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**Antipsychotic prescribing and rehospitalisation
in schizophrenia: A New Zealand study**

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A thesis submitted for the degree of Doctor of Medicine in Psychiatry,
the University of Auckland, 2017

ABSTRACT

Aims

Schizophrenia is a chronic illness, with approximately two-thirds of patients experiencing relapses, often with rehospitalisation. Treatment with antipsychotic medications reduces the relapse rate. Despite half a century of antipsychotic drug availability, doubts remain regarding the translation of research findings into day-to-day practice or into clinical practice guidelines. This study therefore aimed to explore this efficacy–effectiveness debate by examining prescribing correlates of rehospitalisation in a large cohort of treated patients.

Method

Four hundred and fifty-one inpatients discharged with diagnoses of schizophrenia or related disorders in three distinct New Zealand districts between July 2009 and December 2011 were tracked until December 2013. Utilising a national mental health database, rehospitalisation rates and duration were thus obtained for two years following discharge. Discharge variables including treatment history were obtained from clinical records and individual clinicians.

Results

In contrast to treatment guidelines, relatively many (34%) were prescribed multiple antipsychotics and fewer (20%) than expected received clozapine. Māori were prescribed clozapine more frequently (24%) than non-Māori (13%). Compulsory treatment was associated with the use of more long-acting injectable medications than in voluntary patients. Clinician characteristics did not predict prescribing patterns.

Nearly half (44%) of the cohort were rehospitalised within two years. Those with a longer (> 3 weeks) index admission (HR = 0.53, $p = 0.001$) were less likely to be

rehospitalised, as were older patients (> 50 years) (HR = 0.58, $p = 0.04$). Those subject to compulsory treatment appeared more likely to be rehospitalised (HR = 1.3, $p = 0.06$) and spent more time rehospitalised ($p = 0.05$). Antipsychotic types, routes and dosages were not significantly associated with rehospitalisation, except in the case of clozapine (HR = 0.61, $p = 0.01$).

Conclusion

Observed prescribing practice aligned with existing guidelines, except for antipsychotic polypharmacy and clozapine underutilisation. Only the latter appeared to be ethnically influenced. Rehospitalisation rates were higher for patients under the age of 50 and for those with shorter index admissions. Other than the beneficial effect of clozapine, the type and route of prescribed antipsychotics did not significantly affect rehospitalisation rates. This study does not support any claimed advantages of second-generation over first-generation antipsychotics.

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LIST OF ABBREVIATIONS

APA	American Psychiatric Association
APD	Antipsychotic drug
CATIE	Clinical Antipsychotic Trials of Intervention Effectiveness
CI	Confidence interval
CPG	Clinical practice guideline
CPZE	Chlorpromazine equivalents
CUtLASS	Cost Utility of the Latest Antipsychotic Drugs in Schizophrenia Study
DHB	District health board
DOIA	Duration of index admission
EPS	Extrapyramidal symptom
EUFEST	European First Episode Schizophrenia Trial
FGA	First-generation antipsychotic
FGLAI	First-generation long-acting injectable
HR	Hazard ratio
ICD	International Classification of Diseases
LAI	Long-acting injectable
LOS	Length of stay
MHA	Mental Health Act
MOH	Ministry of Health
NICE	National Institute of Clinical Excellence
NOS	Not otherwise specified
PORT	Schizophrenia Patient Outcomes Research Team
PRIMHD	Programme for the Integration of Mental Health Data
RANZCP	Royal Australian and New Zealand College of Psychiatrists
RCT	Randomised controlled trial
SD	Standard deviation
SE	Standard error
SGA	Second-generation antipsychotic
SGLAI	Second-generation long-acting injectable
SOHO	Schizophrenia Outpatient Health Outcome Study
TD	Tardive dyskinesia
WFSBP	World Federation of Societies of Biological Psychiatry

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Certification by Co-Authors

The undersigned hereby certify that:

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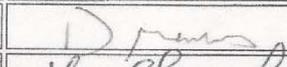
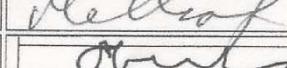
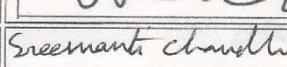
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Appendix

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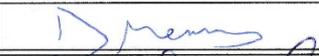
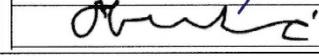
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SECTION 1: INTRODUCTION AND BACKGROUND

1.1 Introduction

Schizophrenia is a chronic and disabling major psychiatric illness. As many as 1% of people meet diagnostic criteria for the disorder over their lifetime (Galletly et al., 2016) and frequently with a profound effect upon both the individuals (Castle, Bassett, King, & Gleason, 2013, p. 93) and their families.

Schizophrenia is geographically ubiquitous and has clinical features that are significantly similar across cultures (Jablensky et al., 1992). It is an illness with a variable longitudinal course, with about 40% having significant long-term disability (Castle et al., 2013).

Schizophrenia or those who suffer from it have been described and conceptualised in many different ways. Initially, Philippe Pinel (1745–1826) proposed five categories of mental disorder on the basis of his observations in the two largest asylums in Paris (Nasarallah & Smeltzer, 2011). He described many patients who would meet modern criteria of schizophrenia. Almost at the same time, in England, Haslam (1764–1844) wrote a summary based on observation of many cases and described the condition as “a form of insanity which occurs in young persons” (Nasarallah & Smeltzer, 2011, p. 15).

A similar concept was represented in the mid-nineteenth century in the work of Benedict Auguste Morel and Karl Kahlbaum (Gelder, Ibor, & Andreasen, 2000, p. 521). Morel (1809–1873) referred to this condition in young persons with progressive cognitive deterioration as ‘démence juvénile’ (Nasarallah & Smeltzer, 2011, p. 16).

The modern concept of schizophrenia, however, primarily developed in the early twentieth century from the interaction between two great clinicians: Emil Kraepelin (1856–1926) and Eugen Bleuler (1857–1939) (Gelder et al., 2000, p. 522). Kraepelin

proposed the name ‘dementia praecox’. He described bizarre thought disturbances, delusions, auditory or other hallucinations, catatonia, abnormalities of volition, and a “pervasive reduction in cognitive and affective capacity” (Nasarallah & Smeltzer, 2011, p. 17). Bleuler subsequently named this entity ‘schizophrenia’ and extended the clinical profile. He also described the ‘four A’s’, his fundamental symptoms of schizophrenia. They are association defects, autism, ambivalence and disturbance of affect. In contrast to Kraepelin, his concept was more dimensional than categorical. All four of the fundamental symptoms can be considered to be on a continuum with normality (Nasarallah & Smeltzer, 2011, p. 21).

Bleuler defined the combination of all four symptoms as pathognomonic for schizophrenia. In the first half of the last century, many clinicians diagnosed schizophrenia by applying the four A’s (Bleuler, 1950; Nasarallah & Smeltzer, 2011). Another approach that had become popular by the middle of the twentieth century was based on the phenomenology that focused on understanding and describing a person’s internal experiences (Nasarallah & Smeltzer, 2011).

In 1937, Kurt Schneider (1887–1967) introduced his criteria based on phenomenological concepts, claiming improved diagnostic precision (Nasarallah & Smeltzer, 2011). He described 11 ‘first rank’ signs. These consist of special auditory hallucinations (audible thoughts, voices arguing, voices commenting), primary delusions (delusional perception), passivity experiences (somatic passivity, passivity of affect, passivity of impulse, passivity of volition) and alienation of thought (thought withdrawal, thought insertion, thought broadcasting). Schneiderian symptoms were included in the first major structured interview developed for use in the international pilot study of schizophrenia (Carpenter, Strauss, & Bartko, 1973; Carpenter, Bartko, Strauss, & Hawk, 1978).

In seven of the nine countries that participated in this study, the World Health Organisation (WHO) found close agreement on the clinical features for the diagnosis of schizophrenia (Nasarallah & Smeltzer, 2011, p. 25). There were two outliers (USA and USSR) and both had far broader approaches than the other seven.

In the United States (USA), largely driven by concerns about inter-rater diagnostic reliability as illustrated in the above WHO study, new approaches for diagnosis evolved. The American Psychiatric Association (APA) produced the third edition of their *Diagnostic and Statistical Manual of Mental Health Disorders* (DSM-III, 1980), followed by DSM-III-R (1987), which incorporated the use of specific, required diagnostic criteria. The current definitions of schizophrenia may be found in the APA's DSM-IV-TR (2000), and the World Health Organization's *International Classification of Disease* (ICD-10, 1992). These definitions incorporate Kraepelinian chronicity, Bleulerian negative symptoms, and Schneiderian positive symptoms, albeit using different combinations and interpretations of these elements, with limited psychopathological rigour (Andreasen, 2007; Tandon, Nasrallah, & Keshavan, 2009).

