an FGA remained in their

allocated treatment arm for the whole year, but this difference was not significant (65% [71/109] vs. 54% [64/118]). These rates are generally somewhat higher than the discontinuation rates observed retrospectively in Lanarkshire in chapter 5, but this may be explained by the demands of the trial rather than a naturalistic study population.

In terms of EPS all SGAs are associated with much fewer adverse effects than haloperidol. The data comparing SGAs with low potency FGAs such as chlorpromazine are less clear. Antipsychotic-associated weight gain, its metabolic consequences and the associated morbidity are a major concern. All of the SGAs with the exception of aripiprazole and ziprasidone caused more weight gain than haloperidol (but not low-potency FGAs). Clozapine, olanzapine, sertindole and zotepine caused the most weight gain. In terms of sedation, clozapine, quetiapine and zotepine were more sedating than haloperidol, and aripiprazole was less sedating. Sexual dysfunction has been less well studied in these trials, but is usually thought to be related to prolactin elevation with risperidone and amisulpride are thought to be the worst culprits of the SGAs in this domain. The full range of potential side-effects should be captured in a systematic way by a single scale, and the GASS (described in chapter 7) has probes on EPS and other neurological problems; sedation; weight gain; incipient diabetes; and sexual and menstrual dysfunction. These are the factors that patients themselves (see chapter 7) and the literature reviewed here regard as the most common and serious side-effects associated with antipsychotic medication.

In summary, antipsychotic medication appears to be acceptable to approximately one-half of patients in the long term, in that they will largely adhere to their

prescription. The SGAs appear to be better tolerated in the short term but as a whole have worrying longer term metabolic effects. In routine clinical practice, treatment acceptability varies from drug to drug in different patients, and the incidence of emergent side-effects can be hard to predict on an individual basis.

Optimal dose of antipsychotic medication

The Cochrane review of chlorpromazine dose (Liu *et al*, 2009) found that on low dose (≤ 400 mg/day), compared to medium dose (401-800 mg/day), more people left for inefficacy of treatment but all measured EPS tended to be lower. When low dose was compared with high dose (>800 mg/day) global state outcomes tended to favour the high dose group, but more people in the high dose group left early due to disabling adverse effects. Significantly less dystonia and other unspecified EPS were reported in the low dose group. The Cochrane review (Li *et al*, 2009) of risperidone dose highlights 4-6mg daily as the optimal balance between drop-outs due to inefficacy (at <4 mg) versus adverse effects (at >6 mg). The studies documented in this thesis did not use chlorpromazine as a comparator as it is not widely prescribed as a maintenance medication for schizophrenia in either Glasgow or Lanarkshire, but the mean dose of 3.4mg in the 115 individuals taking risperidone highlighted in chapter 4 and the mean dose of 6mg in the 74 patients with schizophrenia identified in chapter 5 are similar to the Cochrane derived 'optimal range', suggesting clinicians in the west of Scotland are aware of this issue.

Recently, Uchida *et al* (2011) compared the efficacy between standard dose [World Health Organization defined daily dose (DDD)] vs low dose (50-100% DDD) or very low dose ($<50\%$ DDD) for relapse prevention in schizophrenia in RCTs with

a follow-up duration of at least 24 weeks, in thirteen studies with 1395 subjects. Compared with the standard-dose treatment, the low-dose therapy did not show any statistically significant difference in overall treatment failure or hospitalization, while the standard dose showed a trend approaching significance for superiority in risk of relapse. The very low-dose group was inferior to the standard-dose group in all efficacy parameters. No significant difference was found in the rate of dropouts due to side effects between either standard dose versus low dose or very low dose.

Optimal duration of antipsychotic treatment

There are surprisingly few studies regarding ideal duration of antipsychotic treatment. In the Northwick park first episode study (Crow *et al*, 1986) 25 (46%) of 60 patients randomised to antipsychotics (chlorpromazine, haloperidol, trifluoperazine, pimozide or flupentixol decanoate) had relapsed within 2 years as compared to 46 (61%) randomised to placebo. In the Cochrane review of chlorpromazine (Adams *et al*, 2007), the longer term data (6 months to 2 years) favoured the chlorpromazine group over placebo (n=512, 3 RCTs, RR 0.57 CI 0.5 to 0.7, NNT 4 CI 3 to 5) for relapse prevention. The Cochrane review of haloperidol (Joy *et al*, 2006) found the relapse rate in people maintained on antipsychotic treatment approached that in those withdrawn from treatment over time, but was still consistently lower in those still on treatment at 2 years (RR 0.70, CI 0.57-0.87). Robinson *et al* (1999) examined relapse rates during the five years subsequent to initial recovery in a cohort of 104 individuals after their first episode of schizophrenia, and found a relapse rate of 82% after 5 years (CI 71%-93%). Discontinuing antipsychotic medication was the single biggest factor predicting relapse in this study, raising relapse risk nearly five-fold, with the only other

independent risk factor for relapse being a poor premorbid level of function. A more recent study by Chen and colleagues (2010) from Hong Kong studied 178 patients after they achieved remission on quetiapine following at least one year of treatment subsequent to their first episode of psychosis. Patients were randomised to either placebo or to remain on quetiapine at this point and then followed up for another year. 79% of the placebo group and interestingly 41% of the quetiapine group proceeded to relapse back into psychosis during the one year study period, with the authors noting that more discontinuations due to adverse events were seen in the quetiapine group.

Overall, there is clear evidence to justify recommending that patients with schizophrenia should remain on antipsychotic medication for two and possibly up to five years after an acute episode. Some patients will however relapse despite continued treatment and some others will only have one psychotic episode with or without subsequent treatment. Unfortunately it is difficult to identify who will and who will not relapse at treatment outset.

Antipsychotic polypharmacy

Studies have reported variable rates of regular concurrent antipsychotic prescription depending on the population considered. An Australian study (Keks *et al*, 1999), examining people receiving out-patient treatment for schizophrenia, showed a 13% rate of multiple antipsychotic prescription use, whereas a Japanese study (Ito *et al*, 1999) indicated that the rate of antipsychotic polypharmacy there exceeded 90%. Results from Glasgow contained in chapter 3 indicate a regular antipsychotic polypharmacy rate of 12% in a population of people receiving maintenance treatment for long term psychotic illnesses. Similarly, the data from

Lanarkshire (in chapter 5) suggests regular antipsychotic polypharmacy commonly occurs, varying between 8%-37% depending on which combination is looked at. Further, regular co-prescription of mood stabilisers and antidepressants with an antipsychotic happens frequently in schizophrenia (as detailed in chapter 5) with rates of antidepressant prescription exceeding 60% of cases with those on quetiapine, for example. Evidence elsewhere (Leucht *et al*, 2009) suggests that only clozapine and amisulpride of the SGAs studied have a beneficial effect on depression, as measured by the relevant items on the PANSS.

A further complication when considering antipsychotic polypharmacy is that the combinations used by clinicians are highly varied, as noted in chapters 3 and 5. This makes direct comparison between polypharmacy groups and monotherapy groups difficult because often the number of individuals on the same combination regimens are small. An audit carried out by the Prescribing Observatory for Mental Health (Royal College of Psychiatrists, 2010) found that 74% of people prescribed more than one antipsychotic were prescribed an SGA in combination with a FGA drug. These findings point to the possibility that combination of antipsychotics may even be the preferred polypharmacy practice, although Table 5 in chapter 3 notes a wide variation within antipsychotic polypharmacy between FGAs; SGAs; long acting (depot) injections; and clozapine supplementation. The literature regarding the practice of polypharmacy has generally concluded that '*except in cases where an individual has failed to respond to adequate trial of monotherapies including clozapine, antipsychotic polypharmacy has little support in the medical literature*' (Taylor, 2010). NICE (2010) does recognise that there '*are circumstances where patients and clinicians serendipitously hit upon effective combinations*'. Thus, polypharmacy should only be considered after a failed period of monotherapy,

which should include a failed adequate trial of clozapine. Interestingly a study examining previous clozapine use in those on polypharmacy surprisingly found that only 4% had been given a trial of clozapine before being commenced on polypharmacy (Miller and Craig, 2002). This suggests that polypharmacy is being considered earlier in a patient's management plan than expected and that it is not being reserved for truly treatment-resistant cases.

Despite the frequent practice of antipsychotic polypharmacy, there are few scientific studies examining the issue. A large meta-analysis including a number of studies in the Chinese literature (Correll *et al*, 2009) found a slight therapeutic advantage for antipsychotic co-therapy, but noted clear publication bias in favour of positive studies. Other evidence suggests antipsychotic polypharmacy increases time in hospital (Centorrino *et al*, 2004) and decreases cognitive performance (Elie *et al*, 2009). There is also worrying evidence that antipsychotic polypharmacy increases the risk of metabolic disturbances (Taylor *et al*, 2004).

Legitimate concerns regarding the cost; safety (including the increased likelihood of side-effects); drug-drug interactions; and the possibility of reduced adherence to complex medication regimens exist with regard to long term polypharmacy. Also the risks of unanticipated high dosing need to be borne in mind with antipsychotic polypharmacy. Similarly, the longer term effects of antipsychotic polypharmacy have not yet been fully studied and so this too is an area of concern. Waddington and colleagues (1998) found that '*the greater the maximum number of antipsychotics given concurrently, the shorter was patient survival*'. Subsequently, Joukamaa and colleagues (2006) in Finland added to Waddington's findings by demonstrating '*a graded relationship between the number of neuroleptics*

prescribed and mortality of those with schizophrenia' finding that '*those prescribed three antipsychotics simultaneously were twice as likely to die as those who were prescribed only one*'. Joukamaa *et al* (2006) also stated that this '*could not be explained by coexistent somatic disease or other risk factors known for premature death*'. These concerns exacerbate the problems of premature mortality known to exist in this population (Bushe *et al*, 2010).

Although the long-term effects of antipsychotic polypharmacy prescription are not well defined and there are worries about increasing liability to metabolic problems and premature mortality, as noted above, it is still relatively common in clinical practice as demonstrated in Chapters 3 and 5. Further long term comparisons of antipsychotic monotherapy and polypharmacy are required, particularly in terms of the risk / hazard balance of potential superior efficacy versus increased liability to side-effects.

Clozapine

Treatment resistant schizophrenia is a common clinical problem, leading to significant individual disability and costs to society. Clozapine remains the only medication licensed for treatment resistant schizophrenia, a form of chemotherapy for schizophrenia – the most effective but possibly the most toxic in class. Despite significant safety and side-effect issues noted below, clozapine continues to be widely used in clinical practice, as evidenced by the finding in chapter 3 of this thesis that 18% of all people with schizophrenia seen in secondary care in Glasgow during 2010 were on regular clozapine medication.

Prevalence estimates of treatment resistant schizophrenia vary depending upon the definition used, but up to a third of individuals with schizophrenia have a suboptimal response to adequate trials of antipsychotic medication. Studies based on prescription patterns in routine practice almost universally show a much lower proportion of individuals with schizophrenia are prescribed clozapine, which is exemplified in chapter 3 where a prescription rate of 18% is seen in a secondary care case register. The clozapine prescription rate in Italy of 1.5% has been reported (Tognoni, 2004), and in England data (Downs and Zinkler, 2007) from 41 mental health trusts showed that only 30% of those eligible were actually receiving clozapine. Low rates of clozapine use would imply only the suicidal or most refractory cases are enrolled, which in turn would reflect on the outcomes in these populations. The common alternative to clozapine is antipsychotic polypharmacy, as noted above, and which may only serve to worsen treatment resistance and add to the side effect burden.

