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Prescribing habits in the pharmacotherapy of schizophrenia

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Prescribing habits in the pharmacotherapy of schizophrenia

by

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This research report is submitted to the University of the Witwatersrand in partial fulfilment of the requirements for the degree of Master of Science (Med) in Pharmaceutical Affairs in 2011

Dedication

To Mia

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Acknowledgements

I would like to thank Professor Paul Danckwerts for his support and assistance in supervising the research and write-up of this report

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Declaration

I hereby certify that the research and write-up of this report were undertaken by me with the assistance of Professor Paul Danckwerts. No other parties were involved

Signed

R W King

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Abstract

Background: Many factors affect the prescribing of medication to patients with schizophrenia including variables that relate to physicians and may result in marked variance in the choice of drugs, dosages, drug combinations, route of administration and the use of antipsychotic, anticholinergic, sedative and other adjuvant drugs.

Clinical practice guidelines were developed to address this variance and for other reasons, including the management of side-effects, drug innovation, rising costs, information overload, changes in treatment goals and the management of medication non-adherence. There are advantages and disadvantages to using clinical practice guidelines including those pertaining to context and cultural norms, but they remain the best method of assessing prescribing quality.

Many guidelines are based on the results of randomised clinical trials (with a single drug) or are the consensus of experts in the field. Despite the development and publication of these guidelines over the past two decades, they are frequently not adhered to resulting in much variance in treatment.

Aims and objectives: The aim of the study was to determine to what extent the prescribing of psychotropic drugs in the treatment of schizophrenia was consistent with the most recent version of each of five guidelines that originate outside South Africa (two from the United States and one each from Canada, the United Kingdom, and Australia and New Zealand); and one that was developed locally.

Methodology: A retrospective, cross-sectional prescription chart review with data sampling at three time points (on hospital admission, at fourteen days thereafter and on hospital discharge) was undertaken. A sample population was drawn over a three year period during which the patients' physician had access to the same drug formulary. Seventy patients met the study selection criteria in terms of age, diagnosis and receipt of antipsychotic medication during hospital stay and on discharge. Seventy patients met the study selection criteria, and their prescriptions for psychotropic medication (exclusively) were examined for a number of parameters including: drug class, drug name, dose, route of administration and whether the medication was to be administered routinely or 'as needed'.

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Findings and discussion: As compared with the recommendations made in some or all of the guidelines, first generation antipsychotic agents were over-prescribed especially early on in the patients' hospital stay, whereas second generation antipsychotics were under-prescribed. The profile changed after fourteen days and on discharge there were more patients on second generation drugs than on the older drugs. More patients were discharged on depot antipsychotic treatment than were admitted which is considered a favourable finding, however, many patients receiving the depot form continued to be prescribed the oral drug on a routine basis and for an indefinite period, resulting in antipsychotic polypharmacy.

Anticholinergic drugs were prescribed as prophylaxis for the extra-pyramidal side-effects of the first generation antipsychotic drugs and more than a quarter of the sample received these drugs on discharge, after which they were to be taken routinely and indefinitely.

A similar finding was made with the use of benzodiazepine sedatives, where nearly a quarter of patients received these drugs on discharge - again to be taken routinely and for an unspecified period.

Sodium valproate was given increasingly to many patients in the sample and was prescribed to over a quarter of those upon discharge, without an indication of duration.

Limitations: The study was retrospective in design, without the benefit of the patients' clinical histories and treatment progress, and the findings were compared with guidelines whose age spanned more than a decade and some of which had become redundant.

Conclusions: The study demonstrated some prescribing habits that were not in accord with the guidelines used for comparison in the study. The extent of the disagreement reveals the need for a prospective pilot study that will include the patients' clinical progress in the study design which will provide greater insight into why specific medication parameters were chosen by the physician for the individual patient. If the findings justify it, then a programme promoting better adherence to the most current guidelines should be commenced.

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Chapter 1 – Introduction

1.1. Preamble, aims and objectives

1.1.1. Preamble

The most common intervention performed by physicians is the writing of a prescription (Onalaja *et al*, 2001), however, all elements in the complex process of prescribing and administering drugs are susceptible to many variables including the relative availability of drugs (Bowers *et* al, 2004) and those related to physicians (Hamann *et al*, 2004) including medication errors (Ferner, 1995).

Guidance on psychotropic prescribing exists in many forms, the manufacturer's summary of product characteristics is the most important , however, there are numerous clinical practice guidelines to assist physicians prescribing for schizophrenia including the document 'Guidance on the use of newer antipsychotic drugs for the treatment of schizophrenia (NICE, 2004). However, in clinical practice, psychiatrists' prescribing patters are often divergent (Hodgson & Belgamwar, 2006) and deviate from recommended practice (Paton *et al*, 2003). This is evident in many ways including (*inter alia)*:

- The use of medications on an as required (pro re nata or 'PRN') basis on psychiatric inpatient wards being common and widespread but without clear evidence of effectiveness and may be associated with a greater risk of adverse events (Srivastava, 2009) including cytochrome P450 mediated interactions (Davies *et al*, 2007).

- Prescriptions are often seen for more than one antipsychotic drug despite there being no efficacy advantage (Harrington *et al*, 2002), the practice not being based on scientific evidence (Taylor, 2010) and may result in a need for anticholinergic medication to combat the side-effects that occur as a consequence thereof (Paton *et al*, 2003).

- High dose antipsychotic prescribing is also common in clinical practice (Paton *et al*, 2008)

- Long-acting injections of antipsychotic medication were developed specifically to promote treatment adherence. Approximately 40 to 60% of patients with the diagnosis of

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schizophrenia are partially or totally non-compliant, yet only 30% or less are prescribed medication in this form. (Patel *et al*, 2009)

Despite these prescribing practices, there is a lack of routine data collection regarding acute ward prescribing (Paton & Lelliott, 2004). This is unfortunate because audit is a valuable tool for monitoring compliance to prescribing and administration standards, for encouraging continued improvement in practice (Onalaja *et* al, 2001) and improving prescription writing (Shaughnessy & D'Amico, 1994).

1.1.2. Aim of the study

The study was conducted at a large state psychiatric hospital in South Africa with an annual average admission and discharge rate of over a thousand patients. The hospital is divided into two groups of wards – for forensic and non-forensic patients – prescriptions from only the non-forensic patient were used re used in the study, the aim of which was to determine to what extent the prescribing of psychotropic drugs at the Facility corresponds with six clinical practice guidelines - five that originate outside South Africa and one that was developed locally - for the pharmacological treatment of schizophrenia.

1.1.3. Objectives

The objectives of the study are twofold. Firstly, to obtain the appropriate data from the prescriptions of selected patients, to analyse it and to compare the results with the recommendations made in the guidelines; and secondly, to determine what course of action may be taken should the comparison reveal prescribing that deviates markedly or is idiosyncratic – for example the results may prompt prospective study to quantify and qualify the degree of deviation from the guidelines consulted in the study.

1.2. Clinical practice guidelines

Clinical practice guidelines may be defined as 'systematically developed statements to assist practitioners and patient make decisions about appropriate care for specific circumstances' (Field & Lohr, 1990). In recent years we have witnessed the dissemination of practice guidelines for the treatment of schizophrenia (Essock, 2002). Although these

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guidelines are not a substitute for clinical judgement, professionals are expected to take them fully into account when exercising their clinical judgement (National Institute for Clinical Excellence, 2002), however, in a complex condition such as schizophrenia, it is neither possible nor sensible to be rigid (Rowlands, 2004).

1.3. Drivers for clinical practice guideline development

The broad interest in clinical practice guidelines has its origin in issues that most healthcare systems face: the availability of new medicines (Dassori *et al*, 2000); the management of key adverse events (Briggs *et al*, 2008); rising costs; changes in treatment goals (Chue, 2006); variations in service delivery among providers, hospitals and geographic regions; and the intrinsic desire of healthcare professionals to offer the best care possible (Woolf *et al*, 1999). Furthermore, a number of important questions concerning medication selection, dosing and the management of inadequate response have prompted guideline development and use (Kane *et al*, 2003).

1.2.1 Drug innovation and the management of side-effects

First generation antipsychotics (FGAs) have been used to treat psychosis since chlorpromazine was introduced in the 1950s (Dunlop *et al*, 2003). FGAs are highly effective; their therapeutic mechanism of action is thought to be closely related to the blockade of dopamine receptors which is also the reason for their side-effects including elevated prolactin levels (Volavka & Citrome, 2009) and movement disorders such as Parkinsonism, akathisia, dystonia and tardive dyskinesia (Thompson, 1994; Sernyak *et al*, 2002). All FGAs share these properties (Thompson, 1994).

The pharmacological treatment of schizophrenia has changed dramatically in recent years with the development of second generation antipsychotics (SGAs) (Chakos *et al*, 2001), the mechanism of action of which is serotonin-dopamine antagonism (Kaplan & Sadock, 2006). Although the SGAs have an improved side-effect profile, there is little to guide clinicians in choosing among them (McCue *et al*, 2006).

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1.2.2 Rising costs

In the early 1990s it was predicted that practice guidelines would improve the cost-effectiveness of care (Field & Lohr, 1990). It has been found that when clinicians use clinical practice guidelines organisations, resources are utilised more efficiently (Bahtsevani *et al*, 2004) and costs are reduced (Goel & Trivedi, 2007).

Examination of antipsychotic medication use patterns has suggested that current prescribing practices do not mirror recommended treatment guidelines and this may have adverse economic consequences (Loosbrock *et al*, 2003). An example of this is antipsychotic polypharmacy – it is inconsistent with current treatment guidelines and has been shown to be costly (Eisen *et al*, 2008).

Numerous studies suggest that despite being more expensive than FGAs, SGAs are more cost-effective (Gianfrancesco *et al*, 2002; Hosak & Bahbouh, 2002; Palmer *et al*, 2002; Tilden *et al*, 2002). More recent studies have found the opposite (Davies *et al*, 2007; Rosenheck *et al*, 2006) and Leucht *et al* (2008) have determined that SGA drugs differ in many properties and are not a homogeneous class, making it necessary for the clinician to make an individualised treatment choice based on efficacy, side-effects and cost. This is also the view expressed in the clinical practice guidelines issued by the National Institute for Clinical Excellence (2009) and the American Psychiatric Association (2004). This remains a controversial issue.

1.2.3 Variance in service delivery and the potential for harm

Health care delivered in ignorance of available research evidence, misses important opportunities to benefit patients and may cause significant harm (Dopson *et al*, 1994; Venturini *et al*, 1999).

1.2.4 Information overload and the provision of the best care

Practising clinicians are faced with large amounts of information to absorb in order to be able to advise their patients about the appropriate choice of medication (Bebbington, 2001). In an era of information overload, guidelines to best clinical practice are crucial for patients (Bolster, 1999).

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1.2.5 Changes in treatment goals and the management of antipsychotic non-adherence

The goals of treatment in schizophrenia have evolved from objective improvements in psychotic symptoms to include patient-related factors such as subjective response and quality of life (Chue. 2006). Relapse has the highest impact on quality of life and stable schizophrenia the lowest and so keeping the patient well is the utmost priority (Briggs *et al*, 2008).

Patient satisfaction with antipsychotic therapy is influenced by multiple factors including *inter alia*: lack of involvement in treatment planning or decision making (Chue, 2006), a complicated treatment regimen (Burton, 2005), lack of efficacy (Mojtabai *et al*, 2009) and – most authors agree - drug side-effects (Briggs *et al*, 2008; Chue, 2006; Mojtabai *et al*, 2009). However, McCann *et al* (2009) found the relationship between treatment nonadherence and drug side-effects to be unclear.

Nonadherence to antipsychotic medication has received increasing attention since the 1980s (Marder, 1986) and remains a common and significant problem affecting the continuity of treatment in routine care settings (Charpentier *et al*, 2009; McCann *et al*, 2009; Mojtabai *et al*, 2002; Valenstein *et al*, 2004; Valenstein *et al*, 2006, Zygmunt *et al*, 2002). Figures of non-adherence vary between a third (West *et al*, 2005) and as much as a half (Hudson *et al*, 2004; Lacro *et al*, 2002).

The majority of studies have demonstrated that SGAs are associated with significant improvements in quality of life, functional status and patient satisfaction compared with FGAs (Chue, 2006). Dolder *et al* (2002) compared FGA and SGA adherence in outpatients and found that compliance rates at 6 and 12 months were higher in patients who received the newer drugs. However, in a study be Kilian *et al* (2004) SGAs caused no better quality of life than FGAs. What is clear is that despite the introduction of these drugs, a leading cause of suboptimal outcome remains poor patient adherence to oral medication (Burton, 2005).

1.4. Implementation of clinical practice guidelines

Distribution of guidelines is not the same as implementation (Bero *et al*, 1998; Clark, 2003). Our knowledge of scientific treatment practices does not always translate into better care and outcomes for patients (Drake *et al,* 2009; Fischer *et al*, 2008; McCarthy *et*

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al, 2007; Mojtabai *et al*, 2009; Moran *et al*, 2006; Valenstein *et al*, 2004; Valenstein *et al*, 2006;) and prescribing in everyday practice frequently deviates from guidelines (Harrington *et al*, 2002; Lelliott *et al*, 2002; Mamdani *et al*, 2008).

While the potential of clinical practice guidelines to support implementation of guidelines has been demonstrated, it is not currently being achieved (Grimshaw *et al*, 2004). There may be many reasons for this including *inter alia*: institutional barriers (Cabana *et al*, 1999; Francke, *et al*, 2008) for example, interventions that have strong evidence of efficacy may not be available in routine practice (Singh *et al*, 2003); patient characteristics including co-morbidity (Francke *et al*, 2008), receiving depot antipsychotics (Meagher & Moran, 2003) and being an outpatient (Dickey *et al*, 2003; Mojtabai *et al*, 2009); and physician characteristics such as a lack of support from peers or superiors, as well as insufficient staff and time (Francke *et al*, 2008) and deficiencies in knowledge (Rowlands, 2004). Young *et al* (2006) found that psychiatrists who demonstrated greater adherence to guidelines were male, in midcareer, a caseload with a large proportion of patients with schizophrenia and use of current information from scientific literature or from pharmaceutical company detailing.

Although there are many exceptions (West *et al*, 2005), variations in physician prescribing patterns related to antipsychotic medications emphasize the need to improve guidelines implementation (Buchanan*, et al*, 2002; Chen *et al*, 2000; Leslie & Rosenheck, 2001).

It is the opinion of Delessert *et al* (2007) that 'the future certainly belongs to clinical practice guidelines, which proposes, in addition to the clinical recommendations themselves, a method to check their application in clinical practice'.

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Chapter 2 – Literature Review

A critical review of the literature of the clinical presentation and the pharmacological treatment of schizophrenia, variance in the quality of care and the use of clinical practice guidelines now follows.

2.1. Schizophrenia – clinical presentation and goals of treatment

2.1.1 Diagnostic features

Schizophrenia is a chronic illness that influences virtually all aspects of an affected person's life (American Psychiatric Association, 2004). The Diagnostic and Statistical Manual of Mental Disorders IV (DSM IV) diagnostic criteria are given in Appendix A, and it will be noted that no single symptom is pathognomonic of the illness; the diagnosis involves the recognition of a constellation of signs and symptoms associated with impaired occupational or social functioning (American Psychiatric Association, 1994).

Characteristic symptoms may be conceptualized as falling into two broad categories – positive and negative. Positive symptoms of schizophrenia include delusions, hallucinations, disorganized speech and grossly disturbed or catatonic behaviour; negative symptoms include affective flattening, alogia and avolition. (American Psychiatric Association, 1994)

2.1.2 Phases of the disorder

The course of the illness for the majority of patients comprises a prodromal period, an acute phase, a period of stabilization and a stable phase (American Psychiatric Association, 1994).