Kraepelin and Bleuler did not use the terms 'positive symptoms' and 'negative symptoms'. The positive and negative symptoms, on which diagnosis, research and treatment have been based for more than 25 years, were first suggested by a neurologist named Reynolds, in 1857 (Nasarallah & Smeltzer, 2011, p. 71). Later in the nineteenth century, Hughlings Jackson classified losses of function caused by a presumed anatomic lesion as negative symptoms, and those resulting from excess of normal functioning as positive symptoms (Nasarallah & Smeltzer, 2011). This clinical distinction has persisted and the terms are used in a similar manner today.

'Positive symptoms' tend to be associated with recognition of the disorder and the need for treatment. The negative symptoms tend to contribute particularly to psychosocial

morbidity and reduced functionality. The use of the 'positive' and 'negative' terminology often gives them equal recognition. Standardised and reliable methods have been since developed for assessing these symptoms (Kay, Fiszbein, & Opfer, 1987).

In summary, therefore, the required diagnostic criteria consist of a mixture of positive symptoms (delusions, hallucinations, disorganised speech and behaviour), negative symptoms (affective flattening, alogia, avolition) with a significant decline in personal, social or occupational functioning. A period of illness needs to be continuous for at least six months with at least one month of active phase symptoms. The duration is the most significant difference between ICD-10 criteria and DSM-IV criteria. DSM-IV requires at least once during a person's life an active phase lasting one month, embedded within a six-month period during which signs are continuous. However, ICD requires only an active phase lasting at least one month.

Schizophrenia also has been studied extensively from an epidemiological perspective. Epidemiological studies, however, are complicated by problems of detection, definition and diagnosis (Nasarallah & Smeltzer, 2011, p. 28). Determinants of disease have been sought with studies of the epidemiology of the incidence. In the case of schizophrenia, determinants include both genetic and environmental risk factors. Both are important in the aetiology or pathogenesis of schizophrenia and neither appears to operate in isolation (Tsuang, Bar, Stone, & Faraone, 2004). Because of the variations in study methodology, the frequency estimates have also proved variable. For example, some studies have used medical records, others have evaluated patients from hospitals or clinics and some have used community searches for disabled patients or direct sampling of community members (Jablensky, 2000; Nasarallah & Smeltzer, 2011).

By definition, incidence refers to the rate of new cases of a disease that develop over a defined period of time among a described population. Thus, knowledge about the

incidence over time, place and person points to aetiological factors (determinants) for developing the disease. It depends critically on the ability to identify the point of onset of the disorder. Because of long prodromal periods and often blurred boundaries between the premorbid state and the onset of psychosis, this can be difficult to reliably identify in schizophrenia. Therefore, the first hospital admission, a proxy for disease onset in many studies, is not necessarily a robust or valid indicator of that (Gelder et al., 2000, p. 543).

Prevalence is the proportion of population members affected at a fixed point in time (point prevalence), during a specified period of time (period prevalence) or any time from birth to current age (lifetime prevalence). This is significantly influenced by chronicity or prognosis. The lifetime risk, also known as the morbid risk or expectancy, is a type of incidence risk, which describes the number of cases in a population over the length of an average lifetime.

Correctly determining the distribution of a disease depends on having a reliable and valid diagnosis and the ability to precisely demarcate boundaries between those with the disease and those without it (Tandon, Keshavan, & Nasrallah, 2008). The challenge of diagnosing schizophrenia with greater reliability in the absence of agreed, objective pathognomonic features has contributed to varying estimates of incidence obtained across the multitude of studies (Tandon, Keshavan, et al., 2008). Similarly, prevalence is influenced by several factors, including rates of new case development (incidence), duration of the condition, and mortality or migration patterns associated with the condition.

The investigation that has applied a uniform design and common research tool is that provided by the WHO 10-country study (Jablensky et al., 1992). A prevalence in the range of 1.4 to 4.6 per 1,000 (point prevalence) and incidence rates in the range of 0.16 to 0.42 per 1,000/year population have been indicated in most studies (Jablensky, 2000).

The annual incidence was found to range between 16–40/100,000/year using broad criteria (ICD-9, World Health Organization, 1978) and 7–14/100,000 using narrow criteria (Wing & Nixon, 1975). In a recent meta-analysis (McGrath et al., 2004) and a systematic review (Saha, Chant, Welham, & McGrath, 2005), the incidence (median) rate was reported as 15.2 per 100,000 per year, median point prevalence as 456 per 100,000, annual prevalence as 330 per 100,000, lifetime prevalence as 400 per 100,000 and lifetime morbid risk as 720 per 100,000.

Because of demographic differences such as age-specific mortality and migration, these rates may not reflect the true extent of variation among different populations. The question of whether major differences exist in the prevalence in different populations has not been easy to answer. According to Jablensky et al. (1992), the magnitude of such deviations in schizophrenia, however, is small and comparable with diseases such as ischaemic heart disease, diabetes mellitus or multiple sclerosis.

The lifetime risk for schizophrenia is about 1% (Jablensky et al., 1992) and varies between 0.4% and 1.4%. The prognosis is reported to be better in developing countries than developed countries. The exact reasons for favourable outcomes have yet to be identified (Jablensky et al., 1992).

Sociodemographic variables (age, gender, location of residence, social class, ethnicity, immigration status, marital status) also need to be considered while addressing incidence. For example, it has been claimed that the incidence is higher in males, in densely populated large urban areas, among persons who have never married and among first-generation immigrants (Cantor-Graae & Selten, 2005; Nasarallah & Smeltzer, 2011a, pp. 28–32).

In summary, incidence of schizophrenia shows modest variation and there is no single identifiable risk factor. Ongoing research addressing complex gene–environmental interactions may be better able to shed light on this topic in future.

In Australia, the frequency of schizophrenia in Australian Indigenous communities is unknown but prevalence may be higher than in the wider society (Galletly et al., 2016).

In New Zealand (NZ) in a public health report (Ellis & Collings, 1997) the prevalence of schizophrenia was said to be 0.2% per year. The well-known Christchurch Psychiatric Epidemiology Study (Oakley-Browne, Joyce, Wells, Bushnell, & Hornblow, 1989) did not show any significant gender-differences for schizophrenia and was not sampled for ethnicity. Māori, the indigenous population of NZ, comprise approximately 15% of the total population and questions about a higher rate of mental illness in this group have been raised. The Te Rau Hinengaro survey (Oakley-Browne, Wells, & McGee, 2006) reported 12 months' prevalence of any mental illness as 29.5% in Māori and 19.3% in others, but did not specifically report on schizophrenia.

Historically, one study (Sachdev, 1989) did claim higher prevalence rates of schizophrenia in Māori but stated that most of the epidemiological data in NZ had been based on hospital information. Some publications have been based on clinical experience and ethnographic literature, but not on reliable or valid epidemiological data.

A recent study that focused on this issue specifically (Kake, Arnold, & Ellis, 2008), reported an elevated prevalence of schizophrenia among Māori and a higher proportion of hospital admission for Māori with schizophrenia. This study specifically looked at 12 months' prevalence of schizophrenia in the Māori population of NZ, using mental health data from two national sources for the period 2002–2003. The estimated 12-month prevalence of schizophrenia for Māori was 0.97% and for non-Māori was 0.32%. Based on the capture-recapture analysis in this study (Kake et al., 2008), the one-year

prevalence (age-standardised) of schizophrenia for the Māori population was approximately three times (prevalence ratio 2.76 to 3.10) that of non-Māori for that period. After adjusting for socio-economic deprivation, the prevalence estimates for Māori remained more than twice that of non-Māori. None of these studies, however, commented on the incidence rate.

Schizophrenia may have its onset at any age. The vast majority of cases usually present in adolescence and early adult life. The clinical presentation may differ because of different developmental stages, resulting in a predominance of non-specific psychotic symptoms in age group 15–24, delusions of reference and affective symptoms in age group 25–34, and persecutory delusions and negative symptoms in age group 35–59 (Häfner et al., 1993). The question of whether the lifetime risk of schizophrenia is similar in men and women has not been answered definitively. The onset in men usually peaks during adolescence or young adulthood. It tends to occur at a later age in females. So, the male to female ratio becomes inverted with age, reported as 1:1.9 for onsets after age 40 and 1:4 or even 1:6 for onsets after age 60 (Gelder et al., 2000). The WHO 10-country study (Jablensky et al., 1992) reported the cumulated risks for both males and females up to the age of 54 as approximately equal.

The clinical course of schizophrenia is variable. Typically, it involves a premorbid phase with subtle and non-specific cognitive, motor and/or social dysfunction (Schenkel & Silverstein, 2004), a prodromal phase characterised by attenuated positive symptoms or basic symptoms and declining function (Riecher-Rössler & Rössler, 1998; Schultze-Lutter, 2009), which precedes recognition of a first episode of psychosis and can last from a few days to around 18 months.

An acute episode is usually marked by positive (hallucinations, delusions, behavioural disturbances) and negative symptoms (apathy, social withdrawal, reduced interest in daily

activities). Although this is a common pattern, some people may have positive symptoms very briefly; others may experience them for many years. Still others have no prodromal period and the disorder appears to begin suddenly with an acute episode.