In terms of efficacy, the previously mentioned review (Leucht *et al*, 2009) found clozapine to be the most efficacious antipsychotic compared to low dose haloperidol, and in a separate head to head comparison (Leucht *et al*, 2008) of SGAs including only double blind studies, clozapine proved superior to zotepine and to risperidone (in doses >400mg/day) but was non-superior to olanzapine and quetiapine, although this latter non-superiority was likely due to study designs that required an upper dose limit for clozapine of 400 mg/day.

The superior effectiveness for clozapine is supported by the previously reviewed CATIE and CUtLASS studies. In phase two of CATIE (McEvoy *et al*, 2006) patients were re-randomised to receive open-label clozapine or double blinded risperidone,

olanzapine, or quetiapine, mainly because of lack of therapeutic effect in phase one of CATIE. The time to all-cause medication discontinuation, the primary outcome measure, was significantly better for clozapine compared to all other drugs studied apart from olanzapine. The number needed to treat (NNT) for the all-cause discontinuation for clozapine was 4 compared to risperidone, and 3 compared to quetiapine. Clozapine was significantly superior to olanzapine; quetiapine; and risperidone in terms of time to discontinuation due to inadequate therapeutic effect. In CUtLASS2 (Lewis *et al*, 2006), 136 patients exhibiting a poor response to more than two antipsychotic agents were randomized to receive either clozapine or a non-clozapine SGA, and their quality of life was compared over one year. Clozapine was found to be significantly superior to non-clozapine SGAs with regard to symptoms, and exhibited a trend towards superiority regarding quality of life ($p=0.08$). Lastly, a large observational study (Tiihonen *et al*, 2006) from Finland also showed that following first hospitalisation for schizophrenia, individuals treated with clozapine had the lowest risk of treatment discontinuation, and of re-hospitalisation of all the 'initiated' oral antipsychotics studied.

Clozapine also seems to be a broad spectrum antipsychotic, with robust evidence of effectiveness in suicidality, aggression and substance misuse. In the US, clozapine is approved by the FDA for the management of suicidality in patients with schizophrenia or schizoaffective disorder. In addition, clozapine has been shown to have anti-aggressive properties. For example Krakowski *et al* (2006) undertook a randomized controlled trial of patients with schizophrenia who were not treatment resistant but had had confirmed episodes of assault and persistent aggression during one year of hospitalization. Clozapine was superior to both olanzapine and haloperidol in reducing the number and severity of assaults, and in

reducing overall aggression Krakowski *et al* (2006). Clozapine may also play a role in diminishing substance misuse. For example, Brunette and colleagues (2006) found after 10 years of follow up that clozapine was associated with reduced relapse of substance misuse, compared to other antipsychotics.

Clozapine use is limited by a number of troublesome adverse effects such as hypersalivation, drowsiness and constipation. Recognition of this unique clozapine associated side effect profile led to a wish to modify the GASS described in chapter 7 to specifically probe for these side-effects, and hence the 'GASS for clozapine' was created after literature review and consultation with experts in the field. This new and un-tested scale, and would be suitable for future research, 'GASS for clozapine' is illustrated in the appendix three. Life threatening side effects like myocarditis; cardiomyopathy; agranulocytosis; a lowered seizure threshold and metabolic syndrome can also occur. However, Tiihonen *et al* (2009) compared mortality in 66881 individuals versus the total population of Finland (5.2 million) over 11 years, and found that people regularly taking clozapine had the lowest risk of premature mortality compared to both those on other antipsychotics, and those on no regular medication¹⁷². This protective effect will in part be due to the anti-suicidality mentioned above, but despite its well known metabolic side-effects, death from ischaemic heart disease was no different for clozapine than any other medication studied. Recently, Kelly *et al* (2010) also found in a retrospective cohort study that the risk of cardiovascular mortality did not differ significantly in patients started on clozapine (n=1084) compared to those initiated on risperidone (n=602) over 8-10 years follow up, despite the fact that clozapine is associated with more weight gain than risperidone.

The risk of clozapine-induced leucopenia or agranulocytosis decreases exponentially over time, and after one year of treatment the incidence of agranulocytosis is nearly equivalent to that observed in phenothiazines. Monitoring of clozapine-induced blood dyscrasias has helped minimise the incidence of this serious issue. Based on data from 30 studies, Merrill and colleagues (2005) concluded that clozapine is associated with a low (~0.1%) risk of potentially fatal myocarditis or cardiomyopathy.

Clozapine can not be offered as first line therapy, partly in view of these troublesome side-effects and partly due to lack of evidence for efficacy in first episode psychosis. However, Agid *et al* (2007) were able to offer a trial of clozapine as early as 25 weeks, after patients failed to respond to two trials of SGAs following a standardised first episode psychosis programme. The treatment resistant patients, in this pragmatic study, who received clozapine did experience an improvement in symptoms (mean Brief Psychiatric Rating Scale - BPRS score decreased from 53.5 to 34.5). Those who were also treatment resistant but had refused clozapine exhibited a 2-point increase in mean BPRS score (from 53 to 55) with continued SGAs. Agid *et al* (2007) concluded, perhaps controversially, that clozapine had an important role in first episode patients who had failed to respond to SGAs in the first months of treatment.

There are concerns (Farooq and Taylor, 2011) about the under-utilisation and delayed initiation of clozapine and this may be exacerbated by suboptimal dosing. Plasma level studies generally show that higher clozapine levels correlate with an excellent clinical response, whereas lower clozapine plasma levels were associated with a poor response, suggesting that many patients require doses

greater than 400 mg. This may be further complicated high prevalence of cigarette smoking in this population, which can adversely affect serum levels.

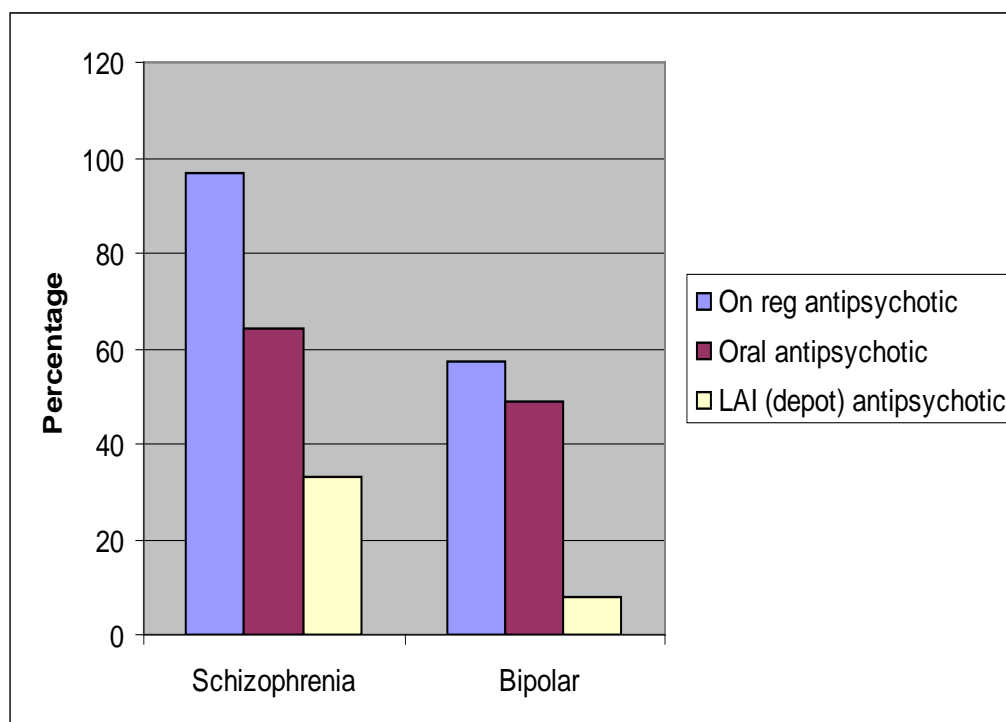
Another less well studied issue is the attitude towards clozapine in staff and patients (Taylor *et al*, 2000). Neilsen *et al* (2009) surveyed patients on clozapine and found that 87% felt the advantages of clozapine outweighed any disadvantages. However, when Neilsen *et al* (2009) systematically questioned one hundred psychiatrists regarding attitudes to clozapine, they discovered that many were reluctant to use clozapine as they felt the patients would not like it, and said they would rather combine two other antipsychotics in treatment resistant cases, emphasising the points made earlier on both the lure and perils of antipsychotic polypharmacy. Farooq and Taylor (2011) suggested that these negative beliefs may be linked to limited experience and knowledge, particularly as clozapine is now a generic drug and less actively marketed. A self perpetuating cycle can then ensue, as trainees do not see the benefits of clozapine, and do not develop confidence in its use. However, results presented in Chapters 3 and 5 of this thesis demonstrate the continued use (and thus continued perceived value) of clozapine, and in Chapter 5 there is data consistent with results from both the CATIE and CUtLASS trials that confirms clozapine's superior effectiveness compared to the most commonly employed SGAs.

Long acting injections (LAIs) or depot antipsychotics

Data from the Psycis case register (Chapter 3, and see Figure 9) reveals that the LAI usage rate in maintenance treatment in this large UK cohort is 33% for broad schizophrenia (one third of the total antipsychotic prescriptions), and 8% in bipolar

disorder (14% of the total antipsychotics prescribed). 23% of men and 18% of women receive LAI maintenance treatment in this cohort. Co-prescription of regular oral antipsychotic medication, in combination with a regular long-acting injection of antipsychotic medication occurs in a significant minority of cases, namely 24.5% of those individuals with schizophrenia, and 28% of those with bipolar disorder. Additionally, the Psycis sample described above which includes both community and hospital based patients, 15% of those individuals receiving regular LAI or depot antipsychotic were currently detained under long term treatment orders under the Mental Health Act, compared to 12% of the total sample, i.e. a negligible difference, suggesting that at the current time in Glasgow the use of LAIs is not necessarily linked to detention under the Mental Health (Scotland) Act, 2003.

Figure 9. PsyCIS cases (n=5221) use of maintenance antipsychotic medication (%) by diagnosis