The acute phase refers to the periods during which the patient experiences an active episode of positive symptoms, with either the onset of symptoms after an asymptomatic period or a marked increase in symptoms over a baseline of less severe symptoms (Dixon *et al*, 1995). During an episode some patients suffer extreme changes in their thinking,

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mood and behaviour. Many patients will be hospitalised during the acute phase of the illness and some patients will be formally detained (Thompson, 1994). Operationally, this phase may be defined as the first 6 to 8 weeks after onset of an episode of positive symptoms (Dixon *et al*, 1995). After a stabilization period of variable duration, the phase of long-term maintenance treatment follows - this refers to the periods during which the patient is not experiencing an acute episode as defined above (Dixon *et al*, 1995)

2.1.3 Goals of treatment

The goals of treatment during the acute phase are to prevent harm, control disturbed behaviour, reduce the severity of psychosis and associated symptoms (e.g. agitation, aggression, negative symptoms, affective symptoms), determine and address the factors that led to the occurrence of the acute episode, effect a rapid return to the best level of functioning, develop an alliance with the patient and family, formulate short- and long-term treatment plans and connect the patient with appropriate aftercare in the community (American Psychiatric Association, 2004; Dixon *et al*, 1995).

During the stabilization phase, the goals of treatment are to reduce stress on the patient and provide support to minimize the likelihood of relapse, enhance the patient's adaptation to life in the community, facilitate continued reduction in symptoms and consolidation of remission and promote the process of recovery (American Psychiatric Association, 2004).

The goals of treatment during the stable (or long-term treatment) phase are to ensure that symptom remission or control is sustained, that the patient is maintaining or improving his or her level of functioning and quality of life, that increases in symptoms or relapses are effectively treated and that monitoring for adverse treatment effects continues (American Psychiatric Association, 2004; Dixon *et al*, 1995; Turner & Stewart, 2006).

2.1.2 Associated descriptive features and mental disorders

The individual with schizophrenia may display inappropriate affect, anhedonia*)*, dysphoric mood, sleep disturbances and substance abuse. Completed suicide occurs in about ten percent of patients (American Psychiatric Association, 1994).

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2.2 The pharmacotherapy of schizophrenia

Schizophrenia is a serious and complex disorder, with treatment requiring a large number and wide range of health and social service resources (Tunis *et al*, 2004). Despite scientific advances in treatment, the efficacy-effectiveness gap is wider for schizophrenia than any other serious medical disorder (McGorry, 2005).

An important component of schizophrenia management includes psychosocial treatments (Bhanji & Tempier, 2002; Huxley *et al*, 2000) which serve as an effective adjunct to the pharmacotherapy for schizophrenia (Haddock & Lewis, 2005; Patterson & Leeuwenkamp, 2008).

It is antipsychotic pharmacotherapy, however, that is the cornerstone of effective treatment for schizophrenia (Leslie & Rosenheck, 2004; Parker *et al*, 2002; Thompson, 1994). Antipsychotic drugs not only promote functional recovery but also prevent symptom relapse (Schooler, 2006) and help manage residual features in patients with chronic schizophrenia (Turkington *et al*, 2006)

2.2.1 Antipsychotic drugs

During the acute phase of schizophrenia, antipsychotic medication eliminates or reduces the intensity of psychotic experiences (Thompson, 1994). The majority of patients with schizophrenia will get better with treatment for an acute episode and leave hospital, but most patients will require maintenance treatment with antipsychotic drugs for some time, perhaps indefinitely, in order to prevent a relapse (Thompson, 1994). The use of antipsychotic agents has been shown to reduce the risk of relapse and hospitalization and help improve patients' long-term functional outcomes (Lieberman *et al*, 2005; McEvoy *et al*, 2006; Stroup *et al,* 2006).

2.2.2 Adjunctive medications

Benzodiazepines, anticholinergic drugs, antidepressants, lithium and anticonvulsants are commonly used adjunctive medications (Casey *et al*, 2003; Chaplin & McGuigan, 1996; Ren *et al* 2005; Siris *et al*, 1994; Wolkowitz & Pickar, 1991).

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2.3 Variations in service delivery and quality of care

The prescribing practices for schizophrenia vary greatly among centres and countries (Bitter *et al*, 2003) and clinical charts are a source of data which may be used to assess the quality of health care (*Brook et al*, 1996). One approach to improving quality of care is to encourage physicians to follow evidence-based practice guidelines (Dickey, 2006). Prior to examining several clinical practice guidelines, the conflicting research findings and opinions over antipsychotic choice, polypharmacy, dosing, route of administration and adjuvant therapy are now explored.

2.3.1 Choice of an antipsychotic

Treatment with FGAs is effective, however, adverse drug reactions are common. Initial studies of the efficacy of SGAs found them to be more efficacious than FGAs in symptom control (Davis *et al*, 2003; Turner & Stewart, 2006), specifically in terms of reducing both positive and negative symptoms, and in preventing relapse (Kane, 2006; Turner & Stewart, 2006). SGAs were also found to be better tolerated (Geddes, 2002; Leucht *et al*, 2003), resulting in a lower incidence of movement disorders including tardive dyskinesia (Kane, 2006; Tandon *et al*, 2008; Turner & Stewart, 2006). Adherence to treatment was also thought to be better - but this issue has remained controversial (Geddes, 2002; Leucht *et al*, 2003).

SGAs are associated with a different profile of adverse reactions, including a higher incidence of metabolic side-effects (Tandon *et al*, 2008), including disturbances in lipid and glucose regulation (Volavka & Citrome, 2009) which may result in diabetes (American Diabetes Association, 2004; Sernyak *et* al, 2002) and weight gain (Sernyak *et al*, 2002; Turner & Stewart, 2006). Despite these potentially serious side-effects, Naber & Lambert (2009) believe that the lower risk of tardive dyskinesia and the better subjective effects should be strong enough reasons to favour these drugs.

Data from two large, independent, major government-funded studies – 'Clinical Antipsychotic Trials in Intervention Effectiveness' (CATIE) (Lieberman *et al*, 2005) and 'Cost Utility of the Latest Antipsychotic drugs in Schizophrenia Study' (CUtLASS) (Jones *et al*, 2006) - of the comparative antipsychotic effectiveness in schizophrenia contradict the widely prevalent belief that the SGAs are vastly superior to the FGAs. Dosing was found to be a key variable in optimizing effectiveness of both FGAs and SGAs (Tandon *et al*, 2008) and the side-effects of SGAs become more severe as dosages increase, often with

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little or no increase in effectiveness (Baldessarini *et al*, 1988; Citrome & Volavka, 2002). CATIE and CUtLASS suggest that SGAs, except clozapine in the treatment-resistant population, offer little, if any, clinical benefits, and moreover, their side-effects are problematic (Foussias & Remington, 2010). The finding that oral SGAs are no more efficacious than FGAs has also been shown in first-episode schizophrenia (Kahn *et al*, 2008) and in patients with chronic schizophrenia (Lieberman *et al*, 2005). In summary, CATIE and CUtLASS showed considerable differences between individual agents and overlaps between the two groups in terms of efficacy and side-effects. Volavka & Citrome (2009) consider the classification of antipsychotics into the two groups no longer to be useful. Furthermore, the effectiveness of antipsychotic drugs varies greatly in a real world setting. (Tiihonen *et al*, 2006).

A Cochrane Review of 21 trials comparing the use of haloperidol with placebo in the treatment of schizophrenia (or other serious psychotic illness) concluded that the drug has a high propensity to cause adverse effects and should be used only if there is no treatment option (Irving *et al*, 2006).

Treatment responsiveness is another factor that should be considered in the selection of an antipsychotic drug. Clozapine is the treatment of choice for patients with treatment-resistant schizophrenia; such treatment should not be delayed or withheld (Taylor *et al*, 2010)

It is clear that there is no single antipsychotic drug that is best for every patient with schizophrenia, as individual responses differ markedly. For successfully individualized treatment, a multitude of antipsychotic options are needed (Naber & Lambert, 2009) and clinical practice guidelines make recommendations in this regard.

2.3.2 Polypharmacy

Polypharmacy – the simultaneous use of multiple psychotropic drugs, be they similar or dissimilar - is a very common practice (Ghaem, 2002). Antidepressants, anti-anxiety medications, mood stabilizers and also the concurrent use of two or more antipsychotics have been implicated (McCue *et al*, 2003). However, rigorous data on combination therapy in schizophrenia are rare; some evidence supports a combination of antipsychotics and antidepressants for negative symptoms and comorbid major

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depressive episodes. The add-on of lithium and mood stabilizers lacks compelling evidence, but might be beneficial for specific subgroups (Zink *et al*, 2010)

Antipsychotic polypharmacy - the use of two or more antipsychotic drugs - appears to be increasing (Gören *et al*, 2010; Langan & Shajahan, 2010) despite it not being evidence-based (Taylor, 2010), is considered to reflect poor prescribing practice (Haw & Stubbs, 2003) and is condemned by numerous bodies (Taylor, 2010). Antipsychotic polypharmacy is associated with patients receiving depot medication (Barnes *et al*, 2009) and with 'difficult-to-treat' patients where there is a need for clinical answers but no evidence base (Barbui *et al*, 2006)

The introduction of SGAs has not improved the practice of polypharmacy. A systematic review of studies, case reports and article reviews by Pandurangi & Dalkilic (2008) showed that polypharmacy with SGAs is not uncommon, and give a prevalence varying between 3.9 and 50%, depending on setting and patient population. SGA polypharmacy may also be found in chronic inpatients with severe and persistent mental illness (Megna *et al*, 2007). Combining FGA depot and SGA oral medication has been noted in forensic patients who exhibited treatment-resistant illness and to ensure adherence to at least part of the treatment (Bains & Nielssen, 2003). There remains little support for co-prescription of antipsychotics but considerable evidence to suggest that such practice worsens adverse effect burden. Co-prescription of SGAs and FGAs should be avoided in all but very exceptional circumstances (Taylor *et al*, 2002)

The problem currently is that the degree of polypharmacy being practiced seems far in excess of the supporting data (Kane & Leucht, 2008). As psychopharmacology becomes more sophisticated, the possibilities for both rational and irrational polypharmacy increase exponentially (Kingsbury *et* al, 2001) and many authors contend that antipsychotic polypharmacy may be a rational approach in some situations (Correll *et al*, 2009) including: when changing gradually from one drug to another (Thompson, 1994); when a second antipsychotic is added to counteract a problem (e.g. safety, tolerance or adherence) arising during monotherapy; where the clinician may have serendipitously hit upon an effective combination (Miller & Craig, 2002); where there has been failure or patient refusal of all reasonable monotherapies (Miller & Craig, 2002; Tapp *et al*, 2003); in treatment-refractory cases for whom it has been proved necessary by experience over several years (Thompson, 1994; Zink *et al*, 2010); where indefinite continuation of combinations initially intended to be brief has occurred (Ereshefsky, 1999) and in

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treatment-emergent positive and/or negative symptoms under clozapine monotherapy may benefit from adding an SGA (Zink *et al*, 2010).

It may be true that different antipsychotics are prescribed together because they have different effects on different symptoms of psychosis and that polypharmacy may represent the optimal application of scientific knowledge and clinical experience combined (Taylor, 2002). Physicians may therefore be making a greater effort to 'fine-tune' treatment response (Clark *et al*, 2002). Taylor (2010) believes that targeted evidence-based antipsychotic polypharmacy may be the way forward. However, the lack of published data makes the practice of using multiple antipsychotic agents a gray area and problematic for the clinician (Schumacher, 2003).

2.3.3 Drug Dose

Most definitions of optimal treatment for patients with schizophrenia assign a central rôle to appropriate antipsychotic medication dosage. The dose of an antipsychotic that a patient will require will depend on several factors including age – older patients generally require lower doses and often have more side-effects than younger patients (Thompson, 1994).

There is evidence that maximum efficacy for typical antipsychotics occurs at 70 – 80% of dopamine receptor occupancy and that these levels can be achieved at doses substantially lower than was previously thought necessary (Kapur *et al*, 1996; McEvoy *et al*, 1991; Stone *et al*, 1995). Literature reviews have failed to show any clinical benefit in prescribing high doses of antipsychotic medications (Davis & Chen, 2004; Freudenreich & Goff, 2002) and data from controlled trials indicate that, above a certain threshold, higher antipsychotic dosages generally increase the occurrence of side-effects without contributing to clinical improvement (McEvoy *et al*, 1991).

Despite this, the prescription of high-dose antipsychotic medications is a well-documented phenomenon, one of the chief reasons for this being antipsychotic polypharmacy (Chaplin & McGuigan, 1996; Harrington *et al*, 2002; Tibaldi*, et al*, 1997), but this may be inadvertent because each individual drug may be within recommended limits (Parket *et al*, 2002).

Tavernor *et al* (2000) found that in a secure psychiatric facility, psychosis rather than aggression best predicted antipsychotic dose, whereas other authors have found that

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patients' history and reputation for violence (not current presentation), treatment non-responsiveness and duration of illness were the determinants (Bitter *et al*, 2003; Chaplin & McGuigan, 1996; Krakowski *et al*, 1993; Lelliott *et al*, 2002; Peralta *et al*, 1994; Wilkie *et al*, 2001)

Another reason for the use of high-dose antipsychotic treatment is pro re nata (PRN)/'as required' prescribing (Ito *et al*, 2005; Paton *et al*, 2008). Yet another reason is idiosyncratic prescribing by some consultant psychiatrists of dosages that are higher than those used by their colleagues, a factor that must be considered when calculating an average dose (Wilkie *et al*, 2001)

Some authors claim that high-dose treatment is warranted in some instances, despite the lack of research evidence to back this up (Mortimer, 1994), however, it is clear that some patients are maintained on high-dose treatment unnecessarily contributing to extrapyramidal side-effects and mortality due to cardiac conduction abnormalities (Glassman & Bigger, 2001; Mehtonen *et al*, 1991).

A different view is held by Oosthuizen *et al* (2001) who found that ultra low-doses of haloperidol (2mg/day) were effective and well-tolerated in first-episode psychosis. The same findings were again noted by Oosthuizen *et al* (2004) when ultra low doses of haloperidol were compared with high dose haloperidol (8mg/day) in the same condition.

By way of an explanation for these variances, Baldessarini *et al* (1998) state that there is no clear relationship between neuroleptic dose and clinical response. Young (2003) advises that dose is only indirectly related to outcomes, and that some patients have a reduction in psychosis at low dosages, while others have no side-effects at high dosages. Indeed, certain patients do best at low dosages, and others do best at high dosages.

However, numerous other studies including those by Soher *et al* (2003) and Owen *et al* (2000) demonstrate that adherence to prescribing guideline dose for antipsychotic medication is associated with improvement in patient outcomes following hospital discharge – including a lower severity of symptoms at six-month follow up than patients who received low or high doses.

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2.3.4 Route of administration: Depot antipsychotic formulation

Long-acting depot antipsychotics were developed in the 1960s and were specifically aimed at promoting treatment adherence in people with chronic illness, thereby enhancing relapse prevention (Davis *et al*, 1994; Kane, *et al*, 1998; Weiden & Glazer, 1997). Prescribing practices for depot antipsychotics differ significantly between countries (Dencker & Axelsson, 1996; Sim, K. *et al,* 2004), within a region and between regions of one country (Taylor *et al*, 1999)

It is generally is accepted that the depot formulations offer a distinct advantage in the ability to document and observe non-adherent behaviour (Adams *et al*, 2001; Marder, 1986), improve medication adherence (Kane, 2003), benefit non-adherent schizophrenia patients (McEvoy, 2006) and facilitate relapse prevention (Kane, 1998).