The initial decade of illness can be marked by repeated episodes of psychosis with partial and variable degrees and duration of inter-episode remission. A stable phase or plateau may then be achieved, when psychotic symptoms are less prominent and negative symptoms and the stable cognitive deficits are increasingly predominant. Recovery of varying degrees can occur at any stage of the illness (Harding, Brooks, Ashikaga, Strauss, & Breier, 1987). The demarcation between various phases of the illness is also imprecise and best thought of as a part of a syndrome at this stage.

With regard to the aetiology of schizophrenia, there is no single cause. It is thought to result from the cumulative effect of a number of risk factors. The most powerful risk factor is having a relative afflicted with the disorder, which highlights the familial–genetic risks. A person’s risk of developing schizophrenia increases steeply with the degree of genetic relatedness to an individual who has the disease (Jablensky, 2000). A meta-analysis of twin studies supports an overall heritability estimate of about 0.8 (Sullivan, Kendler, & Neale, 2003). However, despite advances in the science and technology of molecular biology, the precise mechanism of inheritance remains obscure. The predominant genetic view of schizophrenia regards it as a heterogeneous, polygenic/multifactorial disease (Lichtermann, Karbe, & Maier, 2000).

Many environmental exposures have been examined as possible risk factors but none has been unequivocally validated. These include both biological and psychosocial risk factors during the antenatal and perinatal periods, early and late childhood, adolescence and early adulthood (Maki et al., 2005). The examined environmental factors particularly include

season of birth, maternal exposure to infection, obstetric complications, social and geographical factors, ethnicity, immigration status, life events and substance abuse.

The neurobiology of schizophrenia, however, remains the subject of ongoing research and no diagnostic marker has yet been found. There is good evidence for a dopaminergic dysfunction (Stone, Morrison, & Pilowsky, 2007), and there is also emerging evidence for several susceptibility genes, but details are still under investigation (Harrison & Owen, 2003; Lichtermann et al., 2000).

Because of heterogeneity of the course and multiple aetiological factors, predictors of outcome also depend on a wide range of variables. The explanatory power of clinical predictors varies, depending on the setting, sample size, homogeneity (Gelder et al., 2000, p. 574) of patient groups and measurement error. Therefore, no single characteristic or clinical sign or symptom is strongly associated with long-term prognosis. Rather, there are a number of prognostic indicators that allow a judgement to be made about the course of illness over a limited time period (Gelder et al., 2000). However, there is a good agreement by and large that the best predictor of relapse in the short term remains the withdrawal of antipsychotic medications.

1.2 Background and Context

Schizophrenia is ranked among the top 20 causes of disability worldwide (Lim, Vos, Flaxman, & Danaei, 2013). It is a chronic and disabling illness, with the majority of patients experiencing multiple relapses following resolution of the acute episode (Emsley, Chiliza, Asmal, & Harvey, 2013). Outcomes following an acute episode can be variable, starting from mere improvement of positive symptoms to complete functional recovery, from rehospitalisation to mortality.

Researchers in the recent decades also have focused on the terms 'remission' and 'recovery' rather than just reduction in psychotic symptoms as outcome. The concept of

symptomatic 'remission' (defined as Clinical Global Impression Schizophrenia Scale score of no worse than 'mild', i.e., ≤ 3 in the assessment of overall severity: positive, negative and cognitive subscores and no hospitalisation in the respective time period); and 'recovery' (ability to function in the community) has also led to heterogeneous studies (Lambert et al., 2008) because of the use of different sets of criteria in different studies. Therefore, outcome in schizophrenia remains a multidimensional concept (Lambert et al., 2008), requiring multilevel interventions.

Most patients with schizophrenia (about 80%) would recover from their first episode of illness. Approximately 10%–20% of patients never experience a recurrence after the first episode (Emsley et al., 2013). Relapse rates are reported as low in the first year on placebo but rising substantially thereafter. There is a high rate of relapse within five years of recovery (cumulative first relapse rate 81.9%) from a first episode of schizophrenia (Barnes, Shingleton-Smith, & Paton, 2009; Robinson et al., 1999). The risk of relapse is also reported as higher when not taking medications compared with when taking medications (Emsley et al., 2013; Robinson et al., 1999). An Australian survey in 2010 reported that 6% of patients with schizophrenia experienced a single episode of psychosis followed by good recovery, 54.8% experienced multiple episodes with partial recovery between episodes and 38.8% showed an unremitting course (Morgan et al., 2012).

Psychopathology and social functioning can worsen with repeated relapses in schizophrenia; therefore, relapse prevention is as critical in this group of patients as it is in other chronic illnesses.

In addition to social isolation, ostracism, homelessness, poverty and unemployment, schizophrenia can lead to repeated and prolonged hospitalisation for relapse (Bottlender et al., 2003; Nasarallah & Smeltzer, 2011, p. 11). During the first year after discharge

40% to 50% will be rehospitalised, and up to 85% will eventually be rehospitalised at some time (Carone, Harrow, & Westermeyer, 1991).

Rehospitalisation is multifactorial, influenced by illness, patient, clinician and service factors. Rehospitalisation rates are also a commonly used indicator of the quality of care and have been proposed as one quality indicator for inpatient psychiatry service (Moss et al., 2014). In NZ, higher rates of inpatient admission with a diagnosis of schizophrenia for patients of Māori ethnicity compared with those of European origin have been reported (Abas et al., 2003). Māori ethnicity and older age have been identified as predictors of rehospitalisation (Turner, Boden, & Mulder, 2013).

A significant proportion of direct costs for schizophrenia or related disorders is also imputable to hospitalisations for both the first episode and relapses. Approximately 79% of the direct cost of schizophrenia can be attributed to hospital or other residential care (Taylor et al., 2005). Several studies have reported that schizophrenia accounts for up to 3% of all health care expenditure across the world (Knapp, 2000; Knapp, Mangalore, & Simon, 2004). This includes cost to health care agencies as well as to other parties such as families, sufferers themselves and wider society.

In the USA the total annual cost is estimated to be US\$19 billion, with a mean length of stay in hospital of 15 days (Knapp et al., 2004; Weiden & Olfson, 1995). One Australian study (Fitzgerald et al., 2009) examined the economic costs of relapse of schizophrenia and schizoaffective disorder in an Australian patient population. They reported that hospitalisation due to relapse is associated with an increase in the use of both inpatient and outpatient health care resources. The cost associated with a relapse was reported as AUD \$3,948 per subject and the cost of hospitalisation as AUD \$5,026.

A study by Weiden and Olfson (1995) reported that loss of efficacy accounts for about 63% of rehospitalisations (1.2 billion), and non-adherence for about 37% (705 million).

The economic burden due to loss of efficacy was reported as higher during the first post-discharge year, whereas the burden due to non-compliance was higher during the second post-discharge year. Thus, improving both would have a synergistic effect on relapse rates and hospital costs. Therefore, research focusing on these two important determinants would facilitate the development of more effective management of schizophrenia in real-world circumstances.

Persons with schizophrenia have increased mortality rates compared with the general population (Harris & Barraclough, 1998). Mortality stems from natural causes, especially cardiovascular disorder and unnatural causes such as suicide. Other factors that have been regarded as reasons for this observed increase include an increased incidence of accidents, more frequent association with medical illnesses (e.g., cardiovascular diseases, diabetes mellitus), comorbid substance abuse, general neglect of health, an increased rate of damaging behaviours (e.g., smoking cigarettes, poor diet) and decreased access to health services (Harris & Barraclough, 1998).

In a prospective cohort study (average follow-up of 3.6 years), based on data from a large register of Finnish patients with schizophrenia, the mortality rate was also found to be higher (adjusted relative risk 12.3, 95% confidence interval [CI] 6–24.1) in patients who were not taking medications (Tiihonen et al., 2006). Suicide rate was also high in the group without medications.

In contrast to this, antipsychotics with adverse cardiovascular profiles, especially those with side effects such as metabolic syndrome, are also associated with a two- to threefold increase in cardiovascular mortality and a twofold increase in all-cause mortality (Saha, Chant, & McGrath, 2007) in schizophrenia. The same study reported a median all-cause standardised mortality ratio of 2.58 (Saha et al., 2007). This translates into 13 to 20 years

of shortened life expectancy for persons with schizophrenia (Healy et al., 2012; Saha et al., 2007).

Persons with schizophrenia also exhibit disproportionately high rates of suicide, estimated to be about 10%. Several studies reported the suicide specific standardised mortality ratio for years 1–5 from first admission as 51.5 (95% CI 25–95) and for years 1–10 as 35 (95% CI 18–61) (Healy et al., 2006, 2012).