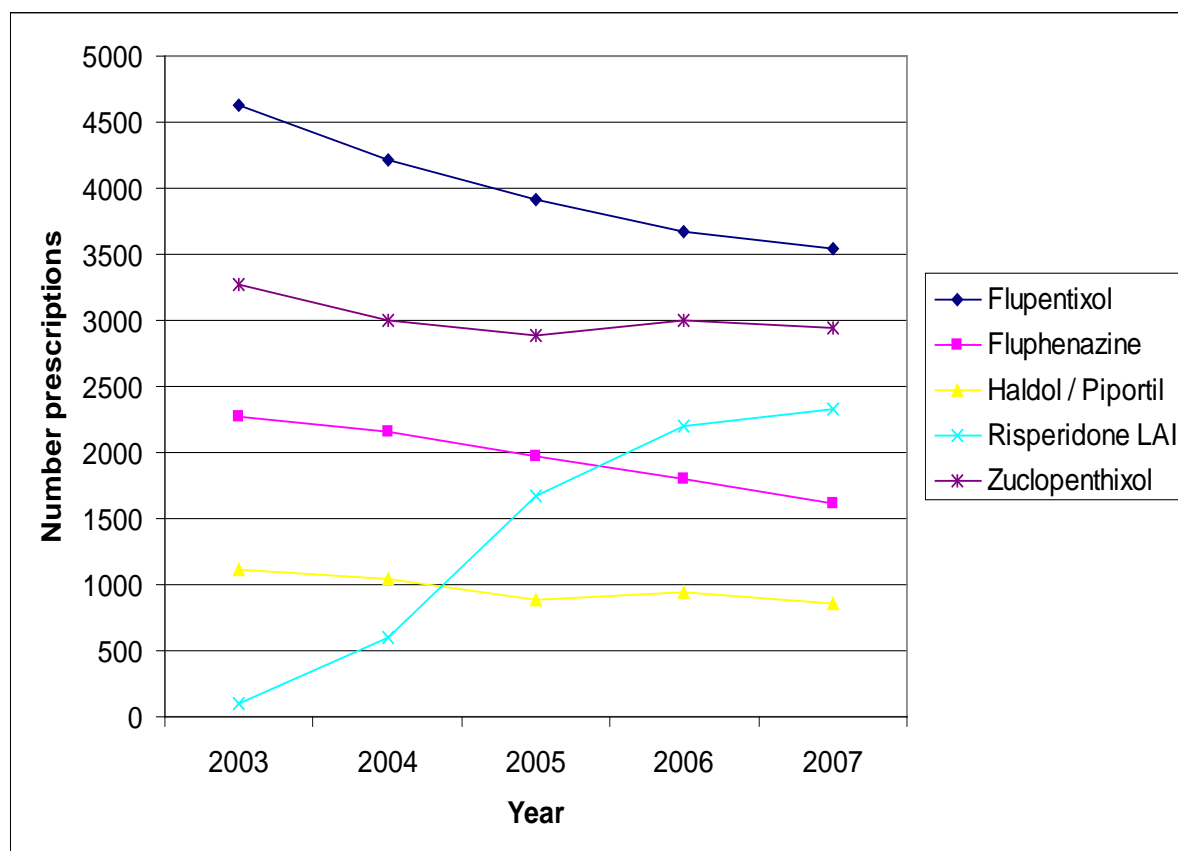
In view of the continuing frequent use of LAIs, it is valuable to review efficacy and effectiveness of LAIs. The first LAI antipsychotic medication introduced was fluphenazine enanthate, in 1966, and the second, fluphenazine decanoate, arrived some 18 months later. Early evidence (Denham *et al*, 1971; Johnson and Freeman, 1973) of the effectiveness of long acting antipsychotic medications came from two mirror image studies, with both studies showing a decrease in the number of admissions to hospital and a reduction in morbidity. A Swedish mirror image study (Gottfried and Green, 1974) also showed reduced hospitalization rates for long acting injections of flupentixol compared to the previous treatment. These mirror image studies catalysed the use of FGA-LAIs in routine clinical practice, and are summarised in greater detail in Figure 11.

Another early influential study (Hogarty *et al*, 1974) compared fluphenazine in oral and LAI forms, with and without social therapy. Importantly the study duration was two years, and the authors found that a lower relapse rate (measured by hospitalization rate) on the LAI formulation was not apparent until after one year of treatment, although the result was not statistically significant (due to small sample size). Interestingly it was the interaction between social therapy and the LAI (rather than the LAI alone) that accounted for the reduced relapse rate in year 2 compared to the oral form. A later similar study (Schooler *et al*, 1980) over 2 years confirmed that intermittent or very low dose fluphenazine decanoate was worse in preventing relapse and rehospitalisation than continuous moderate dosing (12.5 – 50mg each fortnight) regardless of family therapy.

Subsequently, the use of LAI antipsychotic maintenance treatment has become established in chronic schizophrenia, but has had a differential uptake around the

world. The patterns of individual LAI usage in Scotland over a 5 year period are depicted in figure 10. It can be seen that the introduction of risperidone LAI in Scotland in 2003 was followed by increasing use of this drug accompanied by a decrease in prescription rate of FGA-LAIs, mostly notably flupentixol decanoate. The total rate of LAI use however has remained largely unchanged in that 5 year period. Despite the introduction and increasing use of SGA-LAIs it is clear that FGA-LAIs are still widely used in routine clinical practice, as demonstrated in both Chapters 3 and 6 of this thesis.

Figure 10. Trends in individual LAI use over time, 2003-2007, in Scotland (data provided by the Information and Statistics Division (ISD) of the Scottish Government).



Comparing individual LAIs – Chapter 6

Zuclopenthixol decanoate for schizophrenia and other serious mental illnesses has been subject to a Cochrane review (da Silva Freire *et al*, 2009) which found 4 studies allowing comparison of zuclopenthixol decanoate with other long acting (depot) formulations of antipsychotic medication, and concluded that zuclopenthixol decanoate prevented or postponed relapse when compared against other long acting injections of antipsychotic (NNT= 8, CI = 5-53). However they also showed that zuclopenthixol decanoate may induce more adverse effects than the other LAIs (NNH = 5, CI = 3-31) despite a decreased need for anticholinergic medication. In summary, the authors felt there was “*a real difference*” between zuclopenthixol decanoate and the other LAIs studied, despite the limited trial data.

David *et al* (1999) studied flupentixol decanoate for schizophrenia or other similar psychotic disorders and noted there were no placebo trials and not many studies in total, but concluded there was “*nothing to choose between flupentixol decanoate and other depots*”. Furthermore, they observed that no clinical benefit accrued from dosing higher than a ‘standard’ dose of 40mg per fortnight.

When Adams and colleagues (2001) reviewed the data comparing specific FGA-LAIs, they reached the conclusion that “*there were few convincing data that any real differences exist between depots*”. Only the outcome of mental state relapse showed that zuclopenthixol decanoate was statistically superior to the control LAIs (largely fluphenazine – n=296, NNT = 8, CI= 5-53). However publication bias could not be excluded as an explanation for this finding.

The only RCT published at the time of writing that compares a FGA-LAI with a SGA-LAI is that by Rubio *et al* (2006) which compared risperidone long-acting injection (RLAI – also known as risperidone consta), to zuclopenthixol decanoate in patients with schizophrenia and co-morbid substance use (cannabis, cocaine, opiates and ecstasy). This study randomised patients who had been admitted to hospital with worsening psychosis. After stabilising their illness in hospital, 115 of 183 patients interviewed agreed to participate and were alternately allocated to RLAI (n=57) or zuclopenthixol decanoate (n=58) and followed up for 6 months as out-patients. The clinical assessors were blind to the treatment. The primary outcome measure was number of positive urine drug tests during the 6 month. Secondary outcome measures were PANSS subscales and compliance with the weekly psychotherapeutic programme. In terms of the primary outcome measures there was a statistically significant advantage with RLAI for number of positive urine drug tests (8.7 for RLAI versus 10.3 for zuclopenthixol, $p=0.005$). However, relapse rate and survival time to first positive urine drug test did not differ. PANSS scores, particularly for negative symptoms, and measures of EPS showed an advantage for RLAI. The RLAI group also demonstrated better adherence to the psychotherapeutic programme. This study by Rubio *et al* (2006) involved an important group of patients seen in routine psychiatric practice (and not just in addiction specialties) but caution should be exercised in generalising these results to all patients with schizophrenia as patients with co-morbid substance use may differ in terms of aetiology, clinical presentation and treatment response compared with those with no substance misuse disorder.

Rosenheck and colleagues (2011) have published an influential randomised comparison of RLAI with oral SGAs (viewed perhaps wrongly as a homogenous

group), and did not find any statistical superiority to RLAI over the oral SGAs in terms of treatment discontinuation over the two year study. However, this may be due to lack of power as RLAI did lead to less subsequent re-hospitalisation (36% v 43%) and less outpatient contact (122 v 136 total visits) compared to the oral SGAs. This study also failed to achieve its pre-agreed recruitment target. Lastly, clinical experience suggests that RLAI requires oral antipsychotic supplementation (ie dual oral and LAI therapy) over a period of many months possibly as a result of its novel delivery system. Performing a similar comparison with more recent SGA LAI formulations such as paliperidone palmitate will be important as these compounds may not appear to require such prolonged 'dual' oral supplementation.

Prospective observational studies have compared a LAI to one or more oral antipsychotic cohorts, and they adopted various pragmatic outcome measures including risk of readmission and time to all-cause discontinuation of medication. The results were mixed; two studies found a better outcome for FGA-LAI compared to an FGA-oral (Tiihonen *et al*, 2006; Zhu *et al*, 2008). The Schizophrenia Health Outcomes Study (SOHO), funded by the manufacturers of olanzapine, found poorer outcomes for FGA-LAI than oral olanzapine (Haro *et al*, 2007) and a fourth study (Conley *et al*, 2003) found oral antipsychotics to be superior to haloperidol decanoate but equivalent to fluphenazine decanoate.

Tiihonen *et al* (2006) assessed the outcome of patients after their first admission with schizophrenia or schizoaffective disorder in relation to the antipsychotic they were taking on discharge. Initial use of perphenazine LAI was associated with a significantly lower adjusted risk for all-cause medication discontinuation than haloperidol and the second lowest discontinuation rate of the ten drugs studied.

An analysis of rehospitalisation rates, calculated according to the ongoing antipsychotic, showed that perphenazine LAI had the lowest risk of rehospitalisation (68% reduction in fully adjusted relative risk compared to haloperidol). Interestingly, perphenazine LAI performed better on both measures than oral perphenazine.

This initial cohort study from Finland was followed up by a more recent separate study (Tiihonen *et al*, 2011) using the national data bases from 2000-2007, and contrasted oral and LAI formulations of the same individual antipsychotic agents. Oral risperidone was used as the baseline comparator compound rather than haloperidol in view of evolving clinical practice. The main findings from this large (n=2588 individuals consecutively hospitalised for the first time with schizophrenia) study were that 42% did not collect any further prescriptions in their first month after their hospital discharge, and secondly that use of LAI or depot medication reduced the risk of re-hospitalisation by 64% compared to the same molecule in oral form. Finally the use of any antipsychotic medication compared to no antipsychotic of any sort lowered overall mortality during the study period by 55%.

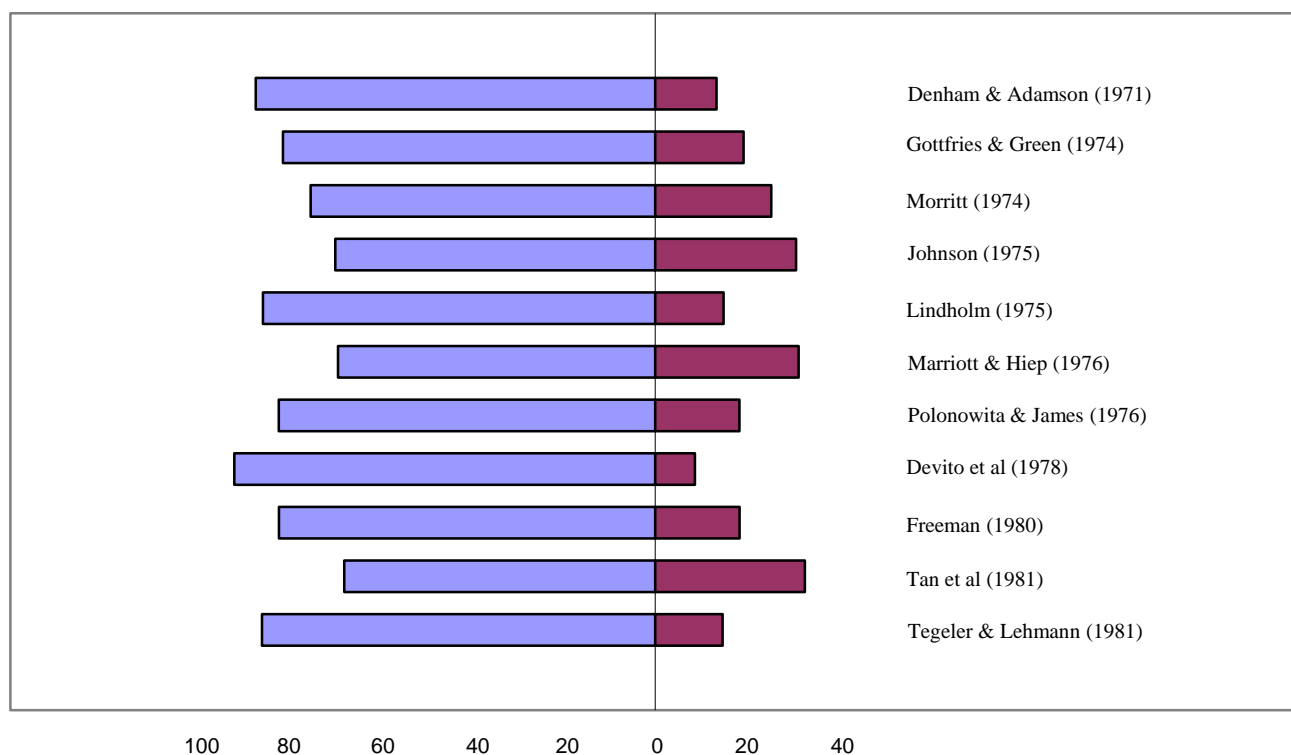
The study by Zhu *et al* (2008) used data from the US-SCAP (Schizophrenia Care and Assessment Program) study to assess the time to all-cause medication discontinuation in the first year after initiation of a FGA-LAI or oral antipsychotic. The same two antipsychotics, haloperidol and fluphenazine, in oral or LAI form were assessed, being the only two FGA-LAIs available in the United States. The LAI-group had a significantly longer mean time to all-cause medication discontinuation and patients receiving a LAI were twice as likely to remain in