However, it has been found that depot formulations play a relatively minor rôle in the treatment of schizophrenia (Heres *et al*, 2006). There may be many reasons for this including the belief that depot treatment is associated with a high risk of extrapyramidal adverse effects (Barnes & Curson, 1994; Möller, 2007) which may reduce adherence to medication and precipitate relapse (Luft & Berent, 2009). This is disputed by Adams *et al* (2001) who found that when comparing existing depot FGAs with oral preparations of the same drug, there was no conclusive difference in extrapyramidal side-effects. Numerous other authors agree with Adams *et al* (Haddad *et al*, 2009; Patel *et al*, 2003; Patel & David, 2005; Taylor, 2009).

It was hoped that when SGA-depot medication became available, staff and patients would re-examine their attitudes (Waddell & Taylor, 2009) and that depot would be used less restrictively (Möller, 2007) including in first-episode patients (Chue, 2007). However, psychiatrists continue to use depot antipsychotics in a conservative way although they attribute positive traits to the method (Jaeger & Rossler, 2010). Patel *et al*, (2010) have noted that depot prescribing rates have continued to decrease over the last 5 years. Ascher-Svanum *et al* (2009) and Verhof *et al* (2008) have noted that patients who receive SGA-depot medication tend to be more severely psychotic and that depot is used as a last resort. Interestingly, a study by Heres *et al* (2006) showed that the main factor for opposing both FGA and SGA depot preparations is the clinicians' assumption that their patients were adherent.

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It is the opinion of Patel & David (2005) that some psychiatrists may not adequately consider the risks and benefits when contemplating prescribing depot medication. Use of long-acting preparations in patients with schizophrenia who are medication nonadherent remains uncommon despite clinical recommendations urging their use (West *et al*, 2008).

2.3.5 Adjuvant medication

Benzodiazepines

Benzodiazepines provide significant effects in terms of short-term sedation in the patient with acute psychotic agitation (Volz *et al*, 2007; Wolkowitz & Pickar, 1991) but long-term anti-psychotic treatment with benzodiazepines has not shown convincing efficacy (Volz *et al*, 2007). A review by Wolkowitz & Pickar (1991) showed that anti-psychotic response was shown to be highly variable, required high doses and when improvement occurred, it diminished within a few weeks. Also, Haw and Stubbs (2007) reported a favourable risk-benefit ratio for the use of benzodiazepines in certain patients.

In a study by Paton *et al* (2000) almost one in ten patients occupying rehabilitation beds had a diagnosis of schizophrenia and received benzodiazepines in the medium- or long-term. Possible reasons for this include inadequate response to antipsychotics alone, an 'antipsychotic sparing effect' of the benzodiazepine, poor review of the drug regimen after a period of acute disturbance, misuse by patients and - in the case of PRN medication - inappropriate use by staff. Maintenance benzodiazepine/hypnotic use has been found to be common (Meagher & Moran, 2003)

Anticholinergic Drugs

Anticholinergic drugs may be prescribed because first-generation antipsychotics (FGAs) are often associated with extrapyramidal symptoms (Ren *et al*, 2005). Some SGAs such as clozapine, olanzapine, and quetiapine have significant affinity for the muscarinic receptors *in vitro*, while aripiprazole, risperidone, and ziprasidone do not (Chew *et al*, 2006). In a recent study of over 5 000 patients receiving SGAs, Eisen *et al* (2008) found that despite the milder side-effect profile of this class of drug, over 1 400 patients received anticholinergic medication which may reflect overuse.

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Mood stabilizers

The off-label prescription of mood stabilizers is very common in psychiatry (Haw & Stubbs, 2005), however, neither in monotherapy nor as adjunctive agents to antipsychotics do these drugs have a beneficial effect that is well-supported in the literature (Berle & Spigset, 2005; Dussias *et al*, 2010). They could be considered as potential adjuncts to antipsychotics in patients with treatment-resistant schizophrenia, although the documentation is sparse (Berle & Spigset, 2005). Leucht *et al* (2002) examined trials of carbamazepine as an adjunctive drug in the treatment of schizophrenia but could find no statistically significant benefit. Mood stabilisers have not been found to be a useful treatment strategy for improving the residual symptoms of schizophrenia (Glick *et al*, 2009).

2.4 The use of prescribing data in routine clinical settings

2.4.1 The need for studies in routine clinical settings

In comparison with hundreds of randomized clinical trials of various pharmacological and psychosocial treatments for schizophrenia, there are relatively few studies of the treatment patterns in routine care settings (Mojtabai *et al*, 2009). In clinical settings, many factors related to the patient, the provider and the treatment setting influence medication decisions, but these influences are minimized in the clinical trial design (Soher *et al*, 2003).

Another reason for studying patterns and outcomes of treatments in every-day practice is because of concerns that recommended evidence-based treatments may not be effective for a significant portion of patients in routine practice (Zarin *et al*, 1998).

2.4.2 The value of collecting prescribing data

There are no routinely collected prescribing data that allow for the quality of prescribing for psychiatric patients to be monitored (Paton & Lelliott, 2004). It should be noted that indicators cannot cover all facets of the care provided to patients, nor can they include the complexity of environmental and personal aspects - the indicators represent a minimal set of requirement to be met in the care of patients with psychosis, and several indicators of prescribing quality in psychiatry have been proposed (Bollini *et al*, 2008).

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The assumption is that prescribing within the parameter represents good practice and the converse thereof (Paton & Lelliott, 2004). Of relevance to this study are the indicators that reflect a categorical concept – that is, whether prescribing for an individual patient is within or outside a stated parameter. A number of these have been identified, *viz.* high dose antipsychotic (Harrington *et al*, 2002; Moran *et al*, 2006; Paton & Lelliott, 2004), antipsychotic polypharmacy (Harrington *et al*, 2002; Moran *et al*, 2006; Paton & Lelliott, 2004), SGA polypharmacy (Paton & Lelliott, 2004), multiple PRN prescribing (Birmingham *et al*, 1999; Paton & Lelliott, 2004), low dose mood stabilisers (Paton & Lelliott, 2004), maintenance (long-term) hypnotic use (especially benzodiazepines) (Mahomed & Paton, 2002; Paton & Lelliott, 2004), polypharmacy (the use of two agents of the same class) (Moran *et al*, 2006), the routine use of anticholinergic agents (Moran *et al*, 2006) and the avoidance of drug interactions (Williams *et al*, 2000).

Recommendations for many of these parameters are specifically addressed in the six clinical practice guidelines that are used in this study.

According to Paton & Lelliott (2004), it seems likely that prescribing will be monitored using indicators of this type. If this is the case, those responsible for using prescribing indicator scores must understand how difficult they are to interpret. When differences between prescribers or groups of prescribers are found, a number of questions should be posed before asking them to review their practice, including case mix and service level factors that might influence prescriber decision making.

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2.5 Clinical Practice Guidelines

2.5.1 The value of clinical practice guidelines in improving the quality of care

A common concern underlying the measurement of the quality of treatment is that patients with psychosis are very vulnerable and have limited advocacy capacity, and are therefore at risk of inadequate care or even neglect (McAlpine & Mechanic, 2000; McNulty *et al*, 2003; Lehman, 1998). One way to improve the quality of care is by the use of evidence-based clinical practice guidelines (Grims & Russell, 1993; Miller & Kearney, 2004).

Evidence-based medicine has been defined as 'the integration of best research evidence with clinical expertise and patients' values (Sackett *et al*, 2000). It differs from the traditional approach to healthcare in that in addition to relying on clinical experience, expert opinion and knowledge, clinicians apply research evidence to individual patients in a way that takes into account their particular experiences, expectations and values (Bhandari *et al*, 2004). The clinical trial is the linchpin of evidence-based medicine (Kane & Leucht, 2008), however, the large gap between evidence generated in the highly controlled paradigms of evidence-based medicine and the reality of everyday practice has been highlighted for research attention (Moran *et al*, 2006).

Evidence-based guideline development can reduce the delivery of inappropriate care (Goel & Trivedi, 2007; Grol *et al*, 1999; Mellman *et al*, 2001; Merritt *et al*, 1997) and achieve more uniformity in the way that people with a certain condition are managed (Goel & Trivedi, 2007; Rowlands, 2004). The quality of mental healthcare and treatment has been significantly improved in the last decade by the use of clinical practice guidelines (Grol & van Weel, 2009; Jakovljević 2007).

Treatment decisions are also typically evaluated by comparing them against norms, such as practice guidelines (Falzer & Garman, 2010). Proponents believe that clinical practice guidelines provide a guide to best practice for use as a benchmark against which to evaluate clinical practice (Turner *et al*, 2009) and higher adherence rates are used as evidence of better quality of care (Walker*, et al*, 2004; Lohr, 1990). There is growing interest in the use of prescribing indicators (specifically) to evaluate care processes and measure the performance of mental health services (Goel & Trivedi, 2007; Paton & Lelliott, 2004).

Other authors caution that there are problems with converting clinical practice guidelines into performance measures because outcomes are associated with a complex interplay among social context, availability of resources and treatment decisions in addition to medication use (Davidowitz *et al*, 2004) and a more balanced perspective is required (Rabinowitz *et al*, 1999). Adherence to practice guidelines has therefore been criticized as inappropriate, but no measurable alternative has been proposed to date (Falzer & Garman, 2010).

Furthermore, although it has been shown in rigorous evaluations that clinical practice guidelines can improve the quality of care (Grimshaw & Russell, 1993), whether they

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achieve this in daily practice is less clear. This is partly because patients, doctors, payers and managers define quality differently (Woolf *et al*, 1999).

Other concerns about clinical practice guidelines include that they may rapidly become out of date (Weiden & Dixon, 1999), be unrealistic in many treatment situations and unaffordable to implement (Gaebel *et al*, 2005), be used by healthcare financers to prevent clinicians from deviating from 'approved practice', be biased in promoting one narrow aspect of a complex issue, they may result in liability concerns (Bhanji & Tempier, 2002), most do not discuss the minimal training needed to use them (Weiden & Dixon, 1999), they may lead to 'cookbook' medicine and the absence of individualized treatment plans (Dixon, 2004) and vary considerably in quality (Boluyt *et al*, 2005; Cates *et al*, 2006; Christiaens *et al*, 2004; de Haas *et al*, 2007; Saturno *et al*, 2003).

2.5.2 Setting, context and cultural issues

Practice guidelines have to be based on – or to consider adequately – scientific evidence with regard to key treatment recommendations (McIntyre, 2002). As schizophrenia shows a highly variable course in different countries, possibly due to cultural influences (Alem *et al*, 2009; Jablensky *et al*, 1992) cross-cultural differences must also be reflected in schizophrenia guidelines, but it is not clear how this may be done (Gaebel *et al*, 2005). No validated process for the adaptation of guidelines produced in one cultural and organisational setting for use in another (i.e. trans-contextual adaptation) was found in the literature by Fervers *et al* (2006) who state that this is increasingly being considered as an alternative to *de novo* guideline development.

Normative and cultural opinions about the value of specific performance often play an important rôle in defining recommendations for practice without making these explicit (De Kort *et al*, 2009; Wollersheim, 2009). Despite a large number of systematic reviews of implementation interventions, many of the fundamental questions regarding what approaches should be used in which settings and for which problems remain unanswered (Bhattacharyya *et al*, 2009).

In South Africa there is often a difference in ethnic background between clinician and patient, a factor that could lead to mistaken assumptions that affects the way in which clinicians adhere to guidelines or make treatment decisions (Herbeck *et al*, 2004; Kuno &

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Rothbard, 2002; Segal *et al*, 1996). According to Koen *et al* (2008), in the interests of mental health care in South Africa, it is becoming necessary for us to implement practical clinical guidelines, and make these readily available in the large variety of settings that characterize this country.

2.5.3 History, methodology and application of the guidelines used in the study

Six of the best known English-language clinical practice guidelines for the treatment of schizophrenia were included in the study. Each is from a country where English is either the primary language or the *lingua franca*, and include two from the United States (one guideline is research-based and the other a consensus of expert opinion), Canada, Australia and New Zealand, the United Kingdom and South Africa.

When the American Psychiatric Association Schizophrenia Guideline project began, no other comprehensive treatment guidelines were available (Weiden & Dixon, 1999). The Association had published its American Psychiatric Association guidelines (APAGs) in 1997 and the review of this evidence published by this group was used to varying extents by other groups such as the one from Canada that produced the Canadian Clinical Practice Guidelines (CCPGs) (Bassett & Addington, 1998). Their shared background information resulted in very few discrepancies between these two guidelines, however, the goals of the organisations that produced them differed in that they aimed to reflect local practices as well as provide increased specificity to the guidelines (Bhanji & Tempier, 2002). The APAGs are supported by the political weight of the American Psychiatric Association, conferring a *de facto* authority, and are considered the closest to establishing a standard of practice (Weiden & Dixon, 1999).

By their very nature, the APAGs and CCPGs lag behind clinical practice and the Expert Consensus Guidelines (ECGs) that were developed by a panel of clinical experts to address important clinical questions unanswered in the research literature. The major advantage to the ECGs (updated in 1999 and also produced in the United States) is that they were relatively comprehensive and current in areas of pressing clinical concern at the time, however, the inherent disadvantage is that the ECGs are recommendations are based on opinions, not sound, scientific research data (Weiden & Dixon, 1999).

Guidelines have existed in England for decades (Woolf *et* al, 1999). The guidelines issued by the National Institute for Clinical Excellence (NICE) in the United Kingdom were the

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result of collaboration by professionals from various disciplines, service users and carers (Rowlands, 2004). The NICE guidelines (NICEGs) were updated in 2009.

2.5.4 Comparative evaluation of clinical practice guidelines

Gaebel *et al* (2005) compared twenty-seven national schizophrenia guidelines from different countries and found recommendations for pharmacotherapy to be similar. However, Bhanji & Tempier (2002) are of the opinion that discrepancies between guidelines are noteworthy because clinical practice guidelines are designed to reduce variations in practice patterns. There is still disagreement among the various experts (Bhanji & Tempier, 2002).

2.6. Overview of literature review

A review of the pertinent literature was undertaken in order to gain better insight into the pharmacotherapy of schizophrenia.

The diagnostic criteria for schizophrenia, the phases of the disorder and the goals of treatment were explored as were the numerous antipsychotic and other drug therapies available to the psychiatrist.

The review revealed suboptimal prescribing practices to be a frequent finding in routine practice. These included irrational polypharmacy (including antipsychotic polypharmacy); the underuse of depot antipsychotic drugs; the inappropriate manner in which anticholinergic agents and benzodiazepine sedatives were used; and the problems of PRN and high dose prescribing.

The rôle of clinical practice guidelines was explored and drivers for their development were identified. These include drug-innovation; the need for the improved management of side-effects; rising costs; variance in service delivery and the potential for harm; information overload; changes in treatment goals and the management of antipsychotic non-adherence. The advantages and disadvantages of using clinical practice guidelines were reviewed, and the need for further studies of prescribing practices in routine clinical settings was noted.

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The literature review prompted the question ‘to what extent do the prescribing patterns at the hospital at which the study was conducted adhere to the relevant clinical practice guidelines in the pharmacotherapy of schizophrenia?’ - a question that this study attempted to answer.

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Chapter 3 – Methodology

The study design, strategy of inquiry, instrumentation, target and sample populations and data analysis are now presented**.**

3.1. Study Design

The analysis of current patterns of care by the use of routine data from electronic patient records or clinical registries may help highlight deficiencies in actual care (Hoelzer *et al*, 1999). The 'chart review' study design has been used successfully to extract relevant data in a number of psychiatric studies (Baldassano *et al*, 2004; Barzman *et al,* 2004; Bloch *et al,* 2005; Dworkin, 1987; Henderson *et al*, 2004; Staller, 2004), and retrospective chart reviews have been used to determine whether current guidelines are being followed (Remington *et al*, 2001).