Moreover, the impact of the illness in schizophrenia is not limited to the patients themselves. It has devastating effects on their families and ultimately on the community. Over the past 50 years the closure of mental hospitals and more emphasis on community-based care has led to a progressive shift of care for patients with schizophrenia to informal care providers such as families and non-profit organisations. Studies on the impact of ‘burden of care’ in schizophrenia have reported loss of time and potential for earning for caregivers, negative impacts on physical and emotional health of caregivers, increased substance abuse, family conflicts, low level of satisfaction and compromised quality of life for caregivers (Awad & Voruganti, 2008).

The objectives of treatment of schizophrenia are therefore to reduce the mortality and morbidity of the disorder. This could be achieved by minimising the frequency and severity of episodes or relapses and by maximising potential functioning. Outcome studies (Juckel et al., 2014; Kane & McGlashan, 1995; Lieberman et al., 2005, Menezes, Arenovich, & Zipursky, 2006) have reported better rates of improvement with optimal antipsychotic and psychosocial therapies. Employing strategies that decrease relapse and the need for rehospitalisation, the costliest treatment alternative, can lessen the societal costs of treating those with schizophrenia. Although estimating the cost usually fails to capture the devastating human dimension of the illness, cost analysis can provide some guidance to the allocation of treatment resources.

Antipsychotics are the cornerstone of schizophrenia management. Prompt administration of effective antipsychotic treatment that patients adhere to is important for good symptom control and for reducing the risk of relapse (Juckel et al., 2014). Despite its poorly understood aetiology and the complexity of multiple kinds of morbidities and disabilities, the knowledge of therapeutic modalities for the treatment of schizophrenia is enormous. There is substantial literature on the efficacy and optimal use of antipsychotic drugs (APDs). There is good evidence to support the use of antipsychotics in its management both during acute phases and for relapse prevention.

Naturalistic studies have shown only 10%–20% of patients did not experience another episode (Robinson et al., 1999b; Robinson et al., 1999a, Shepherd, Watt, Falloon, & Smeeton, 1989) after a single psychotic episode. However, the studies that have tried to identify this group or predictors, prior to considering treatment discontinuation, have not been informative (Emsley, Oosthuizen, Koen, Niehaus, & Martinez, 2012; Emsley et al., 2013). A study by Gilbert, Harris, McAdams and Jeste (1995) reported a mean cumulative relapse rate of 52% over a mean follow-up period of 6.3 months for patients withdrawn from treatment and 16% relapse rate for those who continued on APDs (Gilbert, Harris, McAdams, & Jeste, 1995). A meta-analysis by Leucht et al. (2012) assessed the use of different types of APDs for relapse prevention in schizophrenia. This study reported that, compared with placebo, antipsychotic use significantly reduces relapse rates at one year (27% for antipsychotics vs. 64% for placebo, NNT to prevent one additional relapse = 3), as well as readmission rates (10% vs. 26%, NNT = 5) (Leucht et al., 2012).

Intermittent treatment (only restarting when there are early warning signs and tapering once a patient is in remission) was also less efficacious (Carpenter, Hanlon, Heinrichs, Summerfelt, & Kirkpatrick, 1990; De Hert et al., 2015; Herz et al., 1991; Schooler et al.,

1997), even in first-episode patients (Gaebel et al., 2010; Gaebel, Riesbeck, & Wobrock, 2011; Herz et al., 1991). Therefore, most patients with schizophrenia and related disorders require long-term antipsychotics as the main modality of treatment to prevent relapse.

Historically, with the development of APDs (also known initially as ‘major tranquilisers’ or ‘neuroleptics’) in the 1950s, the management of schizophrenia began to change. Prior to that most of the treatments were palliative, purely sedating, barely effective and even dangerous or barbaric (Gelder et al., 2000, p. 578).

The first trial of the drug chlorpromazine (marketed as Largactil, derived from ‘Large Action’) on patients with schizophrenia was initiated in 1952 by Delay and Deniker (Shen, 1999). Since then, much effort has been put into empirical and/or scientific studies to improve the treatment of schizophrenia. The Cochrane Schizophrenia Group’s Register has summarised almost more than 10,000 controlled trials (Adams et al., 2008). Although chlorpromazine and subsequently developed antipsychotics did not promise a cure for schizophrenia, they profoundly altered the fate of many people with schizophrenia.

Several classes of APDs have been developed over the past two decades, with the intention of developing antipsychotics with fewer side effects. With the development of a number of national and international guidelines, evidence-based medicine also has slowly started to have a major impact on those suffering from schizophrenia. The Cochrane database, a database of systematic reviews and meta-analysis to inform health care decision making, has been providing reviews on relevant issues to ensure evidence-based practice. Even though this trend has been important to smooth out the variability in patient care, it has not been beyond criticism.

Practice guidelines are defined as “systematically developed statements to assist practitioner and patient decisions about appropriate health care for specific clinical

circumstances” (Field & Lohr, 1992, p. 2). In view of practice variability, guidelines represent a major tool for quality management in health care to assure treatment quality and to overcome existing disparities (Hamann, Langer, Leucht, Busch, & Kissling, 2004; Lugtenberg, Burgers, & Westert, 2009). Therefore, like any other clinical guidelines, practice guidelines for schizophrenia should contribute to improved treatment and outcomes for people with schizophrenia. However, guidelines have also received criticism.

In everyday practice, clinicians face the challenge of selecting the most appropriate treatment for their patients and this requires an understanding of the empirical research evidence on medication efficacy (performance under ‘ideal’ conditions). To maximise effectiveness (performance under everyday conditions), treatment options need to be considered in relation to the clinical circumstances of the individual patient (Barnes, 2011).

Effectiveness has been defined as requiring improvement in four domains (Juckel et al., 2014): symptoms of disease (measured using symptom scales), treatment burden (measured using adverse event scales), disease burden (assessed by interview with patients and families), and health and wellness (measured using quality-of-life scales). However, the real-world clinical utility of this comprehensive approach is unclear. Individualised care planning is important to optimise treatment and management of schizophrenia.

Guidelines are largely derived from efficacy data (Gelder et al., 2000, p. 578). One concern is that treatment algorithms for schizophrenia are based on outcome data from randomised controlled trials (RCTs) (Tiihonen et al., 2006). Therefore, samples studied are not always representative of the patient population seen by clinicians during day-to-day practice and most of these trials are of small sample size with strict inclusion and

exclusion criteria. The follow-up for these trials is also short term. As a result, extrapolating data from such trials to the wider community setting has proven to be difficult, whereas large-scale observational studies could provide more information on the outcome data.

Gaebel et al. (2011) have also stated “the methodological quality of many schizophrenia guidelines was at best moderate” (p. 248; Gaebel, Weinmann, Sartorius, Rutz, & McIntyre, 2005). In summary, it is well known that despite wide promulgation, clinical practice guidelines have had limited efficacy on changing physician behaviour.

The most frequently perceived barriers to adherence to clinical guidelines include lack of agreement with recommendations, concerns about applicability to specific patients or lack of evidence (68% of key recommendations); environmental factors such as organisational constraints (52%); lack of knowledge regarding the guideline recommendations (46%); and ambiguous guideline recommendations (43%) (Lugtenberg, Burgers, et al., 2009; Lugtenberg, Zegers-van Schaick, Westert, & Burgers, 2009).

1.3 Purpose of the Study

The varying results from studies using different methodologies create a dilemma in comparative research and for delivering evidence-based services. The traditional RCTs (Nichol, Bailey, & Cooper, 2010) may not always provide valid information that is effectively generalisable; therefore, they may not always be able to provide guidelines for good clinical care in often complex real-life situations. It is well recognised that methodological and financial considerations also necessitate time-limited and shorter RCTs (the gold standard for evaluating efficacy), rather than allowing for a more flexible approach that may be found in routine clinical practice.

In comparison, observational studies serve a wide range of purposes, from reporting a first hint of the potential cause of a disease to verifying the magnitude of previously

reported associations. They can provide data from unselected cohorts in real-world settings (D'Agostino, 2007). Therefore, patients are likely to be more representative of 'real-world' patients. This would allow clinicians to address the 'knowing–doing' gap because findings from a naturalistic study would likely be more generalisable (Kishimoto, Nitta, Borenstein, Kane, & Correll, 2013).

Once treatments have been demonstrated to be efficacious under the stringent conditions of RCTs, the next step is to examine their effectiveness in routine practice. A study based on real-life data may help to inform guideline utility and assist the optimisation of pharmacotherapy.

Given the complex nature of a disease such as schizophrenia, the knowing–doing gap has been a major problem for clinicians. Understanding our failure to translate evidence into practice is therefore a burning issue. The effectiveness of antipsychotic medications varies greatly in a real-world setting. So even though evidence-based guidelines can offer a framework, they do not always address the individual variability clinicians come across during their day-to-day practice. To prevent relapse and rehospitalisation for relapse, it is crucial to address 'efficacy' vs. 'effectiveness' of treatment for schizophrenia.

In the presence of multiple clinical variables and in the absence of a single cause for schizophrenia, the search for correlates of rehospitalisation for relapse is also ongoing. A study examining a cohort from daily clinical practice, addressing associations between clinical variables and outcome, may also help to reduce relapse and hospitalisation rate.