treatment compared to the oral group. The SOHO study (Haro *et al*, 2007) was a 3 year observational study of patients with schizophrenia. The likelihood of not achieving remission, the risk of relapse and the all-cause discontinuation rate of medication were all higher for those treated with FGA-LAI compared to oral olanzapine. By 3 years the baseline medication had been discontinued by 36% of those who initiated treatment with olanzapine, 50% for those who initiated a FGA-LAI (and 53% for those who initiated an FGA-oral drug). Only the SOHO study presented tolerability data and this was limited to descriptive data without statistical analysis. The period-prevalence for EPS was 43% for the FGA-LAI cohort, 31% for FGA-oral cohort and for the various SGA-orals values ranged from 13% (quetiapine) to 32% (risperidone). Assessment of both EPS and TD was based on clinical judgement and not objective rating scales. The proportion of patients who gained >7% weight from baseline to medication-discontinuation was higher for FGA-LAI than FGA-oral (22% versus 16%) as was mean weight gain (2.6 kg versus 1.5kg).

Mirror image studies have been previously reviewed and analyzed in detail (Haddad *et al*, 2009). In each of the 11 mirror image studies, total inpatient days and number of admissions were lower on FGA-LAI than during the preceding treatment period, as indicated in Figure 11. Furthermore where p-values were available, or could be calculated, the differences were statistically significant. Ten (of the 11) studies provided the mean number of inpatient days for the LAI-treatment period and preceding-treatment period. Based on these 10 studies, the mean number of inpatient days per patient fell from 114.9 in the pre-FGA-LAI period to 28.6 during FGA-LAI treatment. This confirmed the conclusions of an

earlier important review (Davis *et al*, 1994) regarding the utility of LAIs in maintenance treatment of schizophrenia.

Figure 11. Summary of all mirror image studies examining time in hospital, comparing FGA-LAIs with oral antipsychotic medications (with permission, Haddad, Taylor, and Niaz). Distribution (%) of total inpatient stay between previous-treatment and FGA-LAI treatment periods for each mirror image study (n=11) with each horizontal bar totalling 100%.



Key: each blue bar represents proportionate time in hospital prior to LAI / depot, with each purple bar depicting proportionate time in hospital after commencement of LAI / depot.

Olfson *et al* (2007) used the California Medicaid database to analyse the use of fluphenazine decanoate (n=948), haloperidol decanoate (n=1631), and risperidone long acting injection (n=116) for 180 days before, and 180 days after initiating

treatment. This study was not included in the 'mirror image' section above as patients who were admitted for 14 days or more were excluded. They found few clinical or demographic differences between the three treatment groups and recent oral non-adherence was frequently seen. Only a small minority of patients continued on the three long acting injections for the full 180 days post-initiation (5%, 10%, and 3% respectively), and the authors noted that California Medicaid patients were less likely than European patients to be given a LAI for maintenance treatment, and the ones that were frequently had comorbid problems. The most striking finding of the Olfson *et al* (2007) study from the US was the extremely low continuation rate of all three LAIs over six months, coupled with supplementary oral polypharmacy.

Chapter 6 of this thesis highlighted data on people with schizophrenia, or related psychosis who were commenced on a long acting antipsychotic injection in a discreet Scottish population of ~500,000 within a defined period (2002 to 2008). An advantage of this study was that all new medication starts in the study period were included, so patients were likely to be representative of clinical populations requiring LAI treatment compared to those included into clinical trials. Risperidone long acting injection (RLAI) was the most popular choice of new start long acting injection outnumbering all the other conventional long acting injections. Compared with RLAI and flupentixol depot, patients on zuclopenthixol decanoate showed significantly better outcomes in terms of time to discontinuation (see Chapter 6) and hospitalization rates. However, fewer of those on zuclopenthixol decanoate were considered 'much improved' or 'very much improved' in terms of CGI compared with flupentixol decanoate or RLAI. These apparent contradictions may reflect the 'real world' nature of the data collection, although the data on treatment

discontinuation and re-hospitalisation are less prone to observer bias. This advantage of zuclopenthixol decanoate is consistent with the conclusion of Adams *et al* (2001) and the Cochrane review of zuclopenthixol decanoate which suggested it may have (a modest) superiority over other FGA-LAIs. The finding that zuclopenthixol decanoate was superior to RLAI is contrary to the findings of the Rubio *et al* (2006) study mentioned above, and the findings in Chapter 6 represent the only other known direct head-to-head comparison of new versus old LAI or depot antipsychotics. However, the limitations of the retrospective non-randomised design in Chapter 6 mean these findings need to be viewed cautiously.

Further research is warranted especially given the cost differential of SGA-LAIs compared to FGA-LAIs, as more SGA-LAIs are being licensed in the UK. Future studies involving LAIs should be of adequate duration to assess relapse, for example 18 months or more, and outcome measures should include relapse, symptomatic improvement and a range of adverse effects including EPS, TD, weight gain and metabolic parameters. Patient satisfaction and cost-effectiveness also need to be examined. To reduce the problem of selective recruitment such studies should be pragmatic and have minimal exclusion criteria.

Conclusions and implications for clinical practice

RCTs; meta-analyses; and observational studies have their individual strengths and weaknesses and reviewing all these study designs together provides the most comprehensive context for the data contained in Chapters 3 to 6.

Several large randomized trials in schizophrenia, including the Clinical Antipsychotic Trial of Intervention Effectiveness (CATIE), have confirmed that although antipsychotics differ markedly in their side-effect profiles they are broadly similar in terms of efficacy in schizophrenia, and this is reflected in the data contained in Chapters 4 and 5, with the notable exception of clozapine. The debate over the false dichotomy between SGAs and FGAs, or atypical and typical antipsychotics has largely moved on (Kendall, 2011) with the conclusions of the most recent meta-analyses (Leucht *et al*, 2009; Crossley *et al*, 2010) confirming a lack of class homogeneity and small or modest differences in efficacy. These studies also demonstrate that the commonly prescribed antipsychotics are easily differentiated by side-effect profile, with the broad distinction being that the older FGAs more likely lead to EPS whereas the newer SGAs are more liable to cause adverse metabolic shifts. However, the differentiation (albeit modest) of three of the SGAs in terms of efficacy according to the strongest meta-analysis available (Leucht *et al*, 2009) – namely amisulpride; olanzapine; and risperidone – from the other SGAs and low dose haloperidol prompts the interesting proposition that in a long term condition such as schizophrenia perhaps even a modest efficacy difference is worth taking seriously, particularly as all these three compounds are now generic (ie cheap). These considerations on efficacy do need to be balanced by the much larger side-effect profile differentials between individual antipsychotics noted above.

The exception to this debate is clozapine, which has superior efficacy and effectiveness (as demonstrated in Chapter 5) but is only licensed for treatment resistant schizophrenia. As observed above, the figures on clozapine usage in Chapter 3 are reassuring but the data elsewhere suggests that clozapine is used

too little or too late (see above). Furthermore, as it is a 'difficult' medication for both patient and clinician in terms of initiation and regular blood monitoring, this can act as a disincentive to clozapine use, and trainee psychiatrists are at risk of not obtaining adequate experience or confidence in the use of clozapine.

There is no sign of an imminent major efficacy breakthrough in antipsychotic development. This means that ensuring the optimum benefit from current antipsychotics is important and for many patients this means improving medication adherence. Although poor adherence has long been seen as a problem in schizophrenia, many thought it would lessen following the introduction of the oral SGAs in the 1990s. This did not happen. Indeed a key finding of the CATIE and related studies was that even in a highly supported clinical trial, patient retention rates on a range of oral SGAs were disappointingly low. This problem of long term adherence to medication is emphasised by the findings of the observational studies which consistently demonstrate low levels of prescription pick up or high rates of discontinuation for antipsychotics. This is important not just in terms of relapse prevention but also in reducing associated morbidity and mortality. From a managerial perspective, clinical strategies that reduce the need for recurrent hospitalisation are also important as up to 70% of the direct costs in mental healthcare are associated with in-patient psychiatric care. It is also worth pointing out that poor medication adherence is a major challenge not just in schizophrenia but in all long term medical disorders such as diabetes mellitus, chronic obstructive airways disease, and hypertension.

LAIs provide one way, although not the only way, to improve adherence. The main advantages of LAIs are that they eliminate covert non-adherence, can improve

adherence, and can be a more convenient way of taking medication for some patients. LAIs do have disadvantages and some patients find it unacceptable to receive medication by injection. In addition adherence can be poor with an LAI just as it can with oral medication, but the key difference is that non-adherence with an LAI is overt. Good adherence with a LAI, as with any drug, requires the prescribing decision to be the result of shared decision-making by the patient and prescriber. Prescribing an LAI in isolation will do little to overcome adherence problems as a LAI does not remove the need to ensure that other elements of care are provided. As newer LAIs become available it will be important to understand their advantages and disadvantages compared with 'treatment as usual'. At this time the extant data suggests comparable efficacy between LAIs with the only exception being some modest data in Chapter 6 and from Adams and colleagues (2001) suggesting that a moderate dose of zuclopenthixol decanoate may be more effective than some other LAIs. The evidence also suggests that a broader range of patients with psychosis could benefit from the LAI formulations of antipsychotics. For example, studies by Tiihonen *et al* (2006, 2009) concluded that LAIs can be of benefit early in the course of schizophrenia compared to oral antipsychotics, notwithstanding possible concerns over coercion and autonomy. However, clinicians can regard LAIs as a treatment of last resort (Waddell and Taylor, 2009) and only use them when the risk of relapse is perceived as high.

Patient safety is an essential consideration at an individual and at a service level – "*first do no harm*". This final Chapter has reviewed the literature on antipsychotic discontinuation and on the side-effect profiles associated with individual antipsychotics. Screening for adverse medication effects should cover the full range of potential adverse effects including weight gain and metabolic

abnormalities and ideally should occur in a systematic manner using a practical but valid scale. It is worth noting that since the GASS was developed, as described in Chapter 7, it has become widely adopted around the UK. This is in part due to GASS being cost-free to use and reproduce; being independent from the pharmaceutical industry; and because effort was made to make it accessible via use of plain English with it contained on only one side of A4 paper. The GASS is no more discriminating than LUNSERS but does contain probes on metabolic related symptoms, and is arguably more user friendly. GASS needs to be studied in other centres, and has not been subject to principal components analysis or an objective validation of individual items (eg whether self report weight gain or tremor correlates with objective assessment).