A descriptive, retrospective, three-times sampling, cross-sectional, chart review was considered a suitable design to compare the prescribing of psychotropic medication with six clinical practice guidelines. If the results of this study prove to be a source of concern, the findings may be used by other researchers to generate a testable hypothesis.

3.1.1. Advantages of the study design

Chart reviews offer a relatively inexpensive way to research the rich readily accessible existing data (Gearing *et al*, 2006), there is no workload for hospital staff, no inconvenience for departments or interruptions of the health-care process, and the data collection is easy to plan and execute (Michel *et al*, 2004). Cross-sectional studies are usually used to determine the prevalence of variables under study - for example: a condition (Mann, 2003). A particularly useful application of a retrospective study is as a pilot study that is completed in anticipation of a prospective study. A retrospective study can help to focus the study question, clarify the hypothesis, determine an appropriate sample size and identify feasibility issues for such a prospective study (Hess, 2004).

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3.1.2 Disadvantages of the study design

There are, however, disadvantages of the design: it is not possible to distinguish the patients by severity of illness or to identify precisely why certain approaches to treatment were undertaken (Remington *et al*, 2001). Acquisition of adequate patient data for clinical management is hard enough, but higher quality patient data are needed for clinical audit and research (Wyatt, 1995). Furthermore, in retrospective chart reviews, missing data can result in a hidden or non-response bias in the results (Worster & Haines, 2004).

3.2. Recommendations made in six clinical practice guidelines for the pharmacological management of schizophrenia.

Many of the original guidelines for the pharmacotherapy of schizophrenia have been updated and the most recent versions were used in the study. The six guidelines included are: the Expert Consensus Guidelines (ECGs) (McEvoy *et al*, 1999), the Canadian Clinical Practice Guidelines (CCPGs) (Addington *et al*, 2005), the Australian and New Zealand Guidelines (ANZGs) (McGorry, 2005), the National Institute for Clinical Excellence Guidelines (NICEGs) (NICE, 2009), the American Psychiatric Association Guidelines (APAGs) (American Psychiatric Association, 2004) and the South African Guidelines (RSAGs) (Stein *et al*, 2005)

A brief overview of the parameters that are considered in this study now follows. The reader is referred to the tables in Appendix B for more detail on the topics. All dosages are in milligrams per day - unless otherwise stated. Where no advice is given in a guideline, no comment was made.

3.2.1 Emergency management – choice of drug and drug dose - Appendix B - Table 1

SGAs are recommended as the first choice by CCPGs, ANZGs, NICEGs and APAGs, with or without benzodiazepines (ANZGs and APAGs). FGAs are given as an option in NICEGs and APAGs but are advised against by ANZGs; zuclopenthixol may be considered (CCPGs) and 'rapid neuroleptisation' is to be avoided (NICEGs). If the patient

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accepts oral medication, this is preferred; if not, parenteral administration may be necessary (ANZGs, APAGs). Suggested doses include: olanzapine 10 (CCPGs); lorazepam 1-2, diazepam 5-10; olanzapine 5-10,quetiapine 50-100 (ANZGs). If the patient is combative, midazolam 5, clonazepam 0.5-2, may be used (ANZGs).

3.2.2 Acute phase (non-emergency) in first episode patient – Appendix B - Table 2

SGAs are the drugs of first choice (ECGs, CCPGs, ANZGs and RSAGs) and also the second choice (ANZGs). Either SGAs or FGAs are the first choice (NICEGs) and may be used as first-line therapy in South Africa where SGAs may not be available (RSAGs). Benzodiazepines are suggested to control agitation while antipsychotic dose is titrated (CCPGs). See Appendix B for the starting, target and maximum daily doses of haloperidol, olanzapine, quetiapine, risperidone, ziprasidone, amisulpride and aripiprazole are given (ECGs, CCPGs, and ANZGs). Dosages may be titrated at not less than weekly intervals (CCPGs, ANZGs) and if poor response increased over four weeks to maximum dose (ANZGs).

3.2.3 Acute phase pharmacotherapy (non-emergency) in multiple episode patient - Appendix B - Table 3

SGAs are recommended as first-line treatment (ECGs, CCPGs, APAGs and RSAGs), however, APAGs acknowledge that FGAs may be appropriate for individual patients. NICEGs recommended either class as the patients' circumstances dictate. Switching from FGAs to SGAs is generally recommended if the patient has relapsed while on FGAs or there are efficacy or tolerability problems (ECGs and ANZGs). FGAs are recommended if there are tolerability problems on SGAs (ANZGs) or if they are unavailable (RSAGs), whereas FGA-depot is considered to be the last resort (ECGs). In the event of treatment-resistance, switch to clozapine (ANZGs). See Appendix B for the starting, average and maximum doses of haloperidol, olanzapine, quetiapine, risperidone, ziprasidone (ECGs and CCPGs). An adequate length of a trial on 'adequate' or 'optimum' doses of a drug is six to seven weeks (ECGs), four to eight weeks (CCPGs), four to six weeks (NICEGs), two weeks to six months (APAGs). It will be noted that the dosages recommended in the multiple episode patient are higher than in the patient with first-episode schizophrenia.

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3.2.4 Stabilization phase pharmacotherapy- Appendix B - Table 4

Controlled trials have provided relatively little guidance for medication treatment during this phase (APAGs). Depression is common during this phase and an antidepressant may be required, medications used for short-term control of agitated behaviour during the acute phase may be inappropriate, and the use of depot formulations should be considered to reduce medication non-compliance (CCPGs).

3.2.5 Stable phase pharmacotherapy- Appendix B - Table 5

SGAs are recommended by ECGs and CCPGs) and FGA or SGA by APAGs. Monotherapy is advised by all. The CCPGs state that there is a high level of individual variability in the dose of antipsychotic required in this phase. Anticholinergic prophylaxis for extrapyramidal side-effects is not recommended by some guidelines (ECGs and APAGs) but permitted by APAGs.

3.2.6 Pharmacotherapy if inadequate response to treatment – Appendix B - Table 6

If the inadequate response was to an FGA, switching to an SGA is recommended or implied in all six of the guidelines used in this study. If the first drug was an SGA, increasing the dose – if tolerated by the patient - is recommended for a short period such as two to four weeks (ECGs and APAGs). Adjunctive therapy (e.g. lithium) is considered to be an option (ANZGs), a trial of an agent with a unique structure and mechanism is also suggested (RSAGs), and if poor adherence is noted, an SGA-depot is advised (ANZGs). All guidelines agree that if sequential trials of FGAs and SGAs have been attempted without success, switching to clozapine is the appropriate course of action. If clozapine alone is unsuccessful, antipsychotic polypharmacy may be attempted; such an augmentation may be needed up to eight to ten weeks, and an agent that does not compound the common side-effects of clozapine should be used (NICEGs). Where severe symptoms are refractory to medication, electroconvulsive therapy should be considered (RSAGs).

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3.2.7 Pharmacological management of symptoms associated with psychosis – Appendix B - Table 7

For aggression/violence, clozapine is recommended (ECGs, CCPGs and APAGs), high potency FGAs and valproate (ECGs), or the use of mood stabilizers and beta-blockers (APAGs).
For agitation/excitement, benzodiazepines are advised (CCPGs, ANZGs and APAGs).
For insomnia, benzodiazepines (ANZGs and APAGs), a sedating antidepressant such as trazodone or mirtazepine (APAGs) or SGA or low-potency FGA (ECGs) are suggested.
For dysphoria/depression, recommended are selective serotonin reuptake inhibitors (SSRIs) (ECGs), 'antidepressants' (CCPGs, ANZGs and APAGs), SGAs (ECGs and CCPGs) and mood stabilizers (ANZGs).
Suicidal behaviour may be managed with SGAs (ECGs and CCPGs), clozapine (ANZGs and APAGs), and if psychotic depression is present, an SSRI is recommended.

3.2.8 Pharmacological management of extrapyramidal side-effects – Appendix B - Table 8

The CCPGs guidelines state that when used in the recommended dosage range, risks of neurological effects from SGAs are minimal, and that anticholinergic medication is usually not recommended with their use. If akathisia is present, however, the use of a benzodiazepine or beta-blocker is advised if dosage reduction is insufficient. Akathisia may also be relieved by benzodiazepines, beta-blockers (RSAGs), diphenhydramine and amantadine (APAGs). For mild tardive dyskinesia, switching from an FGA to an SGA is advised (ECGs and APAGs), but if severe, clozapine could be used (ECT and APAGs). Other extrapyramidal adverse effects may be managed by antipsychotic dose-reduction or switching from high- to low-potency FGAs, or by switching from an FGA to an SGA (RSAGs).

3.2.9 Depot formulation – Appendix B - Table 9

Depot use should be considered for patients who prefer it, those who have trouble taking oral medication reliably and for patients with partial or full non-adherence to pharmacological treatment (ECGs, ANZGs, NICEGs, APAGs and RSAGs). The depot form of the same oral medication should be used (APAGS). The transition from oral to

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depot treatment can begin during the acute phase but it is not a substitute for the acute psychotic episode as it can take months to reach a steady-state (APAGs).

3.2.10 Polypharmacy – Appendix B - Table 10

Non-antipsychotic polypharmacy is often appropriate where it may be justified by co-morbid symptoms. Antipsychotic polypharmacy, however, is strongly discouraged, but considered acceptable under certain circumstances: if switching is in progress (ANZGs and NICEGs), if a patient becomes acutely psychotic while on depot treatment it may be useful to supplement it with oral medication for a temporary period (APAGs), and (as indicated above) if clozapine alone is unsuccessful another antipsychotic may be added. The CCPGs guidelines suggest that clozapine may be augmented with lithium, anticonvulsants, antidepressants, benzodiazepines and electro-convulsive therapy. If clozapine alone is unsuccessful, antipsychotic polypharmacy may be attempted; such an augmentation may be needed up to eight to ten weeks, and an agent that does not compound the common side-effects of clozapine should be used (NICEGs).

3.3. Strategy of inquiry, data collection and instrumentation

In a retrospective chart review, sampling refers to the method by which study cases or records are selected from the target population or database (Worster & Haines, 2004).

3.2.1 Data Collection method/s – Instrumentation

Data was collected using structured record reviews, the data abstraction instrument having been designed specifically for the study - see 'Appendix C'.

3.2.2 Target and sample populations

The target population included all non-forensic patients between 18 and 65 years of age with the diagnosis of schizophrenia and who were prescribed antipsychotic medication during their hospital stay and upon hospital discharge. The sample population included all

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non-forensic patients between 18 and 65 years of age with the diagnosis of schizophrenia, who were admitted to the hospital between September 2007 and September 2010 and who were prescribed antipsychotic medication both during their hospital stay (for two months or longer) and upon hospital discharge. This three year period was chosen to ensure that all the patients in the study were treated with the same range of psychotropic medication which had been made available in September 2007 by the Department of Health, according to Circular Letter Number 35 of 2007. The formulary of relevant drugs used in the study is given in 'Appendix D'.

3.2.3 Sampling type and method

Given that the clinical practice guidelines that were examined make recommendations with respect to the phases of schizophrenia (emergency, acute and stabilization/stable) three data collection points were chosen which correspond roughly to the prescriptions written for patients upon admission, at fourteen days and upon hospital discharge. Another reason why sampling at more than one point is required is to examine the use of polypharmacy; Miller & Craig (2002) explain that a single cross-sectional analysis of frequency of use of combination antipsychotics does not distinguish between short- and long-term use.

A study of the prescribing for a patient upon hospital discharge has merit. Soher *et al* (2003) found that treatment falling within antipsychotic medication dosage guidelines upon hospital discharge was associated with improvement in a limited, but critical range of short-term patient outcomes. Furthermore, a study by Young *et al* (1998) showed that many schizophrenic patients received poor-quality care at outpatient clinics and that most poor care was due to factors that could be modified

A minimum period of hospital stay of two months or longer was decided upon. Missing values were treated by deleting the case - which according to Dworkin (1987) and Worster and Haines (2004) is an acceptable method of dealing with this – and selecting another

A non-probability, purpose, sampling method was used to select the subjects. The chief clerk at the patients' registry used the computerized information system to search the patients' database for the files (containing the prescriptions) of all patients according to diagnostic code for schizophrenia. The files were then drawn and the inclusion and exclusion criteria were applied to determine if the patients' prescribing details were

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appropriate for inclusion into the study. If not, the file was replaced and the next was assessed. The prescriptions of all eligible patients were examined at the three data collection points were examined and details of all psychotropic (only) medication was noted, including: drug class, route of administration, drug name, dosage and whether given routinely or as required ('pro re nata' or 'PRN' for short). Medication for physical disorders was not recorded.

3.2.4 Inclusion criteria

Patients between the ages of 18 and 65 years with the diagnosis of schizophrenia, and who were hospitalized for a period of two months or longer, and were treated with antipsychotic medication during hospital stay and upon discharge were be included in the study.

3.2.5 Exclusion criteria

Forensic patients were excluded from the study, as were patients under the age of 18 years and over the age of 65 years. Also excluded were patients with schizoaffective disorder and those who had been hospitalised for a period shorter than two months.

3.4. Data Abstraction

The following information was recorded: the duration of hospital stay and details of all psychotropic medication prescribed upon admission and discharge of the patient. The class, name, dose, route of administration (orally or by depot injection) and if administered routinely or PRN, of each psychiatric drug (only) was noted.

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3.5. Data Analysis

The use of the following prescribing indicators that were highlighted in the six clinical practice guidelines were examined at the three data collection points described.

3.5.1 Antipsychotic drugs

- Oral FGAs vs. SGAs
- Rapid neuroleptisation/tranquilization
- Antipsychotic polypharmacy (either the concurrent use of depot and oral antipsychotic medication or more than one oral drug – including SGAs)
- High dose antipsychotic therapy (either from the prescription of a single antipsychotic in a dose that is above the recommended maximum, or two or more antipsychotics that, when expressed as a percentage of their respective maximum recommended doses and added together, result in a cumulative dose of >100%). Both the mean and median dosages of antipsychotic and other drugs were used given that use of the mean dose only may result in spurious conclusions.
- PRN antipsychotic sedation
- Depot antipsychotic drugs

3.5.2 Anticholinergic drugs

- Choice
- Dose
- Anticholinergic medication with SGAs (i.e. in the absence of FGAs)
- Prophylactic and routine prescribing of anticholinergic drugs

3.5.3 Sedative drugs

- Choice
- Dose
- Prolonged use of sedative drugs
- Irrational polypharmacy of other psychotropic medication (e.g. the use of two benzodiazepines)

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3.5.4 Choice and dose of adjuvant and other drugs

- Antidepressants
- Lithium
- Anticonvulsants

The descriptive nature of this study and basic statistics that will be used (e.g. percentages) does not warrant the services of a statistician.

3.6 Summary of methodology

The methodology comprised an anonymous, descriptive, retrospective, three-times sampled, cross-sectional, chart review of the psychotropic medication prescribed for all patients with the diagnosis of schizophrenia who were admitted and discharged from the hospital between September 2007 and September 2010 and who were given antipsychotic treatment during hospital stay and upon hospital discharge. Data about the drug class, choice, dose, duration, route of administration and whether given routinely or PRN were analysed and compared with the recommendations made in six clinical practice guidelines for the pharmacological treatment of schizophrenia.

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Chapter 4 - Results

A description of the findings at each of the three sampling points – on admission, after fourteen days and on hospital discharge – now follows

4.1. Prescribing on hospital admission – first- and multiple-episode patient numbers combined

In this study, the patients admitted to the hospital were either newly referred from the psychiatric unit at one of a large number of general hospitals in the geographic catchment area that is served by the Facility or had previously been treated there. Many patients had been detained for treatment, having been assessed as dangerous towards themselves or others and/or were found to be unable to care for themselves or manage their own affairs. Upon arrival, some patients had already been medicated with antipsychotic and other psychotropic drugs - medication that might have been continued for several days before/if a change was made during their stay in hospital. A comparison of the medication received by this diverse group of patients presenting for admission may therefore not necessarily reflect the quality of prescribing at the hospital.