The purpose of the study reported in this thesis is to address the knowing–doing gap by comparing observed practice with the guidelines and to examine the associations between outcome (rehospitalisation) and discharge variables. To a certain extent, it also attempts to inform the 'efficacy' vs. 'effectiveness' issues.

SECTION 2: LITERATURE REVIEW

2.1 Treatment of Schizophrenia and Outcome

This chapter reviews the literature on the treatment of schizophrenia. Treatment of schizophrenia includes antipsychotic medication, and psychological and psychosocial interventions. In view of the purpose of the study, this literature review has focused on the following topics: clinical guidelines for treatment of schizophrenia; evidence of the efficacy and effectiveness of antipsychotic treatment for schizophrenia; and relapse (mainly rehospitalisation) and its associations with other clinical variables (antipsychotic treatment, patient and clinician characteristics, compulsory admission, duration of hospital admissions, numbers of previous admissions).

In conducting the review, the search included literature on schizophrenia spectrum disorders and was limited to English-language sources. Search filters consisted of a combination of subject headings. The search for relevant publications was carried out using a combination of the search words ‘schizophrenia’, ‘treatment’, ‘relapse prevention’, ‘antipsychotic,’ ‘second generation antipsychotics’, ‘first generation antipsychotics’, ‘classical antipsychotics’, ‘depot antipsychotics’, ‘polypharmacy’, ‘compulsory admission’, ‘involuntary admission’, ‘predictors’, ‘outcome’, ‘age’, ‘gender’, ‘ethnicity’, ‘cost’, ‘hospitalisation’, ‘relapse prevention’, ‘efficacy’ and ‘effectiveness’. Electronic databases included MEDLINE, PubMed, EMBASE, PsycINFO, EBSCO, Discovery, Google Scholar and Cochrane.

Literature selected for inclusion covered meta-analysis, observational studies, expert and systematic literature reviews, clinical guidelines, correspondence, RCTs and review articles on the subject. Studies that included only patients under the age of 18 or over the age of 65 were excluded. The search yielded a large number of informative publications,

and publications specifically focused on topics relevant to this study were reviewed.

Studies with unclear methods, low numbers and multiple limitations were excluded, and the literature review aimed to include research in this area since the 1980s.

The guidelines that have been looked at are those of the National Institute of Clinical Excellence (NICE) 2009, the Royal Australian and New Zealand College of Psychiatrists (RANZCP) 2005 and 2016, the Schizophrenia Patient Outcomes Research Team (PORT) 2010 and the American Psychiatric Association (APA) 2004.

Despite ongoing developments in treatment and research in this area, the outcomes for many patients with schizophrenia are still poor (Zipursky, 2014). Because of the heterogeneity of the studies, the reported rate of symptomatic remission (sustained absence of significant symptoms) and recovery (symptomatic remission with functional improvement) in schizophrenia or related disorders has also been variable (17%–60%) (Lambert et al., 2008).

Relapse is a major source of suffering, for both the patients and their families. The monthly relapse rates in schizophrenia are estimated to be around 3.5% per month for patients on maintenance antipsychotic treatment and around 11% per month for those who have discontinued their treatment (Weiden & Olfson, 1995). Approximately 70% of patients would relapse in a year on placebo in comparison with 30% on classical antipsychotics/first-generation antipsychotics (FGAs), and this relapse rate could be lower if adherence could be ensured (Davis, 1975). Societal costs due to relapse have also become a concern; therefore, predictors of relapse have been the targets for research over many years. Apart from lack of efficacy and non-adherence to treatment, a number of other clinical variables have also gained attention as probable predictors of relapse.

It is worthwhile to mention, though, some patients with schizophrenia will relapse despite being adherent to medications because of the nature of the illness (Levy, Pawliuk, Joober, Abadi, & Malla, 2012; Malla et al., 2008).

Since the introduction of antipsychotics almost 50 years ago, attempts have been made to identify predictors of treatment outcome in schizophrenia. Variables such as patient demography, comorbidities (e.g., substance abuse), previous hospital admissions and type or route of antipsychotics have been considered over the years. Studies have used multivariate regression models (taking into account several predictor variables simultaneously and controlling for confounders) to identify predictors in view of the complexity and heterogeneity of the disease.

The six most relevant predictors associated with remission identified by this method are shorter duration of untreated psychosis, better premorbid adjustment, lower psychopathology or illness severity, early improvement in symptoms and medication adherence. Two other variables (female gender and lack of substance use at baseline or persistent substance use during treatment) were identified as less clearly related to remission (AlAqeel & Margolese, 2013; Lambert, Karow, Leucht, Schimmelmann, & Naber, 2010).

A study of first-episode schizophrenia (Emsley, Rabinowitz, & Medori, 2007) reported a remission rate of 23.6% at six months on antipsychotics. The rate is lower than in previous studies (80%). Robinson, Woerner, McMeniman, Mendelowitz and Bilder (2004) reported a better outcome (47.2% achieving remission in 5 years) in a first-episode sample. This study also reported female gender to be associated with better outcome.

Emsley et al. (2008) reported that remission was achieved in 64% of the patients in first-episode schizophrenia, treated with long-acting injectable (LAI) risperidone, a second

generation antipsychotic. This raises the question about adherence to antipsychotics in this specific group. Similar studies on first-episode schizophrenia (AlAqeel & Margoese, 2013; Ceskova, Prikryl, & Kasperek, 2011) found that even though the remission rate was 73% initially following index hospitalisation, it dropped to approximately 50% when patients were reassessed after one, four and seven years. The investigators of the latter study suggested that the response to treatment during the first episode might not be a decisive indicator of longer-term outcomes.

A critical and systematic review by AlAqeel and Margoese (2013) reported a 17% to 78% remission rate (weighted mean = 35.6%) in first-episode schizophrenia and 16% to 62% remission rate (weighted mean = 37%) in multi-episode schizophrenia, with no significant statistical difference between the two remission rates. This study used remission criteria developed by a schizophrenia working group in 2005 (Andreasen et al., 2005). The time of the remission criterion was six months. Another study of first-episode patients reported a 27% remission rate when followed up for five years (de Haan, van Nimwegen, van Amelsvoort, Dingemans, & Linszen, 2008).

The following sections focus on literature reviews of antipsychotic medications, other clinical variables (patient characteristics, duration of hospital stay, treatment variables) and clinical guidelines for the treatment of schizophrenia.

2.2 Existing Medications (Types and Routes)

The treatment of schizophrenia and related disorders has advanced over the past half century with the introduction of APDs, and innovative models of community care. Evidence for the efficacy of APDs is provided by effect size estimates of RCTs and meta-analyses published in the past 50 years.

Over the past two decades, there has also been a major shift in the focus of treatment, from acute symptom control towards maintenance treatment with APDs, remission and

recovery. In addition to treatment with APDs during acute phases of illness, the efficacy of APD maintenance treatment in reducing the risk of relapse and hospital readmission has been established over the past three decades (Kane & McGlashan, 1995). It is worth mentioning that the definitions of relapse have also differed in various studies. For example, the term has been applied to ‘hospitalisation rate’, ‘failure to maintain response’, ‘psychotic exacerbation’, ‘failure to maintain improvement’ and ‘dropout owing to decompensation’ (Kishimoto et al., 2011).

The distinction between efficacy and effectiveness has also been addressed, as it is one of the reasons for the variation in clinical practice (Jones et al., 2006; Lieberman et al., 2005). In order to increase the prevalence of evidence-based practice, efficacious treatment needs to be effective (in usual care settings). Clinical management decisions depend on data on the health and cost impact of psychiatric treatment under usual care, that is effectiveness, and clinical trials, provide information on treatment efficacy under best practice conditions (Wells, 1999). In almost all areas of clinical psychiatry now, the gap between research and practice is of concern, and therefore there is increasingly greater emphasis on effectiveness research (Carroll & Rounsaville, 2003). This trend in research reflects the concern regarding the generalisability of scientific evidence on treatment effects.

Researchers have raised the issue that attributes of the practice context have been largely ignored or considered as not important in ‘traditional models’ of validating new treatments (Schoenwald & Hoagwood, 2001). Therefore, effectiveness studies are increasingly including populations, clinicians and clinical settings that are reflective of usual care circumstances. Transportability research is one way of examining the movement of efficacious intervention to usual care setting, which usually deals with heterogenous populations and high case-load. So, in order to address this efficacy-

effectiveness gap, there are transportability questions that need to be addressed. For example, which aspects of treatment need modification so that effective treatment can be delivered in real-world settings. More and more researchers are focusing on effectiveness studies that encompass representative practice conditions, and thereby societal consequences such as morbidity and costs could be addressed.