The best outcome in most major psychiatric disorders requires an optimized pharmacological treatment to be put in place so that psychological and social treatments can be built around the patient's individual needs for their recovery. Good clinical practice suggests that the decision to use a specific antipsychotic for a particular patient should be made at an individual level, reflecting the evidence base and being an informed decision jointly made by the clinician and patient.

Directions for future research

1. How can clinicians target their antipsychotic treatments more effectively?

There seems to be little data to guide prescriber choice on which patient characteristics, either demographic; clinical; or genetic might inform potential therapeutic response to a specific medication. Currently, this is where the art of psychiatry meets the scientific evidence base, with some of

the data described above on relative efficacy and side-effects being useful but each prescription essentially representing an individualised experiment.

2. How can clinicians measure response to treatment in busy routine practice?

This thesis has demonstrated that a simple 'severity index' such as the Clinical Global Impression scale may be pragmatic but valid enough for use in busy day-to-day practice even though concerns regarding inter-rater reliability need to be addressed. A side-effect scale such as the GASS (see Chapter 7) can also facilitate systematic medication review. Elsewhere in medicine, recording of outcomes in routine clinical practice is more usual, and this should be encouraged in mental health care.

3. Are newer long acting injections of antipsychotic medications superior to the older LAIs, or to oral antipsychotics?

The evidence reviewed above, including the original data in Chapter 6, is not conclusive on this question so a pragmatic independent trial of sufficient duration would add value to the evidence base. In particular there is a notable dearth of new versus old LAI head-to-head scientific comparisons.

4. Is antipsychotic polypharmacy helpful or harmful?

As seen above, the practice of antipsychotic polypharmacy remains common in the UK and elsewhere despite the lack of supporting scientific data. Furthermore, concerns about the adverse health risks of antipsychotic polypharmacy have been noted, so a prospective study of the possible benefits and risks of this practice would be valuable.

REFERENCES

- Adams CE, Awad G, Rathbone J, Thornley B. Chlorpromazine versus placebo for schizophrenia. *Cochrane Database Syst Rev.* 2007 18;(2):CD000284.
- Adams CE, Fenton MKP, Quraishi S, David AS. Systematic meta-review of depot antipsychotic drugs for people with schizophrenia. *Br J Psychiatry.* 2001. 179, 290 – 9.
- Agid O, Remington G, Kapur S, Arenovich T, Zipursky R. Early Use of Clozapine for Poorly Responding First-Episode Psychosis. *J Clin Psychopharm.* 2007; 27(4):369-73
- Allardyce J, Boydell J. Review: the wider social environment and schizophrenia. *Schizophr Bull* 2006; 32(4):592-8.
- Als-Nielsen BI, Chen W, Gluud C, Kjaergard L. Association of funding and conclusions in randomized drug trials: a reflection of treatment effect or adverse events? *JAMA.* 290(7):921-8, 2003 Aug 20.
- Barnes TR. A rating scale for drug-induced akathisia. *Br J Psychiatry* 1989. 154: 672-676
- Barnes TR. Evidence-based guidelines for the pharmacological treatment of schizophrenia: recommendations from the British Association for Psychopharmacology. *J Psychopharmacol;* 25(5):567-620.
- Barnes TR, Shingleton-Smith A, Paton C. Antipsychotic long-acting injections: prescribing practice in the UK. *Br J Psychiatry* 2009; 195 (suppl 52): s37–42
- British National Formulary, 2011. <http://bnf.org>
- Brunette MF, Drake RE, Xie H, McHugo GJ, Green AI. Clozapine use and relapses of substance use disorder among patients with co-occurring schizophrenia and substance use disorders. *Schizophr Bull* 2006; 32: 637
- Bushe CJ, Taylor M, Haukka J. Mortality in schizophrenia: a measurable clinical endpoint. *J Psychopharmacol* 2010;24:17-25
- Butzlaff RL, Hooley JM. Expressed emotion and psychiatric relapse: a meta-analysis. *Arch Gen Psychiatry* 1998; 55:547–52.
- Cantwell R. Substance use and schizophrenia: effects on symptoms, social functioning and service use. *Br J Psychiatry* 2003; 182:324-9.
- Centorrino F, Goren JL, Hennen J *et al.* Multiple versus single antipsychotic agents for hospitalised psychiatric patients. Case control study of risks versus benefits. *Am J Psychiatry* 2004; 161: 700-6.
- Chen EY, Hui CL, Lam MM, Chiu CP, Law CW, Chung DW, *et al.* Maintenance treatment with quetiapine versus discontinuation after one year of treatment in patients with remitted first episode psychosis: randomised controlled trial. *BMJ* 2010. 341:c4024
- Citrome L and Stroup ST. Schizophrenia, Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) and number needed to treat: how can CATIE inform clinicians? *Int J Clin Pract.* 2006; 60, 8: 933-940
- Conley RR, Kelly DL, Love RC, McMahon RP. Rehospitalization risk with second-generation and depot antipsychotics. *Ann Clin Psychiatry* 2003; 15: 23–31
- Conley RR and Mahmoud R. A randomised double blind study of risperidone and olanzapine in the treatment of schizophrenia or schizoaffective disorder. *Am J Psychiatry* 2001; 158: 765-774.

- Correll CU, Rummel-Kluge C, Corves C, Kane JM, Leucht S. Antipsychotic combinations vs monotherapy in schizophrenia: a meta-analysis of randomized controlled trials. *Schizophr Bull* 2009; 35: 443-57
- Correll CU, Schenk EM. Tardive dyskinesia and new antipsychotics. *Current Opinion in Psychiatry* 2008. 21, 151–156.
- Crow TJ, MacMillan JF, Johnson AL, Johnstone EC. A randomised controlled trial of prophylactic neuroleptic treatment. *Br J Psychiatry* 1986; 148:120–7.
- Crossley N, Constante M, McGuire P, and Power P. Efficacy of atypical v. typical antipsychotics in the treatment of early psychosis: meta-analysis. *Brit J Psychiatry*. 2010. 196: 434-439.
- Csernansky JG, Schuchart EK. Relapse and rehospitalisation rates in patients with schizophrenia: effects of second generation antipsychotics. *CNS Drugs* 2002; 16:473–84.
- da Silva Freire Coutinho E , Fenton M , Quraishi , S N . Zuclopenthixol decanoate for schizophrenia and other serious mental illnesses. *Cochrane Database Syst Rev* 2009 (3), CD001164
- David A, Adams CE, Quraishi SN. Depot flupenthixol decanoate for schizophrenia or other similar psychotic disorders. *Cochrane Database Syst Rev*, 1999. CD001470
- Davis JM and Chen N. Dose response and dose equivalence of antipsychotics. *J Clin Psychopharmacology* 2004; 24: 192-208
- Davis J, Chen N, and Glick I. A meta-analysis of the efficacy of second generation antipsychotics. *Arch Gen Psychiatry*. 2003; 60: 553-564.
- Davis JM, Chen N and Glick ID. Issues that may determine the outcome of antipsychotic trials: industry sponsorship and extrapyramidal side effect. *Neuropsychopharmacology* 2008. 33: 971–975
- Davis JM, Matalon L, Watanabe MD, Blake L. Depot antipsychotic drugs. Place in therapy. *Drugs*. 1994. 47 (5), 741 – 73
- Davis JM, Kane JM, Marder SR et al. Dose response of prophylactic antipsychotics. *J Clin Psychiatry*. 1993. 54 (3 suppl) 24-30
- Davis JM, Janicak PG, Singla A, Sharma RP: Maintenance antipsychotic medication, in *Antipsychotic Drugs and Their Side Effects*. Edited by Barnes TRE. New York, Academic Press, 1993, pp 182–203
- Day JC, Wood G, Dewey M, Bentall RP. A Self-rating scale for measuring neuroleptic side-effects. Validation in a group of schizophrenic patients. *Br J Psychiatry* 1995.166: 650-653
- Denham, J. and Adamson,L. The Contribution of Fluphenazine Enanthate and Decanoate in the Prevention of Readmission of Schizophrenic Patients. *Acta Psychiatrica Scandinavica*, 1971. 47, 420-430
- Dolder CR, Lacro JP, Dunn LB, Jeste DV. Antipsychotic medication adherence: is there a difference between typical and atypical agents? *Am J Psychiatry* 2002; 159:103–8.
- Downs and Zinkler. Clozapine: national review of postcode prescribing. *The Psychiatrist* 2007, 31, 384-387.22
- Drake RJ, Haley CJ, Akhtar S, Lewis SW. Causes and consequences of duration of untreated psychosis in schizophrenia. *Br J Psychiatry* 2000; 177:511-5.
- Eagles JM, Gibson I, Bremner MH, Clunie F, Ebmeier KP, Smith NC. Obstetric complications in DSM-III schizophrenics and their siblings. *Lancet* 1990; 335(8698):1139-41.

- Eaton WW, Thara R, Federman E, Tien A. Remission and relapse in schizophrenia: the Madras Longitudinal Study. *J Nerv Ment Dis* 1998; 186:357–63.
- Eberhard J, Riley F, Levander S. Premorbid IQ and schizophrenia. Increasing cognitive reduction by episodes. *Eur Arch Psychiatry Clin Neurosci* 2003; 253:84–8.
- Elie D, Poirier M, Chianetta J, Durand M, Gregoire C, Grignon S. Cognitive effects of antipsychotic dosage and polypharmacy: a study with the BACS in patients with schizophrenia and schizoaffective disorder. *J Psychopharmacol* 2009; doi: 10.1177/0269881108100777 .
- Essock SM, Hargreaves WA, Covell NH, Goethe J. Clozapine's effectiveness for patients in state hospitals: results from a randomized trial. *Psychopharmacology Bulletin* 1996; 32:683-97.
- Falcone T, Mishra L, Carlton E, Lee C, Butler RS, Janigro D, et al. Suicidal behavior in adolescents with first-episode psychosis. *Clin Schizophr Relat Psychoses*; 2007. 4(1):34-40.
- Farooq S and Taylor M. Clozapine: dangerous orphan or neglected friend? *Br J Psychiatry* 2011. 198, 1–3. doi: 10.1192.
- Fenton WS, McGlashan TH. Natural history of schizophrenia subtypes. I. Longitudinal study of paranoid, hebephrenic, and undifferentiated schizophrenia. *Arch Gen Psychiatry* 1991; 48:969–77.
- Fenton WS, McGlashan TH. Natural history of schizophrenia subtypes. II. Positive and negative symptoms and long-term course. *Arch Gen Psychiatry* 1991; 48:978–86.
- Fleischhacker WW, McQuade RD, Marcus RN, Archibald D, Swanink R, Carson WH. A double-blind, randomized comparative study of aripiprazole and olanzapine in patients with schizophrenia. *Biol Psychiatry*. 2009;15:510-7.
- Fuller RG. Hospital departures and readmissions among mental patients during the fifteen years following first admission. *Psychiatr Q* 1930; 4:642–89.
- Geddes J, Freemantle N, Harrison P, Bebbington P. Atypical antipsychotics in the treatment of schizophrenia: systematic overview and meta-regression analysis. *BMJ* 2000; 321:1371-
- Geddes JR, Goodwin GM, Rendell J, et al. Lithium plus valproate combination therapy versus monotherapy for relapse prevention in bipolar I disorder (BALANCE): a randomised open-label trial. *Lancet* 2010; 375: 385–95.
- Geddes J, Newton R, Young G, Bailey S, Freeman C, Priest R. Comparison of prevalence of schizophrenia among residents of hostels for homeless people in 1966 and 1992. *BMJ*. 1994; 308 (6932):816-9.
- Gilchrist A, Taylor M, Wright M, Drury K, Short A, Steel R, Murray P and Lawrie S. Is olanzapine clinically effective? A naturalistic outcome survey in two hospital settings. *Pharmaceutical Journal* 2002. 269, 222-5.
- Gilbert P, Harris J, McAdams LA, Jeste DV. Neuroleptic withdrawal in schizophrenia. Review of the literature. *Arch Gen Psychiatry* 1995. 52, 173–188.
- Gottfries, G.C. and Green, L. Fluphenazine Decanoate in the Treatment of Outpatients. *Acta Psychiatrica Scandinavica*, 1974. Suppl. 225, 15-23.
- Gumley AI. *PhD thesis*. University of Glasgow, 2003.
- Guy, W.B., 1970. Manual for the ECDEU Assessment Battery, (2 edn). National Institute of Mental Health, Chevy Chase, Md.
- Haddad PM, Taylor M, Niaz OS. First-generation antipsychotic long-acting injections v. oral antipsychotics in schizophrenia: systematic review of randomised controlled trials and observational studies. *Br J Psychiatry*. 2009. 195, S20 – 8.