There are, however, a number of findings that may be relevant both on their own and when compared with prescription chart sampling at fourteen days following admission and again upon hospital discharge.

4.1.1. Antipsychotic drug prescribing on admission

Choice of antipsychotic drug on admission

From Table 4.1.1.1 'Choice of antipsychotic drug/s on admission' it will be noted that the orally administered FGAs that were prescribed to patients admitted to the hospital included haloperidol, trifluoperazine and chlorpromazine; the oral SGAs were risperidone and clozapine; and the depot antipsychotic zuclopenthixol. Of the 70 patients in the study, 58 (82.8%) were prescribed FGAs exclusively on a routine basis (haloperidol was chosen in 56 (80%) cases, chlorpromazine in 1 and trifluoperazine in the remaining 1). Eleven patients (15.7%) received SGAs routinely (risperidone was used on 10 occasions and clozapine on 1). Only 1 patient (1,4%) was not prescribed an antipsychotic drug for routine use.

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Also noted in Table 4.1.1.1 is that 2 patients were prescribed a combination of an oral FGA and a depot FGA (trifluoperazine with zuclopenthixol for one and haloperidol and zuclopenthixol for the other).

Table 4.1.1.1. Choice of antipsychotic drug on admission

Drug class and route/ N = number of patients on the drug	**Drug name**	**Mono- / poly-therapy**	**Number of patients on the drug**	**Percentage**
FGA (oral) N=58 (82.8%)	haloperidol N=56 (80%)	monotherapy	53	75.7
		with prn clothiapine	2	2.8
		with depot zuclopenthixol*	1	1.4
	chlorpromazine	monotherapy	1	1.4
	trifluoperazine	with depot zuclopenthixol**	1	1.4
SGA (oral) N=11 (15.7%)	risperidone N=10 (14.3%)	Monotherapy	9	12.8
		with PRN clothiapine	1	1.4
	clozapine	with PRN clothiapine	1	1.4
No antipsychotic			1	1.4
Totals N=70			70	100

For depot use – see * and **

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Dose of antipsychotic drug on admission

Table 4.1.1.2 'Dosage parameters of the two most frequently prescribed antipsychotic drugs on admission' shows the number of patients who received the two most commonly prescribed antipsychotics for monotherapy. Haloperidol antipsychotic monotherapy was given to 51 (72.8%) patients, with an average dose of 4.8mg/d, a standard deviation of 0.83, with a dose range of 2.5mg/d to 7.5mg/d and a median dose of 5mg/d. Eight patients received risperidone antipsychotic monotherapy at an average dose of 4mg/d, with a standard deviation of 2, a dose range of 2mg to 6mg/d and a median dose of 4mg/d. The average and median doses of haloperidol differed by only 0.2mg/d and the average and median doses of risperidone were identical.

Chlorpromazine was used for 1 patient with a dosage of 200mg/d, trifluoperazine was given to 1 patient at a dosage of 5mg/d and the patient who was receiving clozapine was prescribed a dose of 525mg/d.

Of the 2 patients who received zuclopenthixol depot medication in addition to an antipsychotic to be taken orally, average dosages were calculated to be 37.5mg/wk (milligrammes per week) and 50mg/wk.

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Table 4.1.1.2. Dosage parameters of the two most frequently prescribed oral antipsychotic drugs on admission

Drug name	mono-poly-therapy	Number of patients on drug	Percent-age	Average dose (mg/d)	SD* of dose	Range of dose (mg)	Median dose (mg/d)
haloperidol	mono-therapy	51	72.8	4.8	0.8	2.5 - 7.5	5
risperidone	mono-therapy	9	12.8	4	2	2 - 6	4

* standard deviation

4.1.2. Anticholinergic drug prescribing on admission

Choice of anticholinergic drug on admission

As will be noted from table 4.1.2 'Anticholinergic drug prescribing on admission', orphenadrine and biperiden were the only anticholinergic drugs used for newly admitted patients. Ten (14.2%) patients were prescribed anticholinergic medication for routine use (orphenadrine to 9 *i.e.* 12.8% patients and biperiden to the remaining 1). There were no prescriptions for the use of anticholinergic medication for use on a PRN basis.

Dose of anticholinergic drug on admission

Table 4.1.2 also shows that the both the mean and median doses of orphenadrine prescribed for the 9 patients was 100mg/d with a dose range from 50mg/d to 150mg/d. The patient who received biperiden was given a dose of 6mg/d.

Table 4.1.2. Anticholinergic drug prescribing on admission

Drug name	Number of patients on drug	Per-centage	Mean dose (mg/d)	SD* of dose	Range of dose	Median dose (mg/d)
Orphenadrine	9	12.8	100	35.3	50-150	100
Biperiden	1	1.4	6	-	-	-
No anti-cholinergic drug	60	85.7	-	-	-	-
Totals N=70	70	100	-	-	-	-

* standard deviation

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4.1.3. Sedative drug prescribing on admission

Choice of sedative drug on admission

As may be seen in Table 4.1.3 'Sedative drugs prescribed on admission', the benzodiazepines clonazepam and lorazepam were the only sedating drugs that were prescribed. 6 of the 70 patients (8.5%) were given routine (only) sedation (clonazepam in 5 cases and lorazepam in 1). 55 (78.6%) patients received PRN (only) sedation (clonazepam in 31 (44.3%) cases and lorazepam in 24 (34.3%). Seven (10%) patients received both routine and PRN sedation, only 2 patients were not prescribed any sedation.

Dose of sedative drug on admission

Table 4.1.3 also shows that the patients who were prescribed clonazepam on a routine basis received a mean dosage of 3.5mg/d and a median dose of 3.25mg/d. Of the 31 (44.3%) patients who received clonazepam PRN (only), the mean dose was 5.2mg/d, the standard deviation was 5.1 and the dose range was 1mg to 12mg/d. The median dose of PRN clonazepam was 3.5mg/d. The single patient who received lorazepam routinely was given a dose of 2mg/d. Of the 24 (34.3%) prescriptions for lorazepam PRN (only), the average dose was 6.58mg/d, the standard deviation was 5.9 and the dose range was between 1 and 20mg/d. The median PRN dose for lorazepam was 7mg/d.

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Table 4.1.3. Sedative drugs prescribed on admission

Drug name/ N = number of patients on the drug	Routinely / PRN	Number of patients on the drug	Per-centage	Mean dose (mg/d)	SD* of dose	Range of dose (mg)	Median dose (mg/d)
clonazepam N=43 (61.4%)	Routinely	5	7.1	3.5	1.6	1.5-5.5	3.25
	PRN	31	44.3	5.2	5.1	1-12	3.5
	Routinely and PRN	7	10	-	-	-	-
lorazepam N=25 (35.7%)	Routinely	1	1.4	2	-	-	-
	PRN	24	34.3	6.5	5.97	1-20	7
	Routinely and PRN	0	0	-	-	-	-
No sedative drug used N=2 (1.8%)		2	1.8	-	-	-	-
Total N=70		70	100	-	-	-	-

* standard deviation

4.1.4 . Other psychotropic drugs prescribed on admission

Sodium valproate (as Epilim CR©) was prescribed routinely to 7 (10%) patients at a mean dose of 1 314mg/d, with a standard deviation of 429.8, a range from 800mg/d to 1600mg/d and a median dose of 1200mg/d

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4.2. Prescribing at 14 days after admission

4.2.1. Antipsychotic drug prescribing at 14 days after admission

Both first- and multiple-episode patient numbers combined

From Table 4.2.1.1 'Antipsychotic drug prescribing at 14 days after admission (first- and multiple- episode patient numbers combined)' it will be noted that at 14 days, there were 37 (52.8%) prescriptions for FGAs (34 *i.e.* 48.6%) for haloperidol and 1 each for chlorpromazine, trifluoperazine and flupentixol. The table also shows that there were 29 (41.4%) prescriptions for SGAs, (25 *i.e.* 35.7%) for risperidone, 2 for clozapine and 2 for olanzapine). Three prescriptions were for depot antipsychotic monotherapy, however, combination oral and depot antipsychotic drugs were prescribed for 9 (12.8%) patients. Only 1 patient did not receive any antipsychotic therapy.

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Table 4.2.1.1. Antipsychotic drug prescribing at fourteen days after admission (first- and multiple- episode patient numbers combined)

Drug class/route, N = number of patients on drug	Drug name	Mono- / poly-therapy	Number of patients on the drug	Percentage
FGA (oral) N=37 (52.8%)	haloperidol N=34 (48.6%)	monotherapy	26	37.1
		with prn clothiapine	1	1.4
		with depot flupentixol*	4	5.6
		with depot zuclopenthixol**	3	4.2
	flupentixol (oral)	monotherapy	1	1.4
	chlorpromazine	monotherapy	1	1.4
	trifluoperazine	with depot zuclopenthixol**	1	1.4
SGA (oral) N=29 (41.4%)	risperidone N=25 (35.7%)	monotherapy	23	32.8
		with PRN clothiapine	1	1.4
		with depot flupentixol*	1	1.4
	clozapine	monotherapy	1	1.4
		with PRN clothiapine	1	1.4
	olanzapine	monotherapy	2	2.8
FGA depot only N=3 (4.3%)	flupentixol	Monotherapy – see * for combinations	2	2.8
	zuclopenthixol	Monotherapy – see ** for combos	1	1.4
No antipsychotic N=1 (1.4%)			1	1.4

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Antipsychotic prescribing for the 12 first-episode patients at 14 days after admission

Choice of antipsychotic drug for first-episode patients at 14 days after admission

Table 4.2.1.2 'Antipsychotic drug prescribing at fourteen days after admission (first episode patients only' shows that all 12 of the patients who presented with first-episode schizophrenia received antipsychotic medication to be taken routinely by mouth (haloperidol was prescribed for 8 patients, risperidone for 3 and olanzapine for 1).

Dose of antipsychotic drug for first-episode patients at 14 days after admission

The average dose of haloperidol prescribed for patients with first-episode schizophrenia was 6.5mg/d, the standard deviation was 2.6, the lowest dose in the range being 2.5mg/d and the highest 10mg/d. The median dose of haloperidol monotherapy was 5mg/d. The 3 patients who were prescribed risperidone received doses of 3mg/d, 6mg/d and 4mg/d respectively.

Table 4.2.1.2. Antipsychotic drug prescribing at 14 days after admission – first episode patients only

Drug class/ N = number of patients on the drug	**Drug name**	**Number of patients on the drug**	**% of first episode patients**	**Mean dose (mg/d)**	**SD* of dose**	**Range of dose**	**Median dose (mg/d)**
FGA (oral) N=8	haloperidol mono-therapy	8	66	6.5	2.6	2.5-10	5
SGA (oral) N=4	risperidone mono-therapy	3	25	-	-	-	-
	olanzapine mono-therapy	1	8.3	-	-	-	-
Totals N=12		12	100	-	-	-	-

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Prescribing for the 58 multiple-episode patients at 14 after admission

Choice of antipsychotic drug for multiple-episode patients

Table 4.2.1.3 'Antipsychotic drug prescribing at 14 days after admission for multiple-episode patients' demonstrates that 19 (32.8%) of the 58 patients with multiple-episode schizophrenia received haloperidol antipsychotic monotherapy and 22 (37.9%) further patients were prescribed risperidone antipsychotic monotherapy. Other oral antipsychotic monotherapy included flupentixol, chlorpromazine, trifluoperazine, clozapine and olanzapine; depot antipsychotic monotherapy included flupentixol and zuclopenthixol; various antipsychotic polypharmacy may be noted from the table. One patient did not receive any oral antipsychotic medication at this time.

At 2 weeks after admission, 2 patients received depot antipsychotic monotherapy – 1 was prescribed flupentixol and the other zuclopenthixol. Combination depot and oral antipsychotic polypharmacy was given to 6 patients, which included oral haloperidol with flupentixol depot (4 patients), oral haloperidol with zuclopenthixol depot (t3 patients), oral trifluoperazine with zuclopenthixol (1 patient) and risperidone with flupentixol depot (1 patient).

Dose of antipsychotic drug for multiple-episode patients

Table 4.2.1.3 also shows the average dose of haloperidol to be 5.1mg/d, with a standard deviation of 1.5, a dose range of 2.5mg/d to 10mg/ and a median dose of 5mg/d. The average dose of risperidone was 3.4mg/d, with a standard deviation of 1.4, a dose range of 1mg/d to 6mg/d and a median dose of 3.5mg/d. The remaining drugs and dosages for oral antipsychotic monotherapy were: flupentixol of 1mg/d, chlorpromazine of 400mg/d, clozapine of 200mg/d and two prescriptions for olanzapine of 10mg and 20mg respectively

The average dosage of flupentixol depot was calculated to be 7.1mg per week and for zuclopenthixol depot it was 57.5mg per week. The lowest individual dose of flupentixol depot was 5mg per week and the highest was 10mg/wk. The lowest individual dose of zuclopenthixol was 37.5mg per week and the highest was 100mg per week.

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Table 4.2.1.3. Antipsychotic drug prescribing at 14 days after admission – multiple-episode patients receiving haloperidol, risperidone and olanzapine

Drug class/ N = number of patients on the drug	Drug name	Number of patients on the drug	Per-centage	Mean dose	SD* of dose	Range of dose	Median dose (mg/d)
FGA (oral) N=19 (27.1%)	haloperidol mono-therapy	19	32.8	5.1	1.5	2.5-10	5
SGA (oral) N=23 (32.8%)	risperidone mono-therapy	22	37.9	3.4	1.4	1-6	3.5
	olanzapine mono-therapy	1	1.7	-	-	-	-
All other antipsychotic treatment – both oral and depot forms		15	25.8	-	-	-	-
No antipsychotic treatment – neither oral nor depot form		1	1.7	-	-	-	-
Totals N=58		58	100	-	-	-	-

* standard deviation

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4.2.2. Anticholinergic drug prescribing at 14 days after admission (first- and multiple- episode patient numbers combined)

Choice of anticholinergic drug at 14 days after admission

Table 4.4.2. 'Anticholinergic drug prescribing at 14 days after admission (first- and multiple- episode patient numbers combined) gives details of anticholinergic use at this time. At 14 days after admission, no anticholinergic medication was prescribed for any patient with first-episode illness – neither routinely nor PRN. Ten (14.2%) of the full complement of 70 patients in the study were prescribed anticholinergic medication on a routine basis at this time (9 patients received orphenadrine and 1 was given biperiden). With regard to the antipsychotic prescribing associated with the use of anticholinergic drugs, of these 10 patients, 8 were prescribed antipsychotic medication by mouth only, 1 was receiving antipsychotic treatment by both oral and depot routes and 1 patient was receiving no antipsychotic medication at all. There were no prescriptions for anticholinergic drugs to be given PRN.

Dose of anticholinergic drug at 14 days after admission

Both the mean and median doses for orphenadrine were 100mg/d with a standard deviation of 35.3 and a dose range of 50 to 150mg/d, while the dose of biperiden was 6mg/d.