Several paradigms have been identified to understand the efficacy and effectiveness gap (Nordon et al., 2016). For example, real life factors such as characteristics of health-care settings, behaviours of patients, caregivers and as well as physicians' behaviours have been thought to influence the effectiveness of drugs. With regards to study features, efficacy studies most often than not deviate from usual practice conditions. For example, there is usually standardised treatment protocols, homogenous samples, special settings, high treatment compliance and these studies usually exclude patients at immediate risk and with multiple comorbidities. Whereas effectiveness studies evaluate treatment under conditions approximating usual care, even though not always clearly identifying which features of usual care (Wells, 1999). Their designs are more heterogenous, for example, quasi-experimental designs and observational studies. Both efficacy and effectiveness studies could include similar outcomes, but efficacy trials in psychiatry usually evaluate short-term outcomes. Effectiveness studies are more often designed to evaluate long-term clinical and morbidity outcomes (Wells, 1999). A major challenge in effectiveness studies is standardised interventions while preserving usual care conditions. With regards to validity, efficacy studies usually place greater emphasis on internal validity (i.e., the study findings are true for the study population and setting) and effectiveness studies place a higher priority on external validity (i.e., generalisability of the findings to other populations and setting). However, "both types of studies share threats to validity" (Wells, 1999, p. 8). Both studies also use different statistical analyses to address these

variations, for example analysis of covariance or regression techniques and intention to treat analysis. These different methods have their own short-comings too. The common approach is to control for bias for initial group differences and regression analysis. Slowly researchers are utilising more advanced analytical techniques, for example decision analysis, analysis of propensity variables. Mentioning limitation of studies is one way to address these concerns about both types of studies, and thereby readers and clinicians would be able to appreciate these concerns while trying to practice evidence-based medicine.

In this context, studies of psychotropic medications have a similar problem. Adherence rates achieved in practice are usually lower than in clinical trials and it has been difficult to predict the response to APDs. Studies investigating pharmacological response predictors have shown inconsistent results (Correll et al., 2003). A study by Garver, Holcomb and Christensen (2000) also suggested differences in antipsychotic response may be related to differences in the aetiology and consequent pathophysiology of illness.

The pathophysiological basis of schizophrenia remains, however, incompletely understood but it is essential for improving the use of APD treatment and for developing new treatment (Howes et al., 2009). The neurochemically leading theory dominating the neuropharmacological research is the dopamine hypothesis (dysregulation of dopaminergic neurotransmission). Carlsson and Lindquist in 1963 proposed their seminal hypothesis (Lehmann & Ban, 1997) that the blockade of dopamine receptors is responsible for the clinical effects of APDs. In the 1970s, the clinical effectiveness of APDs was found to be directly related to their affinity for dopamine receptors (Creese, Burt, & Snyder, 1976).

The introduction of chlorpromazine (phenothiazine group) in the mid-1950s was the beginning of the modern treatment of schizophrenia. Subsequently, additional chemical

classes of APDs have been introduced (Kane & McGlashan, 1995). The groups include butyrophenone (e.g., haloperidol), thioxanthenes (e.g., flupenthixol, zuclopenthixol), benzoquinolizines (e.g., tetrabenazines), diphenylbutylpiperidines (e.g., pimozide), dibenzoxepine (e.g., loxapine) and indole derivatives (Lehmann & Ban, 1997). These groups of antipsychotics are known as first-generation antipsychotics (FGAs) or classical antipsychotics or 'typical antipsychotics'.

FGAs have been shown to be effective in both acute treatment and preventing relapse (Davis, 1985; Kane & Lieberman, 1987). The efficacy of FGAs in schizophrenia was mainly investigated between 1960 and 1980, by comparing one or more APDs with either a placebo or a sedative agent (Hasan et al., 2012).

All these FGAs produce a demonstrable drug-induced blockade of dopamine (D₂) receptors, despite differences in structure (Lehmann & Ban, 1997). However, chronic administration of these antipsychotics was also believed to be responsible for acute (50%–90%) and chronic (15%–20%) extrapyramidal symptoms (EPSs) (Lehmann & Ban, 1997), sometimes at therapeutic dosages. These side effects are believed to be caused by marked blockade of D₂ receptors in the nigrostriatal brain pathways, which are involved in motor control of our body and refine movements. This is in contrast to the antipsychotic effect, which is caused by blockade of receptors (D₂) in the mesolimbic pathway of the brain. The acute extrapyramidal signs are akathisia, dystonia and parkinsonism and the chronic EPSs mainly present in the form of tardive dyskinesia (involuntary movements of face and jaw). In addition to this concern regarding EPSs, 30%–50% of patients with schizophrenia remain unresponsive to treatment or partially responsive, and negative symptoms of schizophrenia respond poorly to classical APDs. Concerns also rose regarding the effect of EPSs and negative symptoms on the quality of life of patients with schizophrenia and related disorders.

Therefore, clinicians were looking forward to the development of new APDs with good efficacy to alleviate both positive and negative symptoms and reduced side-effect profile to improve tolerability and favour adherence. During the 1980s, research focused on the development of APDs with higher affinity to mesolimbic than to nigrostriatal D₂ receptors (Lehmann & Ban, 1997) and in the 1990s with the introduction of second-generation antipsychotics (SGAs), also known as ‘atypical antipsychotics’, medication treatments for schizophrenia went through significant changes.

The term ‘atypical antipsychotic’ was used originally in the late 1960s in reference to clozapine, because of its greater efficacy and lower propensity to develop EPSs (Lehmann & Ban, 1997). Given the differences between clozapine and other available antipsychotics at the time, research started focusing on the receptor affinity profile of antipsychotics. With the identification and cloning of D₃ and D₄ receptors by Sokoloff and his associates in 1990 and Van Tol and his associates in 1991, the development of SGAs entered a new phase (Lehmann & Ban, 1997).

Triggered by this shift, a growing number of SGAs were accessible for clinical investigation and/or introduced into clinical use, including selective D_{2/3} receptor blockers (e.g., benzamides such as amisulpride, emonapride, raclopride, remoxipride and sulpiride) and selective serotonin S₂ or S₃ receptor blockers (e.g., ritanserin and olanzetron) (Lehmann & Ban, 1997). From the numerous atypical antipsychotics, the first to follow clozapine were remoxipride, risperidone and olanzapine in the 1990s; iliperidol, quetiapine, sertindole and ziprasidone were still in different stages of clinical trial (Lehmann & Ban, 1997). In addition to those with high selectivity for serotonin 5-HT_{2A} and D₂ receptors (serotonin-dopamine antagonists, such as risperidone, olanzapine, quetiapine, sertindole, ziprasidone), antipsychotics with other mechanisms of actions

(e.g., partial dopamine receptor agonist aripiprazole) have been included under the heading of atypical antipsychotics or SGAs.

With the introduction of SGAs in the 1990s, many studies started claiming their superior efficacy over FGAs. Studies have claimed efficacy of SGAs (risperidone) with regard to negative symptoms and in reducing relapse rate (Csernansky, Mahmoud, & Brenner, 2002; Csernansky & Schuchart, 2002). A long-term study comparing risperidone and haloperidol showed a significantly longer median time to relapse in the risperidone group (466 vs. 205 days) (Schooler et al., 2005).

Studies that compared olanzapine and haloperidol also showed promising results (Hamilton, Edgell, Revicki, & Breier, 2000). Green et al. (2006) reported a superior remission rate and retention with olanzapine in comparison to haloperidol in a two-year study.

Several studies have examined the comparative efficacy of FGAs and SGAs for maintenance treatment and showed variable results (Stroup, Alves, Hamer, & Lieberman, 2006; Stroup et al., 2006, 2007). SGAs as a group reduced relapse rates, compared with FGAs, from 23% to 15% (Leucht, Barnes, Kissling, Engel, Correll, & Kane, 2003). There are also several meta-analyses, which reported that certain SGAs might have some advantages over other SGAs and FGAs (overall efficacy, relapse prevention and quality of life) (Kishimoto et al., 2011; Leucht, Corves, et al., 2009; Leucht, Kissling, & Davis, 2009; Leucht, Komossa, et al, 2009). Different antipsychotic medications produce different side effects, which need to be taken into consideration when prescribing (Leucht et al., 2012).

An initial systematic review and exploratory meta-analysis (Leucht, Wahlbeck, Hamann, & Kissling 2003; Leucht, Barnes, et al., 2003) on relapse prevention for SGAs and FGAs reported that both types of antipsychotics reduce relapse rates compared with placebo.

The review also reported a statistically significant superiority for SGAs compared with FGAs. The magnitude of this advantage was reported as modest only, with no conclusion drawn regarding efficacy because of differences in study design. Another published systematic review and meta-analysis (Kishimoto, Argawal, et al., 2011) on relapse prevention (followed for ≥ 6 months), on SGAs versus FGAs, reported a similar finding. Even though individually SGAs were not consistently superior to FGAs, as a group, SGAs were associated with less relapse and hospitalisation than FGAs and the effect size was modest but clinically relevant.