Hamer M, Stamatakis E, and Steptoe A. Psychiatric Hospital Admissions, Behavioural Risk Factors, and All Cause Mortality. *Arch Intern Med*. 2008. 168 (22): 2474-2479.

Haro JM, Suarez D, Novick D, Brown J, Usall J, Naber D. Three-year antipsychotic effectiveness in the outpatient care of schizophrenia: observational versus randomized studies results. *Eur Neuropsychopharmacol* . 2007, 17, 235 – 44

Harrison G, Hopper K, Craig T *et al*. Recovery from psychotic illness: a 15- and 25-year international follow-up study. *Br J Psychiatry* 2001; 178:506–17.

Hegarty JD, Baldessarini RJ, Tohen M, Wateraux C, Oepen G. One hundred years of schizophrenia: a meta-analysis of the outcome literature. *Am J Psychiatry* 1994;151:1409–16

Heres S, Davis J, Maino K *et al*. Why olanzapine beats risperidone, risperidone beats quetiapine, and quetiapine beats olanzapine: an exploratory analysis of head to head comparison studies of second generation antipsychotics. *Am J Psychiatry* 2006; 163 (2): 185-94.

Hickling FW, McCallum M, Nooks L, Rodgers-Johnson P. Outcome of first contact schizophrenia in Jamaica. *West Indian Med J* 2001; 50:194–7.

Hodgson RE, Bushe C & Hunter R. Measurement of long-term outcomes in observational and randomized controlled trials. *Br J Psychiatry*. 2007. S50, s78-s84.NH

Hogarty, G.E., Goldberg, S.C. and Schooler, N.R. Drug and Sociotherapy in the Aftercare of Schizophrenic Patients: Two Year Relapse Rates. *Arch Gen Psychiatry*. 1974. 31, 603-8.

Hor K, Taylor M. Suicide and schizophrenia: a systematic review of rates and risk factors. *J Psychopharmacol*; 2010. 24 (4 Suppl):81-90.

<http://www.scotland.gov.uk/Topics/Statistics/SIMD>

<http://www.scotpho.org.uk/web/site/home/comparativehealth/profiles>

<http://www.statsdirect.com>. Issue 1.8.9, StatsDirect Ltd, 11 Gresham Way, Sale, UK.

Hunt GE, Bergen J, Bashir M. Medication compliance and comorbid substance abuse in schizophrenia: impact on community survival 4 years after a relapse. *Schizophr Res* 2002; 54:253–64.

ICD10 Classification of Mental & Behavioural Disorders, W.H.O. 1992

Ito C, Kubota Y, Sato M. A prospective survey on drug choice for prescriptions for admitted patients with schizophrenia. *Psychiatry Clin Neurosci* 1999; 53 (suppl): S35-40.

Jablensky A, McGrath J, Herman H, Castle D, Gureje O, Evans M, Carrv, Morgan V, Korten A, and Harvey C. Psychotic disorders in urban areas: an overview of the study on low prevalence disorders. *Aust N Z J Psychiatry*. 2000. 34(2): 221-36.

Janssen I, Krabbendam L, Bak M, Hanssen M, Vollebergh W, de Graaf R, *et al*. Childhood abuse as a risk factor for psychotic experiences. *Acta Psychiatr Scand* 2004; 109(1):38-45.

Johnson DAW. and Freeman, HL. Drug Defaulting by Patients on Long-Acting Phenothiazines. *Psychological Medicine*. 1973. Vol 3, No. 1, 115-119.

Jones PB, Barnes TRE, Davies L, *et al*. Randomized Controlled Trial of the Effect on Quality of Life of Second- vs First-Generation Antipsychotic Drugs in Schizophrenia: Cost Utility of the Latest Antipsychotic Drugs in Schizophrenia Study (CUtLASS 1). *Arch Gen Psychiatry*, 2006. 63, 1079-1087.

Jorgensen A, Teasdale TW, Parnas J, Schulsinger F, Schulsinger H, Mednick SA. The Copenhagen high-risk project. The diagnosis of maternal schizophrenia and its relation to offspring diagnosis. *Br J Psychiatry* 1987; 151:753–7.

Joukamaa M, Heliövaara M, Knekt P, Aromaa A, Raitasalo R, Lehtinen V. Schizophrenia, neuroleptic medication and mortality. *Br J Psychiatry* 2006; 188: 122-7.

Joy CB, Adams CE, Lawrie SM. Haloperidol versus placebo for schizophrenia. Cochrane Database Syst Rev. 2006;(4):CD003082.

Kahn RS, Fleischhacker WW, Boter H, Davidson M, et al. Effectiveness of antipsychotic drugs in first-episode schizophrenia and schizophreniform disorder : an open randomised clinical trial. *Lancet* 2008. 371, 1085–1097.

Kane JM. Drug therapy – schizophrenia. *N Eng J Med*. 1996. 334, 1. 34-41.

Karatzias T, Gumley A, Power K, O'Grady M. Illness appraisals and self-esteem as correlates of anxiety and affective comorbid disorders in schizophrenia. *Compr Psychiatry* 2007; 48(4):371-5.

Keks NA, Alston K, Hope J, Krapivensky N, Culhane C, Tanaghow A, et al. Use of antipsychosis and adjunctive medications by an inner urban community psychiatric service. *Aust N Z J Psychiatry* 1999; 33: 896-901.

Kelly DL, McMahon RP, Liu F, Love RC, Wehring HJ, Shim JC, et al. Cardiovascular disease mortality in patients with chronic schizophrenia treated with clozapine: a retrospective cohort study. *J Clin Psychiatry*. 2010; 71(3):304-11

Kendall T. The rise and fall of the atypical antipsychotics. *Br J Psychiatry*. 2011 199:266-268

Kraepelin E. *Dementia praecox and paraphrenia*. Munich, Germany: 1919

Krakowski M, Czobor P, Citrome L, et al. Atypical antipsychotic agents in the treatment of violent patients with schizophrenia and schizoaffective disorder. *Arch Gen Psychiatry*. 2006; 63(6):622-629.

Lambert M, Conus P, Eide P, Mass R, Karow A, Moritz S, Golks D, Naber D. Impact of present and past antipsychotic side effects on attitude toward typical antipsychotic treatment and adherence. *European Psychiatry* . 2004.19:415-422

Lang FH, Johnstone EC, Murray GD. Service provision for people with schizophrenia. II. Role of the general practitioner. *Br J Psychiatry* 1997.171:165-8.

Langan J, Shajahan P. Antipsychotic polypharmacy: review of mechanisms, mortality and management. *Psychiatrist* 2010 ; 34: 58 -62.

Lawrie SM, Johnstone EC In: Johnstone et al (Eds). Schizophrenia and related disorders. *Companion to Psychiatric Studies* Churchill Livingstone: Edinburgh 2011:391-427.

Leucht S, Corves C, Arbter D, Engel RR, Li C and Davis JM. Second-generation versus first-generation antipsychotic drugs for schizophrenia: a meta-analysis. *Lancet* 2009. 373: 31–41

Leucht S, Heres S, Kissling W, Davis JM. Evidence-based pharmacotherapy of schizophrenia. *Int J Neuropsychopharmacol* 2011; 14(2): 269-84.

Leucht S, Komossa K, Rummel-Kluge C, Corves C, Hunger H, Schmid F et al. A Meta-Analysis of Head-to-Head Comparisons of Second-Generation Antipsychotics in the Treatment of Schizophrenia. *Am. J. Psychiatry* 2008; 166:152-163.

Leucht S, Wahlbeck K, Hamann J, Kissling W: New generation antipsychotics versus low-potency conventional antipsychotics: a systematic review and meta-analysis. *Lancet* 2003; 361: 1581–1589

Levine, S.Z., Rabinowitz J, Engel R et al., Extrapolation between measures of symptom severity and change: An examination of the PANSS and CGI, *Schizophr. Res.* 2007, doi:10.1016/j.schres.2007.09.006

- Lewis SW, Barnes TRE, L, Davies L. et al. Randomised control trial of effect of prescription of clozapine versus other second-generation antipsychotic drugs in resistant schizophrenia. *Schizophrenia Bulletin*, 2006. 32, 715-723.
- Lewis SW, Buchanan RW. *Fast Facts – Schizophrenia*, 2nd edition. Oxford: Health Press, 2003.
- Lieberman JA, Stroup TS, McEvoy JP *et al.* Effectiveness of antipsychotic drugs in patients with chronic schizophrenia. *N Eng J Med* 2005; 353:1209-1223.
- Li C, Xia J, Wang J. Risperidone dose for schizophrenia. Cochrane Database of Systematic Reviews 2009; 4.
- Liu X, De Haan S. Chlorpromazine dose for people with schizophrenia. Cochrane Database of Systematic Reviews 2009; 2.
- Lowe-Ponsford F, Baldwin D. Off label prescribing by psychiatrists. *Psychiatric Bulletin* 2000 24: 415-7.
- Mallinckrodt, C.H., Sanger, T.M., Dube, S., et al (2003) Assessing and interpreting treatment effects in longitudinal clinical trials with missing data. *Biological Psychiatry*, 15, 754-760.
- Mangalore R, Knapp M. Cost of Schizophrenia in England. PSSRU Discussion Paper 2006
- Marder SR, Glynn SM, Wirshing WC et al. Maintenance treatment of schizophrenia with risperidone or haloperidol: 2 year outcomes. *Am J Psychiatry* 2003; 160:1405–1412
- Marshall M, Lewis S, Lockwood A, Drake R, Jones P, Croudace T. Association between duration of untreated psychosis and outcome in cohorts of first-episode patients: a systematic review. *Arch Gen Psychiatry* 2005; 62(9):975-83.
- McEvoy JP, Lieberman JA, Stroup TS *et al.* Effectiveness of clozapine versus olanzapine, quetiapine, and risperidone in patients with chronic schizophrenia who did not respond to prior atypical antipsychotic treatment. *Am J Psychiatry* 2006; 163: 600-610
- McGlashan TH. The Chestnut Lodge follow-up study. II. Long-term outcome of schizophrenia and the affective disorders. *Arch Gen Psychiatry* 1984; 41:586–601.
- McGuffin P, Farmer AE, Gottesman II, Murray RM, Reveley AM. Twin concordance for operationally defined schizophrenia. Confirmation of familiarity and heritability. *Arch Gen Psychiatry* 1984; 41:541–5.
- McKenzie K, Samele C, van Horn E, Tattan T, van Os J, Murray R. Comparison of the outcome and treatment of psychosis in people of Caribbean origin living in the UK and British Whites. Report from the UK700 trial. *Br J Psychiatry* 2001; 178:160–5.
- McKenzie K, van Os J, Fahy T *et al.* Psychosis with good prognosis in Afro-Caribbean people now living in the United Kingdom. *BMJ* 1995; 311:1325–8.
- Leff J, Sartorius N, Jablensky A, Korten A, Ernberg G. The International Pilot Study of Schizophrenia: five-year follow-up findings. *Psychol Med* 1992; 22:131–45.
- McNulty SV, Duncan L, Semple M, Jackson GA, Pelosi AJ. Care needs of elderly people with schizophrenia. Assessment of an epidemiologically defined cohort in Scotland. *Br J Psychiatry* 2003; 182: 241-7.
- Medcalc Software, Mariakerke, Belgium. www.medcalc.be
- Menezes PR, Johnson S, Thornicroft G *et al.* Drug and alcohol problems among individuals with severe mental illness in south London. *Br J Psychiatry* 1996; 168:612–9.
- Merrill DB, Dec GW, Goff DC. Adverse cardiac effects associated with clozapine. *J Clin Psychopharmacol.* 2005; 25(1):32-41.