Table 4.2.2. Anticholinergic drug prescribing at 14 days after admission (first- and multiple- episode patient numbers combined)

Drug name	Number of patients on the drug	Per-centage	Mean dose (mg/d)	SD* of dose	Range of dose	Median dose (mg/d)
orphenadrine	9	12.8	100	35.3	50-100	100
biperiden	1	1.4	6	-	-	-
No anti-cholinergic	60	85.7	-	-	-	-
Totals N=70	70	100	-	-	-	-

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4.2.3. Sedative drug prescribing at 14 days after admission (first- and multiple-episode patient numbers combined)

Choice of sedative drug at 14 days after admission

As will be noted from Table 4.2.3 'Sedative drug prescribing at 14 days after admission (first- and multiple- episode patient numbers combined)', 6 (8.5%) patients were prescribed sedation on a routine basis only (5 patients received clonazepam and 1 lorazepam). Forty-eight patients (68.5%) were prescribed PRN sedation only (32 *i.e.* 45.7% received clonazepam and 16 *i.e.* 22.8% were prescribed lorazepam). Both routine and PRN sedation were given to 7 (10%) patients while a further 7 patients (10%) were not prescribed any sedation.

Dose of sedative drug at 14 days after admission

Table 4.2.3 also shows that the average dose of clonazepam prescribed routinely (only) was 5.2mg/d, with a standard deviation of 3.9 and a range of 1mg/d to 12mg/d. The median dose was found to be 5mg/d. The dose for the patient who received lorazepam routinely was 6mg/d. The average dose of clonazepam PRN (only) was 5.1mg/d, the standard deviation was 6.7, a range of 1mg/d to 24mg/d and a median dose of 4.5mg/d. The average dose of lorazepam PRN (only) was 5.9mg/d, with a standard deviation of 6.8, a range of 1mg/d to 20mg/d and a median dose of 7mg/d.

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Table 4.2.3. Sedative drug prescribing at 14 days after admission (first- and multiple- episode patient numbers combined)

Drug name/ N = number of patients on the drug	Routinely / PRN	Number of patients on the drug	Per-centage	Mean dose (mg/d)	SD* of dose	Range of dose (mg)	Median dose (mg/d)
clonazepam alone N=43 (61.4%)	Routinely	5	7.1	5.2	3.9	1-12	5
	PRN	32	45.7	5.1	6.7	1-12	4.5
	Routinely and PRN	6	8.6	-	-	-	-
lorazepam alone N=18 (25.7%)	Routinely	1	1.4	3	-	-	-
	PRN	16	22.8	5.9	6.8	1-20	7
	Routinely and PRN	1	1.4	-	-	-	-
clonazepam routinely with lorazepam PRN		1	1.4	-	-	-	-
lorazepam routinely with clonazepam PRN		1	1.4	-	-	-	-
No sedative drug used N=7 (10%)		7	10	-	-	-	-

* standard deviation

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4.2.4. Other psychotropic drugs prescribed at 14 days after admission

Sodium valproate

Sodium valproate (as Epilim CR) was prescribed routinely to 14 patients (20%) (2 of whom were first-episode patients). 13 (18.5%) of these were also receiving an antipsychotic drug for oral administration and one was prescribed a depot. Sodium valproate was prescribed at a mean dose of 1200mg/d with a standard deviation of 389.2, a range of 600mg/d to 1600mg/d and a median dose of 1200mg/d.

Fluoxetine

At 14 days following admission, fluoxetine was administered to 2 patients at dosages of 20mg/d and 40mg/d. Neither of these patients received sodium valproate.

Lithium carbonate

1 patient received lithium carbonate at a dosage of 400mg/d. This patient did not receive sodium valproate or an antidepressant.

4.3. Prescribing on hospital discharge – first- and multiple-episode patient numbers combined

4.3.1. Antipsychotic drug prescribing on hospital discharge

Choice of antipsychotic drug on discharge

As will be noted from Table 4.3.1.1 'Antipsychotic drug prescribing on hospital discharge' 69 (98.5%) patients received routine antipsychotic medication to take home when discharged from the hospital. FGA antipsychotic monotherapy to be taken routinely by mouth was given to 6 (8.6%) patients (5 received haloperidol and 1 chlorpromazine); no PRN FGAs were prescribed. SGA antipsychotic monotherapy to be taken routinely by mouth was prescribed for 31 (44.3%) patients, which included 21 (30%) prescriptions for risperidone, 2 for amisulpride, 2 for olanzapine and 6 (8.6%) for clozapine.

Depot (only) antipsychotic medication was prescribed for 5 (7.1%) patients (2 received flupentixol and 3 zuclopenthixol). Only 1 patient was not given antipsychotic medication upon discharge.

Antipsychotic polypharmacy was prescribed for 27 (38.5%) patients upon hospital discharge. This combination pharmacotherapy included: 2 orally administered drugs for 3 patients (clozapine with amisulpride for 1 patient and clozapine with risperidone for 1 patient) and an orally administered antipsychotic with a depot to 24 (34.3%) patients (this comprised flupentixol with haloperidol, risperidone or clozapine in 15 (21.4%) patients; and zuclopenthixol with the same drugs in 9 (12.8%) patients). No PRN SGAs were prescribed.

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Table 4.3.1.1 Antipsychotic drug prescribing on hospital discharge

Class/route N = number of patients on drug	Drug name	Mono- / poly-pharmacotherapy	Number of patients on drug	Percentage
FGA (oral) N=18 (25.7%)	haloperidol N=17 (24.3%)	monotherapy	5	7.1
		with depot flupentixol	8	11.4
		with depot zuclopenthixol	4	5.7
	chlorpromazine	monotherapy	1	1.4
SGA (oral) N=46 (65.7%)	risperidone N=31 (44.3%)	monotherapy	21	30
		with depot flupentixol	6	8.6
		with depot zuclopenthixol	4	5.7
	amisulpride	monotherapy	2	2.8
	olanzapine	monotherapy	2	2.8
	clozapine N=11 (15.7%)	monotherapy	6	8.6
		with depot flupentixol	1	1.4
		with depot zuclopenthixol	1	1.4
		with amisulpride	1	1.4
		with risperidone	2	2.8
FGA depot only N=5 (7.1%)	flupentixol	monotherapy	2	2.8
	zuclopenthixol	monotherapy	3	4.2
No antipsychotic treatment N=1			1	1.4

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Antipsychotic drug dose on hospital discharge

As will be noted from Table 4.3.1.2 'Dosage parameters of the two most frequently prescribed antipsychotic drugs on discharge', the average dose of haloperidol for the 5 (7.1%) patients who received the drug upon hospital discharge was 5.1mg/d, the standard deviation was 1.6 and the range was from 2.5mg/d to 7.5mg/d. The median dose was 5mg/d. For the 21 (30%) patients who were prescribed risperidone, the average dose was 4.6mg/d, the standard deviation 1.4 and the range was between 1mg/d and 6mg/d. The median dose was 4mg/d.

The average dose of flupentixol depot received by the 17 (42.3%) patients upon discharge was 9.2mg/wk with a range from 5mg/wk to 20mg/wk. For zuclopenthixol depot the average dose was 53.4mg/wk with a dose range between 37.5mg/wk and 100mg/wk.

Table 4.3.1.2 Dosage parameters of the two most frequently prescribed antipsychotic drugs on discharge

Drug name	mono-poly-therapy	Number of patients on drug	Per-centage	Average dose (mg/d)	SD* of dose	Range of dose (mg)	Median dose (mg/d)
haloperidol	mono-therapy	5	7.1	5.1	1.6	2.5-7.5	5
risperidone	mono-therapy	21	30	4.6	1.4	1-6	4

* Standard deviation

4.3.2. Anticholinergic drug prescribing on hospital discharge

Choice of anticholinergic drug on hospital discharge

As is shown in Table 4.3.2 'Anticholinergic drug prescribing on hospital discharge', upon hospital discharge there were 20 (28.5%) patients who received anticholinergic medication to be taken routinely (17 for orphenadrine and 3 for biperiden). No prescriptions for PRN anticholinergic drugs were noted.

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Dose of anticholinergic drug on hospital discharge

Table 4.3.2 also shows that the average dose of routinely administered orphenadrine was 111.7mg/d, the standard deviation was 28.1, a dose range from 50mg/d to 150mg/d and a median dose of 100mg/d. For biperiden the average dose was 4.3, the standard deviation was 1.1, the dose range was from 4mg/d to 6mg/d and a median dose of 6mg/d.

Table 4.3.2 Anticholinergic drug prescribing on hospital discharge

Drug name	Number of patients on drug	Per-centage	Mean dose (mg/d)	SD* of dose	Range of dose	Median dose (mg/d)
orphenadrine	17	24.3	111.7	28.1	50-150	100
biperiden	3	4.3	5.3	1.1	4-6	6
No anti-cholinergic drug	50	71.4	-	-	-	-
Totals	70	100	-	-	-	-

* standard deviation

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4.3.3. Sedative drug prescribing on hospital discharge

Choice of sedative drug on hospital discharge

Upon hospital discharge there were 16 (22.8%) patients who received prescriptions for benzodiazepines to be taken routinely (11 *i.e.* 15.7% for clonazepam and 5 *i.e.* 7.1% for lorazepam). Only 1 prescription limited the duration of the clonazepam to be taken routinely – this was for 14 days following hospital discharge. 5 (7.1%) prescriptions for PRN benzodiazepines (4 for clonazepam and 1 for lorazepam) were noted. No benzodiazepine sedatives were given to 49 (70%) patients and none received both routine and PRN sedation.

Dose of sedative drug dose on hospital discharge

The average dose of the routinely administered clonazepam was 1.1mg/d, with a dose range from 0.5mg/d to 2mg/d and a median dose of 1mg/d. The average dose of routinely administered lorazepam was 1.9mg/d with a dose range between 1mg/d and 2.5mg/d and a median dose of 2mg/d. The average dose of PRN clonazepam prescribed for four patients was 5.9mg/d and the median dose was 1.5mg/d. The maximum dose of PRN clonazepam (including routine prescribing) was 24mg/d and for lorazepam the figure was 2.5mg/d.

Table 4.3.3. Sedative prescribing on hospital discharge

Drug name/ N = number of patients on drug	Routinely / PRN	Number of patients on drug	Per-centage	Mean dose (mg/d)	SD* of dose	Range of dose (mg)	Median dose (mg/d)
clonazepam N=43 (61.4%)	Routinely	11	15.7	1.1	0.59	0.5-2	1.0
	PRN	4	5.7	5.9	10.1	1-24	1.5
lorazepam N=18 (25.7%)	Routinely	5	7.1	1.9	0.54	1-2.5	2
	PRN	1	1.4	-	-	-	-
No sedative drug used N=7 (10%)		49	70	-	-	-	-
Totals		70	100	-	-	-	-

* standard deviation

4.3.4. Other psychotropic drugs prescribing on hospital discharge

Sodium valproate was prescribed for routine use by 20 (28.5%) patients and the antipsychotic drugs taken with this varied. 6 patients received haloperidol in addition to sodium valproate (additionally, 2 of these patients received flupentixol depot and 2 zuclopenthixol depot). 7 (10%) patients received risperidone in addition to sodium

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valproate (with 2 of these also receiving flupentixol depot and 2 zuclopenthixol depot). A further 5 (7.1%) prescriptions were noted with combinations of sodium valproate and clozapine, 1 for amisulpride and sodium valproate and the remaining patient was given zuclopenthixol depot but no oral antipsychotic.

The average dose of sodium valproate was 1120mg/d, with a standard deviation of 375 and a range from 400mg/d to 2000mg/d. The median dose of sodium valproate was 1200mg/d.

Two of the 70 patients were prescribed fluoxetine, both at a dosage of 20mg/d (the same 2 patients who had received the drug at 14 days following admission. The same patient who was prescribed lithium carbonate previously continued to receive this at the same dosage of 400mg/d. 2 other patients received citalopram at a dosage of 10mg/d, 1 of whom was also given sodium valproate.

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Chapter 5 – Discussion

The results of the data analysis are now compared with the clinical practice guidelines used during this study, in order to assess to what extent there is agreement. The degree of concordance will determine whether or not further research is warranted to ensure that the prescribing for patients with schizophrenia is characterised as evidence-based, efficacious and safe, with less variance and greater fidelity to guidelines that are generally and universally accepted as a standard of good practice.

5.1. The choice of antipsychotic drugs in the study

5.1.1 Oral antipsychotic drug choice

As has already been mentioned, the majority of patients in this study were referred by external sources and the prescribing on admission may not be an accurate reflection of the pharmacotherapeutic practices of the clinical staff at the hospital. Despite this caveat, the very high frequency of the use of the FGA drug haloperidol by 56 (80%) patients at a dose of 5mg/d by 48 (68.6%) of these, suggests that 'haloperidol 5mg/d' is the standard prescribing practice for a patient with predominantly psychotic symptoms to the hospital.

A total of 58 (82.5%) patients received FGAs, whereas 11 (15.7%) were prescribed SGAs (10 of which were for risperidone). The preponderance of the use of FGAs over SGAs is not in keeping with the recommendations given in the clinical practice guidelines that were examined for the purpose of comparison in the study

Of note is that 'rapid neuroleptisation' was not prescribed for any patient on admission, which is consistent with the NICEGs but may reflect the fact that patients are generally referred from other centres where the patients' initial presentation may have included a greater degree of behavioural disturbance.

After 14 days in hospital, more definitive treatment is likely to have been commenced and the number of prescriptions for oral FGAs at this data collection point decreased to 37 (52.8%), including 34 (48.6%) for haloperidol. The number of prescriptions for oral SGAs rose to 30 (42.8%), including 25 (35.7%) for risperidone - these figures are for both first-

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and multiple-episode patients combined – and are more consistent with the guidelines which recommend SGAs as the drug class of first choice for both the emergency- and the non-emergency- management of the acute phase of schizophrenia.

FGAs are suggested as an option by the NICEGs if the patient and physician choose these drugs over SGAs after considering the advantages and disadvantages of both groups. The RSAGs state that FGAs may be used where SGAs are unavailable in South Africa – which is not the case in this study according to the list of available drugs in Appendix D. The ANZGs specifically advise against the use of FGAs. It will be remembered that switching from FGAs to SGAs is recommended by the ANZGs and ECGS if the patient has relapsed while on FGAs or if there are efficacy or tolerability problems and are possible reasons (*inter alia)* for greater emphasis on the prescribing of SGAs.

A high use of oral SGAs was not found when the prescriptions for only first-episode patients at fourteen days of hospital treatment were analysed: 8 of the 12 patients received haloperidol and 4 an oral SGA. Given the greater susceptibility to adverse effects of FGAs and the importance of medication compliance, SGAs are considered the drugs of first choice for first-episode schizophrenia by the ECGs, CCPGs, ANZGs and RSAGs.

By the time of hospital discharge, the orally administered antipsychotic prescribing profile showed a further reduction in the use of FGAs to 18 (24.7%) and another increase in the use of SGAs to 46 (65.7%).

The decline in oral FGA prescribing from 58 (82.8%) at the time of admission, to 27 (52.8%) after 14 days, to 18 (24.7%) may therefore be considered a positive trend according to the guidelines studied, as may the increase in oral SGA use from 11 (15.7%) newly admitted patients, to 29 (41.4%) after 14 days, to 46 (65.7%) by the time of discharge.

However, there was a concomitant increase in the use of antipsychotic polypharmacy which is discouraged by all the guidelines studied. The prescribing of oral FGA with depot FGA was noted twice on admission, this increased to 8 (11.4%) after 14 days, and to 12 (17.1%) patients on discharge. Similarly, the prescribing of oral SGA and depot FGA increased from nil on admission, to one after 14 days to 11 (15.7%) on discharge. There were no instructions on any of the prescriptions examined for a tapering or discontinuation

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of the oral antipsychotic. It is possible that such a request was made in the discharge letter to the out-patient psychiatrist, but as the clinical notes were not examined it is not known if this was the case.