However, in most of these studies, the comparator was haloperidol and definitions of relapse were variable as was the methodology. Use of the high potency FGA haloperidol could cause higher EPSs and could contribute to a higher rate of relapse, either directly or indirectly through non-adherence. This is supported by the 12-month double-blind RCT by Rosenheck et al. (2003) that did not support the superiority of olanzapine over haloperidol, when haloperidol was prescribed in combination with prophylactic benztropine (anticholinergic medications usually prescribed for treating EPSs).

The exact incidence of tardive dyskinesia (TD), an EPS, with the SGAs has not yet been determined, but one-year studies showed the rate to be 0.5–0.8%, as compared with several studies with the FGAs (5% per year) (Nasarallah & Smeltzer, 2011). Several other studies mentioned an annual incidence of 3% in SGAs versus 7.7% with FGAs for TD (Correll, Leucht, & Kane, 2004; Correll & Schenk, 2008). However, carefully conducted trials have raised questions about putative advantages in EPS tolerability, even with high potency comparators such as haloperidol, when appropriate dose equivalence is used (Rosenheck et al., 2003).

In recent years, there has also been a major concern because many psychotropic drug trials are financially supported by industry and ‘funding bias’ has been pointed out by

several authors (Johnsen & Jørgensen, 2008). A review of head-to-head RCT comparison of SGAs showed results were in favour of the funding party in many studies and this led to contradictory results (Heres et al., 2006).

Interindividual differences in drug response with APDs are also well known and this could be due to the influence of genetic, environmental and pathophysiological factors on pharmacokinetics (refers to absorption, bioavailability, distribution to tissues, metabolism and excretion of drugs) and pharmacodynamics (concerned with receptor binding, postreceptor effects and chemical interactions) of the drugs (Dahl, 2002). The metabolism is catalysed by a number of enzymes including the polymorphic cytochrome p450 enzyme system. Therefore, there are also ethnic differences in metabolism, response and side effects. For example, it has been mentioned in the literature that TD and other EPSs have been observed to be higher in African-American patients (Nasarallah & Smeltzer, 2011). Asian and Hispanic patients have been found to need lower doses of APD to achieve a similar response compared with other ethnicities; they are also more sensitive to EPSs (Chaudhry, Neelam, Duddu, & Husain, 2008).

Discovery of the SGAs, however, has reduced the problem of movement disorders to a certain extent (Correll et al., 2004; Leucht, Pitschel-Walz, Abraham, & Kissling, 1999), but from 1994 to 2001 the metabolic adverse effects of SGAs became apparent to clinicians and researchers (Buckley, Miller, Singer, Arena, & Stirewalt, 2005; Kishimoto et al., 2011; McEvoy et al., 2005). The prevalence of diabetes is reported as two- to threefold higher in people with schizophrenia than in the general population (Smith et al., 2008). Smith and colleagues' (2008) meta-analysis found that SGAs were associated with a small increased relative risk of diabetes compared with FGAs. Epidemiological surveys reported an increased incidence of diabetes and weight gain and an increased risk of cardiovascular disease (Ananth, Venkatesh, Burgoyne, Gadasalli, & Gunatilake, 2004;

Ananth, Parameswaran, & Gunatilake, 2004) in patients treated with SGAs. In the NZ context, this is important because Māori have lower life expectancy and higher rates of heart disease and diabetes than NZ Europeans (Ministry of Health, 2008). Therefore, prescription of SGAs in vulnerable groups requires a robust physical health monitoring programme.

Antipsychotic treatment may also have some secondary effects of improving cognitive performance in the very early stages of psychosis. However, again the jury is still out about any differences in the degree of cognitive improvement between first- and second-generation agents (Harvey & Keefe, 2001; Keefe et al., 2007; Keefe, 2014).

The paradigm that one type of antipsychotic may be more efficacious than another started to change specifically after two RCTs: the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) study (Lieberman et al., 2005) and the Cost Utility of the Latest Antipsychotic Drugs in Schizophrenia Study (CUtLASS) (Jones et al., 2006). These publicly funded effectiveness studies failed to show a clear difference between FGAs and SGAs (Jones et al., 2006; Lieberman et al., 2005). Both studies included chronically ill patients and did not show any superiority of certain SGAs over certain FGAs. They are both important studies with regards to their design, number of patients and duration of illness. Both focused on real-world effectiveness. However, both studies had limitations.

In the CATIE study, the FGA perphenazine was compared with four different SGAs (olanzapine, quetiapine, risperidone and ziprasidone) and the primary outcome measure was discontinuation of treatment for any cause in a sample of chronic schizophrenia patients. The reported overall rate of discontinuation ranged from 64%–82% and participants receiving olanzapine had a significantly longer time to discontinuation (9.2 months vs. median time to discontinuation of 4.6 months) compared with other SGAs and perphenazine. This study had a high drop-out rate (64%). Olanzapine was used in a

broader dosage range (7.5–30mg/day) than is used in clinical practice, and had undergone a partial unblinding (Glick, 2006; Meltzer & Bobo, 2006; Naber & Lambert, 2009).

Perphenazine dosage was 20.8mg per day in this study and patients with tardive dyskinesia were excluded from the perphenazine group.

The CUtLASS 1 study (Jones et al., 2006) showed no inferiority of a group of various FGAs (preferentially sulpiride) compared with SGAs (risperidone, olanzapine, amisulpride, zotepine and quetiapine) in a sample of patients with chronic schizophrenia. However, the study sample was small ($N = 227$ included, $N = 185$ for the follow-up after 52 weeks) and SGAs and FGAs were compared as two homogeneous groups (Möller, 2008). CUtLASS also compared SGAs with clozapine in open-label (i.e., not masked to patients and clinicians, raters were blind) randomized trials. Primary outcome was quality of life and symptoms were the main secondary outcome. The choice of individual medication in each class was made by the clinician in advance of randomisation.

There were number of criticisms. One major criticism was that the populations in CATIE and CUtLASS may not be the most sensitive to detect differences between two groups of APDs. The expectation that patients with a long duration of illness and possibly treatment resistant would improve significantly could be seen as a design problem. While perphenazine is less prone to cause EPS, it is not the most commonly used FGA worldwide, and haloperidol would have been a better comparator, therefore is not reflective of current practice. Patients with tardive dyskinesia were excluded from perphenazine arm even though this is usually the most common reason for discontinuation in the case of FGAs. The discontinuation rate in CATIE study is extremely high. The reasons for discontinuation are also not very clear from this study. It would have been helpful to know the reasons in order to have some understanding. Was it due to inefficacy or intolerability, or were there any other reasons such as patient's

wishes? Another problem was the inadequate blinding; rather than administering twice daily regime for everyone, quetiapine and ziprasidone in this study were taken twice daily whereas half of those on perphenazine, risperidone and olanzapine were taken once a day and half to twice-daily.

Similarly, in CUtLASS, there was insufficient information on how the decision to use a specific antipsychotic was made by doctors. The majority in the FGA group received sulpride, again, not an antipsychotic used frequently in real world practice. The non-random selection of medications within each class and small number of patients per group made it impossible to consider pair-wise comparisons between different groups of APDs (Naber & Lambert, 2009).

Another study that is frequently mentioned is the open-label European First Episode Schizophrenia Trial (EUFEST), funded by three pharmaceutical companies without any influence on study design, data collection, data analysis or publication (Kahn et al., 2008). This study included only first-episode schizophrenia patients; haloperidol was compared with four different SGAs (amisulpride, olanzapine, quetiapine and ziprasidone). Treatment discontinuation was the primary outcome measure. In contrast to CATIE and CUtLASS, this study investigated less chronically ill patients and the retention rate was also higher compared with two previous studies (CATIE and CUtLASS). This pragmatic trial showed SGAs had some advantages over FGAs (Kahn et al., 2008) but symptom reduction was almost the same in all groups. This may be due to subjective effects and due to reduced risk of tardive dyskinesia in the SGAs group, facts that most clinicians would agree with in light of their clinical experience. However, risperidone was omitted from this study, which was a surprise given its wide use in first episode patients. Also the dose of quetiapine (50mg) was very surprising as it was well below the licensed dosage.

A meta-regression analysis (Geddes, Freemantle, Harrison, & Bebbington, 2000) that compared atypical antipsychotics (amisulpride, clozapine, quetiapine, olanzapine, risperidone and sertindole) with classical antipsychotics (haloperidol and chlorpromazine) also concluded that there is no compelling evidence to indicate that SGAs are more effective or better tolerated than FGAs. There are no data to support a change to SGAs for people with schizophrenia experiencing adequate symptom control and minimal side effects with an FGA (Buchanan et al., 2010).

The results of the CATIE study (Lieberman et al., 2005) also raised important issues about the tolerability profiles of different new generation compounds; their cost-effectiveness benefits have been challenged too (Rosenheck et al., 2006).