Miller AL, Craig CS. Combination antipsychotics: pros, cons, and questions. *Schizophr Bull* 2002; 28: 105-9.

Miller PM, Byrne M, Hodges A, Lawrie SM, Johnstone EC. Childhood behaviour, psychotic symptoms and psychosis onset in young people at high risk of schizophrenia: early findings from the Edinburgh high risk study. *Psychol Med* 2002; 32(1):173-9.

Miller P, Lawrie SM, Hodges A, Clafferty R, Cosway R, Johnstone EC. Genetic liability, illicit drug use, life stress and psychotic symptoms: preliminary findings from the Edinburgh study of people at high risk for schizophrenia. *Soc Psychiatry Psychiatr Epidemiol* 2001; 36(7):338-42.

Mojtabai R, Nicholson RA. Interrater reliability of ratings of delusions and bizarre delusions. *Am J Psychiatry* 1995; 152:1804-6

Morgan C, Kirkbride J, Leff J, Craig T, Hutchinson G, McKenzie K, et al. Parental separation, loss and psychosis in different ethnic groups: a case-control study. *Psychol Med* 2007; 37(4):495-503.

Negi R. A randomized controlled study to determine whether the use of LUNTERS improves clinician awareness. Abstract presented at Royal College of Psychiatrists' General & Community Faculty meeting, Newcastle, 2007.

NICE. CORE INTERVENTIONS IN THE TREATMENT AND MANAGEMENT OF SCHIZOPHRENIA IN ADULTS IN PRIMARY AND SECONDARY CARE (UPDATED EDITION). 2010.

Nielsen J, Dahm M, Lublin H, and Taylor D. Psychiatrists' attitude towards and knowledge of clozapine treatment. *J Psychopharmacology* 2009. doi:10.1177/0269881108100320.

NIMHE. *Early intervention for people with psychosis*. Leeds: National Institute for Mental Health in England, 2003.

Olfson M, Marcus SC, Ascher-Svanum H. Treatment of schizophrenia with long-acting fluphenazine, haloperidol, or risperidone. *Schiz Bulletin*, 2007. 33 (6), 1379 – 87.

Owens DC. How CATIE brought us back to Kansas: a critical re-evaluation of the concept of atypical antipsychotics and their place in the treatment of schizophrenia. *Advances in Psychiatric Treatment*. 2008, 14: 17-28.

Park J, McAlaney C, and Connolly M. Improving patient care and clinical governance through utilisation of a clinical information system. *Clinical Governance*. 2008. 13, 4. 254-59.

Patel MX and David AS. Medication adherence: predictive factors and enhancement strategies. *Psychiatry* 2007. 6: 357-361

Patel MX, Taylor M, David AS. Antipsychotic long-acting injections: mind the gap. *Br J Psychiatry* 2009 (Suppl.) 52, S1–S4.

Paton C, Barnes TRE, Cavanagh MR, Taylor D, Lelliott P, and the POMH-UK project team. High-dose and combination antipsychotic prescribing in acute adult wards in the UK: the challenges posed by p.r.n. prescribing. *Br J Psychiatry* 2008 192:435-439; doi:10.1192

Paton C, Lelliott P, Harrington M *et al*. Patterns of antipsychotic and anticholinergic prescribing for hospital inpatients. *J Psychopharmacol* 2003; 17 (2): 223-9.

Perera G, Soremekun M, Breen G, and Stewart R. The psychiatric case register: noble past, challenging present, but exciting future. *Br J Psychiatry* 2009. 195: 191-193

Pinikahana J, Happell B, Taylor M, Keks NA. Exploring the complexity of compliance in schizophrenia. *Issues Ment Health Nurs* 2002; 23:513–28.

Pitschel-Walz G, Leucht S, Bauml J, Kissling W, Engel RR. The effect of family interventions on relapse and rehospitalization in schizophrenia – a meta-analysis. *Schizophr Bull* 2001; 27:73–92.

- Ram R, Bromet EJ, Eaton WW, Pato C, Schwartz JE. The natural course of schizophrenia: a review of first-admission studies. *Schizophr Bull* 1992; 18:185–207.
- Robinson DG, Woerner MG, Alvir JM, Bilder RM, Hinrichsen GA, Lieberman JA. Predictors of medication discontinuation by patients with first-episode schizophrenia and schizoaffective disorder. *Schizophr Res* 2002; 57:209–19.
- Robinson D, Woerner MG, Alvir JM, Bilder R, Goldman R, Geisler S, et al. Predictors of relapse following response from a first episode of schizophrenia or schizoaffective disorder. *Arch Gen Psychiatry* 1999; 56(3):241-7.
- Rosenheck RA, Davis S, Covell N, et al. Does switching to a new antipsychotic improve outcomes? Data from the CATIE Trial. *Schizophr Res* 2009. 107: 22–29.
- Rosenheck RA, Krystal JH, Lew R et al. Long-Acting Risperidone and Oral Antipsychotics in Unstable Schizophrenia. *N Eng J Med*. 2011; 364:842-51
- Rossell SL, Coakes J, Shapleske J, Woodruff PW, David AS. Insight: its relationship with cognitive function, brain volume and symptoms in schizophrenia. *Psychol Med* 2003; 33:111–9.
- Royal College of Psychiatrists. Prescribing Observatory for Mental Health. Royal College of Psychiatrists. <http://www.rcpsych.ac.uk>
- Rubio G, Martinez I, Ponce G, Jimenez-Arriero MA, Lopez-Munoz F, Alamo C. Long-acting injectable risperidone compared with zuclopenthixol in the treatment of schizophrenia with substance abuse comorbidity. *The Canadian Journal of Psychiatry / La Revue canadienne de psychiatrie* 2006; 51: 531-539.
- Sackett DL, Haynes RB, Guyatt GH, et al. *Clinical Epidemiology. A basic science for clinical medicine*. eds Boston: Little, 1991. Brown & Co.
- Saha S, Chant D, McGrath J, A systematic review of mortality in schizophrenia: is the differential mortality gap worsening over time? *Arch Gen Psychiatry* 2007; 64:1123-31
- Schooler NR, Levine J, Severe JB, Brauzer B, DiMascio A, Klerman GL, et al. Prevention of relapse in schizophrenia: an evaluation of fluphenazine decanoate. *Arch Gen Psychiatry* 1980; 37: 16–24.
- Semple DM, McIntosh AM, Lawrie SM. Cannabis as a risk factor for psychosis: systematic review. *J Psychopharmacol* 2005;19(2):187-94
- Shajahan P, Keith S, Majjiga C, Murphy J, MacRae A, Bashir M, Taylor M. Comparing the effectiveness of aripiprazole and quetiapine in schizophrenia and related psychoses. *J Clin Psychiatry* 2009;. 70(5): 692-698
- Shepherd M, Watt D, Falloon I, Smeeton N. The natural history of schizophrenia: a five-year follow-up study of outcome and prediction in a representative sample of schizophrenics. *Psychol Med Monogr Suppl* 1989; 15:1–46.
- Simpson GM & Angus JW. A rating scale for extrapyramidal side effects. *Acta Psychiatrica Scandinavica*, 1970. 212: 11–19.
- St Clair D, Blackwood D, Muir W, Carothers A, Walker M, Spowart G, et al. Association within a family of a balanced autosomal translocation with major mental illness. *Lancet* 1990; 336(8706):13-6.
- Stewart R, Soremekun M, Perera G et al. The South London and Maudsley NHS Foundation Trust Biomedical Research Centre (SLAM BRC) case register: development and descriptive data. *BMC Psychiatry* 2009. 9: 51

Stroup TS, Lieberman JA, McEvoy JP *et al.* Effectiveness of olanzapine, quetiapine, risperidone, and ziprasidone in patients with chronic schizophrenia following discontinuation of a previous atypical antipsychotic. *Am J Psychiatry* 2006; 163:611-622

Swofford CD, Kasckow JW, Scheller-Gilkey G, Inderbitzin LB. Substance use: a powerful predictor of relapse in schizophrenia. *Schizophr Res* 1996; 20:145–51.

Tacchi MJ and Scott J Improving medication adherence in schizophrenia and bipolar disorders. John Wiley & Sons Ltd, 2005. Chichester.

Taylor M, Mackay K and Shajahan P. Quetiapine use in Bipolar Disorder - What does the evidence tell us? *Clinical Medicine: Therapeutics* 2009;1 657-667.

Taylor D, Young C, Esop R, Paton C, Walwyn R. Testing for diabetes in hospitalised patients prescribed antipsychotic drugs. *Br J Psychiatry* 2004; 185: 152 -6.

Taylor D. Antipsychotic polypharmacy - confusion reigns. *The Psychiatrist*. 2010; 34: 41-43

Taylor D, Shapland G, Laverick J *et al.* Clozapine – a survey of patient perceptions. *The Psychiatrist*. 2000 24: 450-452.

Thompson CM. Characteristics associated with outcome in a community mental health partial hospitalization program. *Community Ment Health J* 1985; 21:179–88.

Thornley B, Adams C. (1998) Content and quality of 2000 controlled trials in schizophrenia over 50 years. *BMJ* 1998;317:1181-4

Tiihonen J, Haukka J, Taylor M, Haddad P, Patel M, and Korhonen P. A Nationwide Cohort Study of Oral and Depot Antipsychotics After First Hospitalization for Schizophrenia. *Am J Psychiatry*. 2011. doi: 10.1176/appi.ajp.2011.10081224.

Tiihonen J, Lönnqvist J, Wahlbeck K, *et al.* 11-year follow-up of mortality in patients with schizophrenia: a population-based cohort study (FIN11 study). *Lancet*. 2009; 374(9690):620-627.

Tiihonen J, Wahlbeck K, Lonnqvist J *et al.* Effectiveness of antipsychotic treatments in a nationwide cohort of 2230 patients in community care after first hospitalisation due to schizophrenia and schizoaffective disorder: observational follow up study. *BMJ*, 2006; 333 (7561): 224

Tognoni. Pharmacoepidemiology of psychotropic drugs in patients with severe mental disorders in Italy. Italian Collaborative Study Group on the Outcome of Severe Mental Disorders. *Eur J Clin Pharmacol*. 1999; 55(9):685-90.

Tran PV, Hamilton SH, Kuntz AJ, *et al.* Double blind comparison of olanzapine versus risperidone in the treatment of schizophrenia and other psychotic disorders. *J Clin Psychopharmacology* 1997; 17:407-18

Tsuang MT, Woolson RF, Fleming JA. Long-term outcome of major psychoses. I. Schizophrenia and affective disorders compared with psychiatrically symptom-free surgical conditions. *Arch Gen Psychiatry* 1979; 36:1295–301.