5.1.2. Depot antipsychotic drug choice and antipsychotic polypharmacy

Although the increase in polypharmacy may be viewed unfavourably, the greater use of depot antipsychotic (albeit with FGA preparations) is more in accord with the guidelines studied. Whereas on admission to the hospital, only 2 (2.8%) patients were receiving depot antipsychotic drugs; at 14 days, this figure had increased to twelve (17.1%); and upon hospital discharge, there were 29 (41.3%) prescriptions for depot preparations. It has been noted that because adherence to medication is a significant factor in the relapse of patients with schizophrenia, use of the depot form of an antipsychotic is encouraged. It is recommended by ECGs, ANZGs, NICEGs, APAGs and RSAGs for patients who prefer it and for patients who may not be relied upon to take medication as prescribed.

Depot monotherapy was not noted on the prescriptions of newly admitted patients but 3 (4.3%) patients received this after 14 days, and 5 patients on discharge. It is likely that the 2 patients who received both oral and depot FGAs on admission had not presented for the first time and were patients with multiple-episode schizophrenia.

As has been noted in the review of the literature preceding this study, antipsychotic polypharmacy is discouraged by many authors on the grounds that there is no evidence-base for the practice and is seen to be counter-productive because it may result in more severe adverse reactions and thereby may reduce patients' compliance with medication. All the guidelines consulted recommend monotherapy particularly for the stable phase of schizophrenia – the increase in the use of antipsychotic polypharmacy noted on hospital discharge is not concordant with this principle, although the small increase in depot antipsychotic monotherapy may be encouraging.

5.2. Antipsychotic drug dosage and titration

Given that the use of antipsychotic polypharmacy bedevils attempts to compare the dose of an antipsychotic used in routine practice with the monotherapeutic doses found in clinical practice guidelines, it was necessary to make use of small sample sizes at some

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data collection points. Only the dosages of haloperidol and risperidone lent themselves to any useful analysis.

5.2.1. Dosages of haloperidol monotherapy

The average dose of haloperidol antipsychotic monotherapy given to 51 (72.8%) newly admitted patients was 4.8mg/d and the median dose was 5mg/d. For 8 (11.4%) first-episode patients after two weeks in hospital, the average dose was 6.5mg/d and the median dose was 5mg/d. For the 19 (32.8%) multiple-episode patients after two weeks in hospital, the mean dose was it was 5.1mg/d and the median dose was 5mg/d. For the 5 (7.1%) patients on discharge the mean dose was 5.1mg/d and the median dose was 5mg/d.

The mean and median doses were nearly identical at the sampling times - apart from the 8 first-episode patients who received haloperidol two weeks after admission. At that point, the mean dose of 6.5mg/d was higher than that prescribed for multiple-episode patients, however, the median dose was the same (5mg/d). The value of 6.5mg/d lies in the range of 5mg/d – 10mg/d which the guidelines recommend as an average target dose range for first-episode patients, however, it is difficult to draw a comparison with the guidelines because the number of first-episode patients in the study is so small.

5.2.2 Dosages of risperidone monotherapy

On admission to hospital, the mean and median dosages of risperidone were the same (4mg/d).

Three of the first-episode patients received risperidone monotherapy at 14 days after admission at dosages of 3mg/d, 4mg/d and 6mg/d. Although the patient numbers are small, the starting dosages are in excess of the guidelines for risperidone *viz.* 1mg/d - 2mg/d (ECGs), 0.5mg/d - 1mg/d (CCPGs) and 2mg/d (ANZGs).

Twenty-two (37.9%) multiple-episode patients received risperidone monotherapy at 14 days after admission at an average dose of 3.4mg/d, with a standard deviation of 1.4, a dose range of 1mg/d to 6mg/d and a median dose of 3.5mg/d. The mean and median doses were again almost identical, and these values correspond to the target daily doses

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recommended by the CCPGs of 2mg/d - 6mg/d and are lower than the 6mg/d suggested by the ECGs. These conclusions are acceptable given that only one of the patients received a depot antipsychotic.

Upon discharge, the 21 (30%) patients who were prescribed risperidone received a dose of 4.6mg/d, with a standard deviation of 1.4, a dose range of 1mg/d to 6mg/d and a median dose of 4mg/d. The median dose of risperidone at this point differed by only 0.6mg/d which may be therapeutically relevant, however, both dosages are in keeping with the guidelines mentioned above.

5.3 Choice of Anticholinergic drugs used in the study

It has been noted that on admission to hospital, anticholinergic drugs was prescribed for routine use by 10 (14.2%) patients; there were no PRN prescriptions for these drugs. The clinical practice guideline recommendations for the pharmacological management of extrapyramidal side-effects do not include the use of anticholinergic agents, and the prophylactic use of anticholinergic drugs is not recommended by the ECGs and the CCPGs. Although their use is permitted by the APAGs, these guidelines recommend using SGAs (except with high doses of risperidone) if there is a history of sensitivity to extra-pyramidal side-effects (other than tardive dyskinesia). Without the clinical history of the individual patients who received anticholinergic drugs for routine administration, it is not possible to determine if the agents were used in a way that is in keeping with guideline recommendations.

For extrapyramidal side-effects (other than akathisia and tardive dyskinesia), switching from an FGA to an SGA is advised and if the symptoms are severe, clozapine is suggested (ECGs and APAGs). Other options include dose-reduction or switching from high- to low-potency FGAs.

At 14 days following hospital admission, the same 10 (14.3%) patients who had been prescribed anticholinergic drugs continued to receive them. This was not in response to the commencement of depot antipsychotic drugs because of the 10 patients only 1 had been prescribed a depot since admission and the other patient was on no antipsychotic medication at all.

Of these 10 patients, 4 were not prescribed an FGA by mouth or via depot injection, 3 were given the SGA risperidone by mouth and the remaining patient received clozapine.

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The CCPGs state that 'anticholinergic medication is not usually recommended with the use of SGAs' - rather the reverse - the APAGs and RSAGs suggest prescribing these drugs if a patient develops extrapyramidal side-effects on an FGA. It is therefore not clear why the 3 patients who received risperidone were prescribed an anticholinergic drug for routine administration, nor is it evident why a patient who was not receiving antipsychotic treatment should be receiving an anticholinergic drug routinely. It is possible that the patient who received both clozapine and biperiden at all three data collection points was given the anticholinergic drug for clozapine-induced hyper-salivation or excessive sweating occasioned by the use of the drug, however, the potential of a pharmacodynamic interaction exists with this combination of drugs because clozapine has marked intrinsic anticholinergic properties.

On discharge, more than a quarter of the prescriptions (20 patients *i.e.* 28.6%) included anticholinergic drugs to be taken routinely. Of these, 6 were to be taken with an orally administered antipsychotic only (1 prescription was for the FGA chlorpromazine and 5 for SGAs including 3 for risperidone, 1 for amisulpride and 1 for clozapine). Three of the prescriptions for a routinely administered oral anticholinergic included a depot antipsychotic only, while the remaining 11 prescriptions for routine anticholinergic drug use included a combination of a depot and an oral antipsychotic drug (in each case the depot was an FGA but the oral medication differed in that there were 7 FGAs and four SGAs).

It is noteworthy that 7 of the 10 patients who were prescribed routine anticholinergic drugs at 14 days after hospital admission, received the same drugs upon discharge, with no stipulation as to the intended duration of use.

In summary, anticholinergic drugs were used increasingly over the three data collection points with more than a quarter of patients receiving them upon hospital discharge. The use of anticholinergic drugs in the study is not consonant with the recommendations of the clinical practice guidelines that refer to them.

5.4. Anticholinergic drug dose and titration

There was little guidance for the use of anticholinergic agents in the guidelines and comparisons could not be drawn.

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5.5. The choice of sedative drugs used in the study

On admission to hospital, 6 (8.6%) patients were prescribed benzodiazepine sedatives to be taken routinely, all of whom remained on the medication for at least 14 days, and 3 of the 6 received sedatives upon discharge (1 patient received clonazepam and 2 lorazepam).

Benzodiazepines are recommended to manage acute agitation in the emergency situation (ANZGs and APAGs) as well as in non-emergency management while titrating the dose of the antipsychotic (CCPGs). Midazolam and clonazepam are recommended by the ANZGs for the management of the combative patient.

Benzodiazepine sedation may have been prescribed as an anticonvulsant. Given that the patients' clinical notes were not examined in this study, it is not possible to determine if the sedation was given for seizure control.

A total of 16 (22.9%) patients were given benzodiazepine sedatives for routine use on discharge – only one prescription (for clonazepam) limited the number of tablets to be dispensed. The long-term use of benzodiazepines is not supported by the guidelines studied.

5.6. Sedative drug dose and titration

The mean and median dosages of routinely administered clonazepam and lorazepam were very similar from hospital admission to discharge, however, some of the mean and median dosages of medication given PRN differed considerably at two sampling points. These included the PRN prescribing of clonazepam on admission (where the mean dose exceeded the median dose by 1.7mg/d) and on discharge (where the mean dose was 4.4mg/d higher than the median dose). These differences demonstrate how calculating only the average dose of medication may not reflect the prescribing practice.

Unfortunately, little mention is made in the guidelines with regard to the dosages of benzodiazepines, however, the use of lorazepam PRN as it was prescribed could have been toxic at a dose of 24mg/day.

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5.7. Other drugs - choice and dose

5.7.1. Sodium Valproate

On admission to hospital there were 7 (10%) patients who received sodium valproate, at 14 days into their hospital stay the number had risen to 14 (20%) and on discharge more than a quarter of patient - 20 in number (28.6%) - had been prescribed the drug. The mean and median dosages of sodium valproate were either the same or very similar.

The use of mood stabilisers is recommended by the ANZGs for severe depression and by APAGs and ECGs for aggression and violence. The reason for the high number of prescriptions for sodium valproate found in this study is not clear. It is possible that the drug was used as an adjunct to antipsychotic medication in patients with treatment-resistant schizophrenia, given that 5 of the 10 patients who were given sodium valproate and clozapine on hospital discharge, but there is no clear evidence base for this practice. It was not limited to one prescriber, but to three consultant psychiatrists, and may be an idiosyncrasy of the Facility but this is speculation - the reason is unknown at this time.

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Chapter 6 – Conclusions, Limitations and Recommendations

6.1. Conclusions

Given that the clinical practice guidelines utilised in this study are based on evidence-based practice and a consensus of experts, they were considered a satisfactory standard against which to compare the prescribing practices of psychiatrists treating schizophrenia at the Facility. While the findings highlight concerns that have been identified by other studies, there are also encouraging trends towards less variance in prescribing. Some of these points are now expanded upon.

With regard to the prescribing of antipsychotic medication, as compared with the clinical practice guidelines consulted in the study there was an overuse of FGAs and an underuse of SGAs. This was noted with reference to both oral and depot drugs despite the depot form of the SGA risperidone having being available throughout the three years over which the sample population was hospitalised. It will be remembered that it is good practice for an oral SGA be followed by a depot SGA, not a depot FGA which was always the case in this study.

Although the numbers were small, the antipsychotic prescribing at 14 days is a concern given that the use of FGAs predominated and the average doses were higher than both the multiple-episode patients and the recommendations made in the guidelines for first-episode patients. The use of depot antipsychotic drugs is a positive finding, however, it is compromised by the increase in antipsychotic polypharmacy - most often due to oral and depot co-prescribing.

Routine anticholinergic drugs were given to the same 10 patients on admission as at 14 days thereafter. This is a practice that is not recommended by the guidelines consulted which suggest the use of an SGA if extrapyramidal side-effects are troublesome. It was surprising that there was no evidence of PRN anticholinergic use instead of regular use. It was also surprising that 4 patients who had been prescribed oral SGA monotherapy and 1 who was not on any antipsychotic medication were also receiving an anticholinergic drug. The potential for a pharmacodynamic interaction that exists with clozapine – which was one of the SGA drugs prescribed with an anticholinergic drug – has been mentioned.

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On hospital discharge, more than a quarter of patients were given anticholinergic agents to be taken routinely despite a lack of correlation with the use of oral or depot FGAs. This may be viewed as irrational pharmacotherapy and is not supported by the relevant guidelines. The use of benzodiazepine drugs was generally in keeping with the guideline recommendations in that they were prescribed PRN, however, the dose range of up to 24mg/d of lorazepam was unacceptably high. The reasons for 16 patients receiving ongoing routine benzodiazepine treatment is not clear from the prescriptions and is not recommended in the guidelines examined.

The high frequency of prescribing of sodium valproate was an unexpected finding. The use of the drug is recommended in the guidelines for aggression/violence and for severe depression, however, more than a quarter of all patients with schizophrenia received the drug on hospital discharge despite one of the exclusion criteria for patient selection was schizoaffective disorder. It is not clear why sodium valproate was used so frequently, especially given that there is no evidence-base for the prescribing of the drug.

While there are numerous other conclusions that may be reached from comparing the results of the data analysis of this study and comparing the parameters with those found in the clinical practice guidelines examined, a number of relevant points have been identified.

6.2. Limitations

There are a number of limitations to this study including its retrospective design with convenience sampling which may have resulted in bias.

The patients' clinical files that provide details of symptoms and progress with treatment were not examined and some of the reasons for the variance in prescribing parameters could not be determined. Examples of where this would be have been helpful include: to ascertain why sodium valproate was prescribed for so many patients; whether or not oral-depot antipsychotic polypharmacy was to have been temporary or on-going; why benzodiazepine drugs were prescribed for routine use to a large number of patients on discharge and why anticholinergic agents were used with SGA antipsychotic monotherapy. These and other questions may be answered with the benefit of detailed clinical records.

Another factor is the age of the guidelines used in this study. This a source of concern given that they range from 1998 to 2009 – a span of eleven years - the oldest of the six

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being the South African document. The local guideline was written before the use of SGAs became commonplace, whereas the pharmacy at the hospital where the study was conducted is able to supply patients with not only oral SGAs, but also in depot form.

6.3. Recommendations

By comparing the findings of this study with established standards of best practice, several concerns have been highlighted. Given the limitations of this retrospective study of prescribing data exclusively, it is recommended that a prospective pilot study with the relevant clinical information in addition to the data from the prescriptions for psychotropic agents be undertaken to qualify and quantify with greater precision the extent of fidelity or the lack thereof to standards of international best practice in the pharmacotherapy of schizophrenia.

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Appendix A

Diagnostic criteria for schizophrenia

A. *Characteristic symptoms:* Two (or more) of the following, each present for a significant portion of time during a 1-month period (or less if successfully treated):

(1) delusions

(2) hallucinations

(3) disorganized speech (e.g. frequent derailment or incoherence)

(4) grossly disorganized or catatonic behaviour

(5) negative symptoms, i.e. affective flattening, alogia or avolition

B. *Social/occupational dysfunction:* For a significant port of the time since the onset of the disturbance, one or more major areas of functioning such as work, interpersonal relations, or self-care are markedly below the level achieved prior to the onset (or when the onset is in childhood or adolescence, failure to achieve expected level of interpersonal, academic or occupational achievement).

C. *Duration:* Continuous signs of the disturbance persist for at least 7 months. This 6-month period must include at least 1 month of symptoms (or less if successfully treated) that meet Criterion A (i.e. active-phase symptoms) and may include periods of prodromal or residual symptoms. During these prodromal or residual periods, the signs of the disturbance may be manifested by only negative symptoms or two or more symptoms listed in Criterion A present in an attenuated form (e.g. odd beliefs, unusual perceptual experiences).

D. *Schizoaffective and Mood Disorder exclusion:* Schizoaffective Disorder and Mood Disorder With Psychotic Features have been ruled out because either (1) no Major Depressive, Manic, or Mixed Episodes have occurred concurrently with the active-phase symptoms; or (2) if mood episodes have occurred during active-phase symptoms, their total duration has been brief relative to the duration of the active and residual periods.

E. *Substance/general medical condition exclusion:* The disturbance is not due to the direct physiological effects of a substance (e.g. a drug of abuse, a medication) or a general medical condition.