Tsuang MT, Woolson RF, Fleming JA. Premature deaths in schizophrenia and affective disorders. An analysis of survival curves and variables affecting the shortened survival. *Arch Gen Psychiatry* 1980; 37:979–83.

Uchida H, Suzuki T, Takeuchi H, Arenovich T, Mamo DC. Low dose vs standard dose of antipsychotics for relapse prevention in schizophrenia: meta-analysis. *Schizophr Bull*. 2011. 37(4):788-99.

van Os J, Wright P, Murray RM. Follow-up studies of schizophrenia I: natural history and non-psychopathological predictors of outcome. *Eur Psychiatry* 1997; 12:327s–41s.

von Knorring L & Linstrom. Principal components and further possibilities with the PANSS, *Acta Psychiatrica Scandinavia Supplementum* 1995. 388: 5-10.

Waddell L, Taylor M. Attitudes of patients and mental health staff to antipsychotic long-acting injections: systematic review. *Br J Psychiatry* 2009. 195, S43 – S50.

Waddington JL, Youssef HA, Kinsella A. Mortality in schizophrenia: antipsychotic polypharmacy and absence of adjunctive anticholinergics over the course of a 10 year prospective study. *Br J Psychiatry* 1998; 173: 325-9.

Walsh E, Fahy T. Violence in society. *BMJ* 2002; 325(7363):507-8.

Wiersma D, Nienhuis FJ, Slooff CJ, Giel R. Natural course of schizophrenic disorders: a 15-year followup of a Dutch incidence cohort. *Schizophr Bull* 1998; 24:75–85.

Wiersma D, Wanderling J, Dragomirecka E *et al.* Social disability in schizophrenia: its development and prediction over 15 years in incidence cohorts in six European centres. *Psychol Med* 2000; 30:1155–67.

Yeomans D, Taylor M, Currie A, et al. Resolution and remission in schizophrenia: getting well and staying well. *Adv. Psychiatric Treat*, Mar 2010; 16: 86 - 95.

Zhu B , Ascher-Svanum H , Shi L , Faries D , Montgomery W , Marder SR. Time to discontinuation of depot and oral first-generation antipsychotics in the usual care of schizophrenia . *Psychiatr Serv* , 2008. 59 (3), 315 – 17 .

Appendix 1

Clinical Global Impression

(adapted from Guy W, 1976)

Patient Information

Name:

Date:

CMHT:

Severity of Illness at Beginning of Treatment

Considering your total clinical experience with this particular population, how mentally ill is the patient at this time?

1	Normal, not at all ill
2	Borderline mentally ill
3	Mildly ill
4	Moderately ill
5	Markedly ill
6	Severely ill
7	Among the most extremely ill patients

Severity of Illness at End of Treatment

Considering your total clinical experience with this particular population, how mentally ill is the patient at this time?

1	Normal, not at all ill
2	Borderline mentally ill
3	Mildly ill
4	Moderately ill
5	Markedly ill
6	Severely ill
7	Among the most extremely ill patients

Global Improvement

Rate total improvement, compared to the condition at admission, how much has he/she changed?

3	Very much improved
2	Much improved
1	Minimally improved
0	No change
-1	Minimally worse
-2	Much worse
-3	Very much worse

Guidance notes: Completion of the Clinical Global Impression (CGI) should be self explanatory. Less experienced clinicians may wish to confer with senior colleagues before assigning a rating.

2. Severity of positive symptoms. Positive symptoms can be conceived as being pathologically "added" to the patient's experiences and behaviour. They include hallucinations in all sensory modalities; and primary and secondary delusions, be they persecutory, religious, somatic, hypochondriacal, grandiose, or nihilistic. Conceptual disorganisation or thought disorder; and overarousal and hostility are included here. The scale is a global summary assessment of these symptoms.

0 = none or absent

1 = mild. The symptom(s) are clearly established but not pronounced and interfere little with day-to-day functioning.

2 = moderate. The symptom(s) represents a serious problem, occurring only occasionally, or only intruding modestly on daily life.

3 = marked. Frequent and marked manifestations distinctly impacting on functioning, but not all consuming and usually can be contained at will.

4 = severe. Gross psychopathology, being frequent and highly disruptive and / or distressing. Often necessitating direct or close supervision by clinicians, carers, or family members.

3. Severity of negative symptoms. Again, a global summary measure, this psychopathology can thought of in general terms as something that has been subtracted or taken away from the patient. Typically these include social and emotional withdrawal; decreased or absent volition and motivation; lack of spontaneity and flow of conversation; poor rapport; blunting of affective response; and difficulty in abstract thinking.

0 = normal, or absence of any the features above that can be classed as pathological.

1 = mild. Little initiative, stilted conversation or facial expression. No pronounced effect on day-to-day function.

2 = moderate. Aloof or distant, with reduced expressiveness. Little spontaneous talk. Can be encouraged into activity.

3 = marked. Flat affect, may avoid eye-contact. Virtually no initiative or interest in environment. Concrete thinking, with one or two brief replies.

4 = severe. Neglectful of personal needs. Indifferent to interviewer, very occasional replies. Profound apathy and isolation.

4. Severity of drug-related side-effects. Overall summary assessment, including extra-pyramidal side-effects; dystonias; akathisia; tics; and choreoathetosis of the face, mouth and tongue, trunk, and limbs. Also included is weight gain; sedation; and sexual dysfunction entirely attributable to medication effects.

0 = absent or none.

1 = mild, or minimal. Could be extreme normal.

2 = moderate. Clearly observable, with minor subjective distress and impairment in functioning. Probably not continuously present.

3 = marked. Continuous and debilitating, but not overwhelmingly unpleasant.

4 = severe. Continuous with extreme subjective distress or discomfort. Viewed as a profound handicap.

5. Impairment in quality of life. A summary assessment entirely attributable to illness rather than social circumstance. Takes account of social and occupational roles including extent of relationships; time utilisation; and activities of daily living. Psychological fulfillment can be rated here, paying attention to sense of purpose; curiosity; empathy; and any anhedonia.

0 = none. Full and varied life, in work or at home.

1 = minimal. Minor concern over domestic or social situation. Able to live and work independently if opportunity exists.

2 = moderate. Difficulty living independently or performing work over long periods. Able to attend to personal and financial needs, and usually sociable.

3 = marked. Rarely able to live independently. May have legal trouble, or have been a victim of crime. Has difficulty socialising. Needs help with the more complex tasks of daily living eg. finances.

4 = severe. Completely dependent on others; seriously disabled; unaware of surroundings; and in a hopeless position.

Appendix 2

Confirmatory letter of ethical approval from Greater Glasgow Primary Care Trust regarding
GASS study (chapter 7)

Primary Care Division

Gartnavel Royal Hospital
1055 Great Western Road
Glasgow G12 0XH
Tel: 0141 211 3600
www.nhs.org.uk



Dr Linda Waddell
SHO in Psychiatry
Greater Glasgow Primary Care Trust
Flat 1, 42 Cecil St
Glasgow
G12 8RJ

Date 18 April 2006
Your Ref
Our Ref
Direct line 0141 211 3824
Fax 0141 211 3814
E-mail anne.mcmahon@gartnavel.gla.comen.scot.nhs.uk

Dear Dr Waddell

Full title of study: Validation of a new self rating scale for measuring atypical antipsychotic side effects
REC reference number: 06/S0701/6

Thank you for your letter of 26 March 2006, responding to the Committee's request for further information on the above research and submitting revised documentation.

The further information was considered at the meeting of the Committee held on 13 April 2006. A list of the members who were present at the meeting is attached.

Confirmation of ethical opinion

On behalf of the Committee, I am pleased to confirm a favourable ethical opinion for the above research on the basis described in the application form, protocol and supporting documentation as revised.

Ethical review of research sites

The favourable opinion applies to the research sites listed on the attached form.

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.

Approved documents

The final list of documents reviewed and approved by the Committee is as follows:

Document*	Version	Date
Application	one	20 January 2006
Investigator CV	one	11 January 2006



	Protocol	one	11 January 2006
	Protocol	two	13 February 2006
P	Questionnaire <i>tractmark</i>	two - GASS	13 February 2006
	Questionnaire	two - LUNTERS	13 February 2006
	Questionnaire	one - GASS	11 January 2006
	Questionnaire	lunters	
P	GP/Consultant Information Sheets	one	11 January 2006
	Participant Information Sheet	one - cases	11 January 2006
	Participant Information Sheet	one - controls	11 January 2006
P	Participant Information Sheet	Cases - two	13 February 2006
P	Participant Information Sheet	Controls - two	13 February 2006
P	Participant Consent Form	Cases - two	13 February 2006
F	Participant Consent Form	Controls - two	13 February 2006
	Participant Consent Form	one - cases	11 January 2006
	Response to Request for Further Information		26 March 2006
	Response to Request for Further Information		13 February 2006

Research governance approval

The study should not commence at any NHS site until the local Principal Investigator has obtained final research governance approval from the R&D Department for the relevant NHS care organisation.

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.

06/S0701/6	Please quote this number on all correspondence
------------	--

With the Committee's best wishes for the success of this project

Yours sincerely

A W McMahon
Research Ethics Co-ordinator (Manager) on behalf of Dr Paul Fleming, Chair

Email: Anne.McMahon@gartnavel.gla.ac.uk

Enclosures: *List of names and professions of members who were present at the meeting and those who submitted written comments*
Standard approval conditions
Site approval form

Copy to: NHS Greater Glasgow Primary Care Division - R&D Directorate

SF1 list of approved sites

Appendix 3

GASS for Clozapine

Name: _____

Date: _____

Caffeine intake:cups/day

Smoker: Y / Ncigarettes/day

Current Medications: _____

**Has there been a recent change in your smoking habit?: Increase/Decrease
by.....cigarettes/day**

This questionnaire is being used to determine if you are suffering from excessive side effects from your medication. Please put a tick in the column which best indicates how often or how severely you have experienced the following side effects.

Over the past week :		Never	Once	A few times	Everyday	Tick if severe or distressing
1	I felt sleepy during the day					
2	I felt drugged or like a zombie					
3	I felt dizzy when I stood up or have fainted					
4	I have felt my heart beating unusually fast or irregularly					
5	I have experienced jerking limbs or muscles					
6	I have been drooling					
7	My vision has been blurry					
8	My mouth has been dry					
9	I have felt sick (nauseous) or have vomited					
10	I have felt gastric reflux or heartburn					
11	I have had problems opening my bowels (constipation)					
12	I have wet the bed					
13	I have been passing urine more often					
14	I have been thirsty					
15	I have felt more hungry than usual					
16	I have been gaining weight					
17	I have felt breathless					
18	I have had chest pain					

I have also experienced:

(please write down any other side effects that you may have experienced over the past week)

16

17

18

Staff Information

1. Allow the service user to fill in the side-effects scale themselves. All questions relate to the previous week.

2. **Scoring**

0 Points	"Never"
1 point	"Once"
2 points	"A few times"
3 points	"Everyday"

3. **Results**

0-16	absent/mild side-effects
17-32	moderate side-effects
33-48	severe side-effects

4. **Side-effects covered include:**

1-2	Drowsiness and sedation
3	Postural hypotension
4	Tachycardia
5	Myoclonus
6	Hypersalivation
7-8	Anticholinergic side-effects
9-10	Gastrointestinal side-effects
11	Constipation
12	Nocturnal enuresis
13-14	Screening for diabetes mellitus
15-16	Weight gain

5. The column relating to the severity/distress experienced with a particular side effect is not scored, but is intended to inform the clinician of the service user's views and condition.