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F. *Relationship to a Pervasive Developmental Disorder:* If there is a history of Autistic Disorder or another Pervasive Developmental Disorder, the additional diagnosis of Schizophrenia is made only if prominent delusions or hallucinations are also present for t least a month (or less if successfully treated).

(source: American Psychiatric Association: *Diagnostic and Statistical manual of Mental Disorders, 4th Ed.* Washington, DC, American Psychiatric Assoc. 1994)

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Appendix B - Table 1 - Emergency (see glossary) pharmacotherapeutic management of the acutely psychotic patient (First choice is in bold)

Recommendation	ECGs (1999)	CCPGs (2005)	ANZGs (2005)	NICEGs (2009)	APAGs (2004)	RSAGs (2005)
Emergency management: Choice of class of antipsychotic/ sedative		**SGAs**/ Zuclopenthixol	S**GAs.** Avoid FGAs. **Benzodiazepines** SGA	**SGA**/FGA Avoid 'rapid neuroleptisation'	**SGA**/FGA with/without benzodiazepine	
Route of administration		**Oral, IMI (intramuscular injection) or rapidly-dissolving form** of SGA	If accepts give **oral medication.** If refuses give IMI	For further information see NICE guideline on the management of violence	If patient accepts, give **orally (rapidly dissolving forms)** If refuses give via parenteral route	
Choice of drugs and dosages		**Olanzapine 2.5-10mg** (10mg is most frequently used)	If non-combative: **lorazepam 1-2mg or diazepam 5-10mg.** olanzapine 5-10mg or quetiapine 50-100mg If combative: **midazolam 5mg** clonazepam 0.5-2mg or olanzapine		If accepts orally: no choice of drug given If patient refuses oral medication: **haloperidol**/ **ziprasidone**/ **olanzapine** – no dosages given Can use droperidol in extreme emergency	

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Appendix B - Table 2 - Acute phase pharmacotherapy (non-emergency) in first episode patient (First choice is in bold)

Recommendation	ECGs (1999)	CCPGs (2005)	ANZGs (2005)	NICEGs (2009)	APAGs (2004)	RSAGs (2005)
Choice of class of antipsychotic/ sedative, dosages and titration	**SGA** Starting dose (mg/day) haloperidol 2-5, olanzapine 5-10, quetiapine 50-100, risperidone 1-2, ziprasidone 40-80 Average target dose (mg/day): haloperidol 5-10, olanzapine 10-15, quetiapine 300, risperidone 4, ziprasidone 80-120	**SGA** **Benzodiazepine** Start with low dose of SGA (mg/day) risperidone 0.5-1.0, olanzapine 5-10, quetiapine 100. Titrate at not less than weekly intervals to target dose of SGA (mg/day): risperidone 2-6, olanzapine 10-20, quetiapine 600 Benzodiazepines to control agitation while antipsychotic dose is titrated.	**SGA** as first and second line. Increase within 7 days to initial target dose (mg/day) risperidone 2, olanzapine 10, quetiapine 300, amisulpride 400, aripiprazole 15 Maintain for 3 weeks. If poor response, increase over next 4 weeks to maximum dose (mg/day) risperidone 4 olanzapine 20 quetiapine 600 amisulpride 800 aripiprazole 30	**SGA or FGA** Choice of drug is made with relative potential of individual drugs to cause side-effects in the specific patient		**SGA** In settings in South Africa where SGAs are not available, clinicians must rely on FGAs Use lower doses of antipsychotic drugs in first episode psychosis - (300g – 500g chlorpromazine equivalents) Give each drug trial a reasonable length of time before switching to another antipsychotic (4 to 6 weeks)

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Appendix B - Table 3 - Acute phase pharmacotherapy (non-emergency) in multiple episode patient (First choice is in bold)

Recommendation	ECGs (1999)	CCPGs (2005)	ANZGs (2005)	NICEGs (2009)	APAGs (2004)	RSAGs (2005)
Choice of class of antipsychotic/ sedative, dosages, titration and duration of trial of drug	**SGA** **I**f the patient is acutely ill despite good compliance with FGA, switch to **SGA.** If the patient is non-compliant or denies illness persistently use depot. FGA depot is last resort. Starting dose (mg/day) haloperidol 2-5, olanzapine 5-10, quetiapine 50-100, risperidone 1-2, ziprasidone 40-80 Average dose (mg/day) haloperidol 8-12 olanzapine 15-20 quetiapine 300-600 risperidone 6 ziprasidone 160 Length of trial is 6-7 weeks for drugs given above	**SGA** Introductory range (total mg/day) risperidone 0.5-1 olanzapine 5-10 quetiapine 100 Titrate up to initial target dosage in 1-2 weeks Usual target dose (total mg/day): risperidone 2-6 olanzapine 10-20, quetiapine 600 Maximum dose (total mg/day): risperidone 8 olanzapine 20 quetiapine 800 Adequate trial of 4-8 weeks on max tolerated dose in recommended range of 300mg chlorpromazine equivalents for FGAs and within approved dosage ranges for SGAs	**SGA** If acutely ill despite good compliance with FGA, switch to **SGA.** If on FGA but efficacy or tolerability problems, switch to **SGA.** If side-effects with SGA, switch to FGA or another SGA. If treatment resistance switch to clozapine	**SGA or FGA** Choice of drug is made with relative potential of individual drugs to cause side-effects in the specific patient Start with a dose at the lower end of the licensed range and titrate upward only within the range given in the *British National Formulary* Carry out a trial at optimum dosages for 4-6 weeks	Selection is guided by patients' previous experience with antipsychotics including efficacy, side-effects and preference for route of administration. **SGAs** are preferred, however, the debate over the relative advantages and disadvantages of FGAs and SGAs is acknowledged. Consider the patient's history of dose needs and response, clinical condition and severity of symptoms. Titrate the dose as quickly as tolerated to target therapeutic dose, then raise dose/change drug after 2-4 weeks. Initial response may take 2-4 weeks, full response up to 6 months. FGA dose is optimal at extrapyramidal threshold	**SGA** In settings in South Africa where SGAs are not available, clinicians must rely on FGAs Use a dose range of 300g – 1000g chlorpromazine equivalents – preferably less than 700g chlorpromazine equivalents Give each drug trial a reasonable length of time before switching to another antipsychotic (4 to 6 weeks)

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Appendix B - Table 4 - Stabilization phase pharmacotherapy

Recommendation	ECGs (1999)	CCPGs (2005)	ANZGs (2005)	NICEGs (2009)	APAGs (2004)	RSAGs (2005)
Stabilization phase		Depression is a common problem in first episode patients and antidepressant medication may be required. Medications selected for short-term control of agitated behaviour during the acute psychotic phase may not be optimal for efficacy and tolerability. The use of depot formulations is an evidence-based pharmacological intervention for reducing noncompliance with oral medication.			Controlled trials have provided relatively little guidance for medication treatment during this phase	Drug holidays and intermittent treatment are not recommended Onset of depression after treatment of the acute psychotic episode is particularly important to treat Systematic reviews of adjunctive drugs to augment antipsychotic treatment (e.g. lithium, carbamazepine) do not show a statistically significant improvement – (see Leucht *et al*, 2002)

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Appendix B - Table 5 - Stable phase pharmacotherapy

Recommendation	ECGs (1999)	CCPGs (2005)	ANZGs (2005)	NICEGs (2009)	APAGs (2004)	RSAGs (2005)
Type of antipsychotic agent for first-line use	SGA	SGA			FGA or SGA	
Monotherapy vs. polypharmacy	Monotherapy	Monotherapy	Monotherapy	Monotherapy	Monotherapy	Monotherapy
Anticholinergic prophylaxis for EPSE	Not recommended	Not recommended			Permitted	
Dose/ other		There is a high level of individual variability in the dose of antipsychotic required to achieve functional recovery with minimal side-effects.				Longer term antipsychotic drug treatment than previously is recommended, especially if SGAs are used Dosages may be reduced to 300g – 600g chlorpromazine equivalents

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Appendix B - Table 6 - Pharmacotherapy in the event of inadequate response to treatment

Recommendation	ECGs (1999)	CCPGs (2005)	ANZGs (2005)	NICEGs (2009)	APAGs (2004)	RSAGs (2005)
Inadequate response to treatment	For persistent positive symptoms, if the inadequate response was: to FGA, switch to SGA; to SGA, switch to different SGA or raise dose of first SGA; to sequential trials of FGAs and SGAs, switch to clozapine or another SGA or increase dose of SGA; to multiple previous trials including clozapine there was no expert consensus. For persistent negative symptoms, if the inadequate response was due: to FGA, switch to SGA; to SGA, switch to different SGA; to sequential trials of FGAs and SGAs, switch to clozapine or another SGA; to multiple previous trials including clozapine – no expert consensus	Treatment non-response to adequate trials of antipsychotic drugs from two different classes is an indication for a trial of clozapine	If the patient is receiving an FGA and there are persistent symptoms or side-effects, switch to an oral SGA. If the patient is receiving an FGA and was adherent to treatment, switch to an oral SGA. If treatment resistant schizophrenia is present, and at least two different antipsychotic drugs (at least one of the drugs should be a non-clozapine SGA), the offer the patient clozapine. If resistance persists, the most effective prior drug should be reinstated and adjunctive therapy used e.g. lithium. If there is poor adherence, consider SGA-depot/clozapine	If the patient's illness has not responded adequately to treatment despite the sequential use of adequate doses of at least two different antipsychotic drugs (at least one of the drugs should be a non-clozapine SGA), the offer the patient clozapine. For people with schizophrenia whose illness has not responded adequately to clozapine at an optimised dose, consider a second antipsychotic to augment treatment with clozapine. An adequate trial of such an augmentation may need to be up to 8-10 weeks. Note: Choose a drug that does not compound the common side-effects of clozapine	If the patient is adhering to treatment and has an adequate plasma concentration of medication but is not responding to treatment, alternative treatment should be considered. If the patient is able to tolerate a higher dose of antipsychotic medication without significant side-effects, raising the dose for a finite period, such as 2-4 weeks, can be tried, although the incremental efficacy of higher doses has not been well established. If a dose adjustment does not result in an adequate response, a different antipsychotic medication should be considered	Switching from one class of medication to another and using high doses of medication may be helpful. Even within the FGAs, there is a range of medication including some agents with unique structures and mechanisms (e.g. pimozide). Most importantly, clozapine is a useful consideration. There is good evidence that clozapine can be effective in patients who have failed several previous trials of antipsychotics. Where severe symptoms are refractory to medication, the need for electro-convulsive therapy should be considered.

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Appendix B - Table 8 - Pharmacological management of extra-pyramidal side-effects

Recommendation	ECGs (1999)	CCPGs (2005)	ANZGs (2005)	NICEGs (2009)	APAGs (2004)	RSAGs (2005)
Tardive dyskinesia	If mild, switch to SGA. If severe, switch to clozapine or SGA				To manage tardive dyskinesia use SGA. Can use clozapine	
Other extrapyramidal side-effects		When used in recommended dosage range, risks of neurological side-effects from SGAs are minimal. A benzodiazepine or beta-blocker may be prescribed for akathisia if dosage reduction is insufficient. Anticholinergic medication is usually not recommended with the use of SGAs			If history of sensitivity to EPSE, use SGA except high doses of risperidone To treat EPSE other than tardive dyskinesia, use benztropine mesylate, trihexyphenidyl, amantadine, propranolol, lorazepam or diphenhydramine	If patient is intolerant to a particular FGA, switch from high- to low-potency FGA or to SGA. Reducing the dose of the antipsychotic and/or administering a short course of anti-cholinergic medication prophylactically while the antipsychotic drug is being introduced Akathisia may be relieved by benzodiazepines, anti-cholinergic medications or beta-blockers

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Appendix B - Table 9 - Depot formulation

Recommendation	ECGs (1999)	CCPGs (2005)	ANZGs (2005)	NICEGs (2009)	APAGs (2004)	RSAGs (2005)
Depot formulation	For patients who have had trouble taking oral medication reliably, who have poor insight/denial of illness, or who prefer depot		Depot should be reserved for two groups: - those who opt for it voluntarily, and - those who despite a series of comprehensive psychosocial interventions aimed at promoting adaptation and adherence repeatedly fail to adhere and relapse frequently Depot use in first episode patients: Depot may be an alternative to clozapine for poor adherence Depot medication in the management of acute relapse: Use the lowest possible dose and the maximum dosing interval. Short-term benzodiazepines or oral neuroleptics supplementation may be required.	Depot should be considered for people who would prefer this option after an acute episode or patients or to convert non-adherence (either intentional or unintentional) to adherence is a clinical priority within the treatment plan At the start of treatment, give a dose at the lower end of the licensed range and titrate upward only within the dose range given in the *British National Formulary* or *SPC*	Depot should be considered if the patient prefers or if repeated partial or full non-adherence to pharmacological treatment is present If depot is indicated the depot form of the same oral medication is the logical choice for initial treatment during the acute phase. The transition from oral to long-acting injection form can begin during the acute phase; however, the long-acting injection agents are not prescribed for acute psychotic episodes because these medications can take months to reach a stable steady-state and are eliminated very slowly Also see under polypharmacy	Depot is a useful option in the non-compliant patient with schizophrenia

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Appendix B - Table 10 - Polypharmacy

Recommendation	ECGs (1999)	CCPGs (2005)	ANZGs (2005)	NICEGs (2009)	APAGs (2004)	RSAGs (2005)
Polypharmacy		Persistent positive symptoms: Use clozapine alone, then clozapine augmentation (e.g. lithium, anticonvulsants, antidepressants, benzodiazepines, ECT. Thereafter use combination strategies: these have been proposed essentially on the basis of case reports.	Polypharmacy of any kind such as combination of an antipsychotic agent, a mood stabilizer and a benzodiazepine or an antidepressant, may be justified by comorbid symptom dimensions, which are extremely common in psychotic disorders. Antipsychotic polypharmacy: should not be used except during transitional periods when switching is in progress. There is little evidence that combining antipsychotic medications is useful; conversely this increases the side-effect burden	Do not initiate regular combined antipsychotic medication except for short periods, e.g. when changing medication	There may be circumstances with it is useful to prescribe a depot during acute treatment, e.g. if a patient experiences an exacerbation of psychotic symptoms while receiving depot it may be useful to continue the depot while temporarily supplementing it with oral medication	

WITHDRAWN

Appendix C

Data collection form for the anonymous collection of prescription details – psychotropic drugs only

Subject number (1 to 100)	
Duration of hospital stay	

Prescription on admission

Drug No.	Drug class	Drug name	Route	Dosage	Routine/PRN
1					
2					
3					
4					
5					
6					

Prescription at 14 days after admission

Drug No.	Drug class	Drug name	Route	Dosage	Routine/PRN
1					
2					
3					
4					
5					
6					

Prescription on discharge

Drug No.	Drug class	Drug name	Route	Dosage	Routine/PRN
1					
2					
3					
4					
5					
6					

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Appendix D

Formulary of relevant drugs available during the study

Antipsychotic drugs

amisulpride, chlorpromazine, clothiapine, clozapine, flupentixol, haloperidol, olanzapine, pimozide, risperidone (oral and depot forms), sulpiride, ziprasidone and zuclopenthixol.

Anticholinergic drugs

biperiden and orphenadrine

Anxiolytic/Sedative-hypnotic drugs

clonazepam, lorazepam, diazepam, oxazepam and zopiclone

Mood stabilizers/Anticonvulsant drugs

lithium carbonate, carbamazepine, lamotrigine, phenytoin, sodium valproate and valproic acid

Antidepressant drugs

amitriptyline, bupropion, citalopram, duloxetine, escitalopram, fluoxetine, imipramine, mianserin, moclobemide, paroxetine, sertraline, tranylcypromine, trazodone and venlafaxine

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