Therefore, with the exception of clozapine, the benefits (fewer EPSs, overall change in positive and negative symptoms with some of the SGAs) (Gründer et al., 2016; Leucht, Corves, et al., 2009) from modern APDs were achieved at the cost of side effects such as weight gain, increased diabetes and cardiovascular problems, and in the absence of major gains in effectiveness or tolerability. A meta-analysis of head-to-head comparisons of SGAs in schizophrenia (Leucht, Komossa, et al., 2009) stated, with regard to overall efficacy (positive and negative symptoms scale), amisulpride, clozapine, olanzapine and risperidone were better than FGAs with medium to small effect sizes. Other SGAs (aripiprazole, quetiapine, sertindole, ziprasidone and zotepine) did not show superiority over FGAs in overall efficacy and positive and negative symptoms scale scores (Hasan et al., 2012).

A number of epidemiological analyses also have shown that the non-adherence rate, one of the most common reasons for relapse in schizophrenia, is not significantly different from that occurring with classical compounds (Dolder, Lacro, Dunn, & Jeste 2002; Gilmer et al., 2004; Valenstein et al., 2004). A recently published meta-analysis (Leucht

et al., 2012) also reported no significant difference in relapse rates between trials using first- or second-generation agents.

Therefore, large-scale studies and meta-analyses (Jones et al., 2006; Leucht, Corves, et al., 2009; Leucht, Komossa, et al., 2009; Lieberman et al., 2005) have started to question whether there are any clinically important differences in outcomes between FGAs and SGAs (Hartling et al., 2012).

Hospitalisation is the most expensive treatment alternative for patients with schizophrenia, accounting for between one-third and two-thirds of total health care costs (Knapp, 2000). One retrospective, naturalistic study (Advokat, Hill, & Comaty, 2008) specifically compared the length of stay (LOS) of hospitalised patients with schizophrenia for different APDs and also looked at rehospitalisation rates after discharge. They examined two patient cohorts. One group was hospitalised between 1991 and 1994 and another between 2001 and 2004. Researchers subsequently focused on three groups within the cohort: patients initially prescribed and maintained on FGAs, patients initially prescribed FGAs but switched to SGAs during hospitalisation (FGA/SGA group), and patients prescribed and maintained on SGAs. Their data for the 1991–1994 cohort suggested fewer patients discharged after treatment with an SGA were rehospitalised, compared with those treated with FGAs ($p \leq 0.05$). The analysis of the second cohort, however, did not show any differences between FGAs, FGAs/SGAs and SGAs in the number of patients subsequently rehospitalised. In this study, during both time periods, inpatients on FGAs had relatively shorter lengths of stay compared with the other two groups. However, once discharged, patients on SGAs were less likely to be rehospitalised. Their inference was that a group of inpatients might have responded better to an SGA than to an FGA, and this outcome might be a result of an initial longer LOS in hospital. The study also suggested that the fact that 10 years later all patients had a

shorter LOS on SGAs could be explained by the change of health policy, decrease in the availability of beds and improved community care.

A study by Rabinowitz et al. (2001) on SGAs other than clozapine reported that rehospitalisation rates were similar for patients on risperidone (33%) and olanzapine (31%) and both of these were lower than for the patients treated with FGAs (48%). However, the cost of SGAs is much higher than that of conventional/classical APDs and the clinical as well as economic evidence is inconclusive to make treatment choice between FGAs and SGAs except clozapine (Davies et al., 2007). The RCT by Davies et al. (2007) also suggested that classical or conventional APDs may be cost saving and associated with a gain in quality-adjusted life-year (QUALY) compared with SGAs except clozapine. Studies on clozapine all along showed that rehospitalisation is lower than with conventional APDs (27.8% vs. 56.2%) (Conley, Love, Kelly, & Bartko, 1999; Honigfeld & Patin, 1990) and other SGAs (Bagnall et al., 2003). The use of SGAs has also not reduced the practice of polypharmacy (use of multiple antipsychotics) (Centorrino et al., 2004, 2005; Stahl & Grady, 2006), another ongoing concern in patients with schizophrenia.

Therefore, the introduction of these new generation compounds has not resulted in significant differences in outcome (relapse and rehospitalisation rates) (Advokat & Comaty, 2004), medication adherence (Awad, 2004; Nakonezny & Byerly, 2006), attitude towards medications or quality of life (Advokat et al., 2008). Except clozapine, no single type of antipsychotic medications seems more satisfactory across the board than any other when considering efficacy and effectiveness.

Clinicians have become sceptical and the notion of 'two dichotomous groups' of APDs has become a major source of debate. In view of this ongoing confusion, the World Psychiatric Association's pharmacopsychiatry section published a statement in 2008,

after reviewing approximately 1,600 RCTs of APDs in schizophrenia with regard to the effectiveness of 62 antipsychotic agents (Tandon, Belmaker, & Gattaz, 2008). This analysis concluded that if differences in EPSs are minimised by careful dosing, there is no convincing evidence to support any advantages of SGAs over FGAs. The studies claiming an extrapyramidal side-effect advantage for SGAs continue to attract criticism because of the inappropriate comparator dosage of FGAs. Finally, this analysis could not detect a different efficacy among the SGAs apart from clozapine, which was superior to all other antipsychotic agents in treatment-resistant schizophrenia.

Medications produce different responses in individual patients, so identification of specific situations or individuals from real-life data might help to improve evaluation of their therapeutic value and cost-effectiveness (Basu, 2004; Polsky, Doshi, Bauer, & Glick, 2006; Salkever, Slade, & Karakus, 2006). Given the ongoing confusion over the FGAs/SGAs issue, simple trials that evaluate the comparative effectiveness of APDs in real-world settings might prove helpful (Stroup, Alves et al., 2006).

The ‘typical’ (FGA) and ‘atypical’ (SGA) medications have now become embedded in the professional vernacular, despite much evidence suggesting that “atypicality has not proven to be a valid concept” (Owens, 2010, p. 228). There is also no pharmacological characteristic that links all ‘new’ antipsychotics as was once predicted (Owens, 2008). It is important to understand the different mechanisms for the future direction of treatment for schizophrenia.

Ongoing debate about the different types of APDs opens up once again the full range of antipsychotics—new and old—for consideration as schizophrenia treatment options. In clinical decision making, beyond the fact that new generation medications (except clozapine) extend the options in treatment, there is little to support any overall superior inherent value at this stage (Gelder et al., 2000; Owens, 2008).

To complicate the situation further, it is a well-known fact that rates of non-adherence to oral medications are high in schizophrenia (Novick et al., 2010; Tiihonen et al., 2011), as they are in many chronic medical illnesses (Dunbar-Jacob & Mortimer-Stephens, 2001). Adherence to oral APDs has been estimated to occur in as many as 42% (Leucht et al., 2011) of patients. The range varies from 20% to 89%, with an average of 50%. The CATIE study reported a discontinuation rate of 74% at 18 months (Lieberman et al., 2005) and the EUFEST study reported a discontinuation rate of 42% at 12 months (Kahn et al., 2008). Many of the studies were based on questionnaires, so patients unwilling or unable to participate were not included. Therefore, non-adherence rates could be higher in unselected patient populations (Buchanan et al., 2010).

Non-adherence to maintenance treatment with APDs is associated with higher rates of relapse and psychiatric hospitalisation (Gilmer et al., 2004), in addition to lack of efficacy of APDs. A review in 2008 (Llorca, 2008) reported that at least 50% of patients will be partially non-adherent within one year and 75% within two years of discharge. The adherence rates fall from between 60% and 85% during month 1 of treatment to as low as 50% by month 6 (Byerly, Fisher, Carmody, & Rush 2005). It is worthwhile to mention that poor adherence to APDs could also be due to adverse effects, the patient's level of insight, the severity of the illness, the complexity of the treatment regime and the relationship the patient may have with the mental health practitioner (Fenton, Blyler, & Heinssen, 1997).

Improving adherence in this group of patients with schizophrenia is a complex task. It includes both identifying risk factors for non-adherence and ensuring treatment. This leads to the question of the extent to which LAIs have a role in relapse prevention. There are a number of advantages of LAIs in addition to addressing the adherence problems. These include stabilisation of blood levels, avoidance of first-pass metabolism and

probable fewer side effects because of lower peak plasma concentration (Adams, Fenton, Quraishi & David, 2001). Furthermore, patients on injectable antipsychotics meet regularly with health care professionals for treatment and can therefore be monitored closely (Viala et al., 2009).

A number of LAI antipsychotics have been developed over the years. LAIs were first introduced in 1966 in an attempt to improve the long-term treatment of schizophrenia. A comprehensive report on LAIs by Patel, Taylor and David (2009) commented that 40%–60% of patients with schizophrenia were either totally or partially non-adherent to an antipsychotic regime, but despite this ongoing concern, only less than 30% were on LAIs. The reason varies from suboptimal knowledge of this route due to limited data from real-life settings, to an assumption that LAIs are not acceptable to patients and could be perceived as coercive.

Research also has focused on the efficacy of LAIs, and the results have been variable. Studies have shown that LAIs can be more effective than oral antipsychotics (Adams et al., 2001; Davis, Metalon, Watanabe, & Blake, 1994; Glazer & Kane, 1992) and can address the adherence issue. The efficacy of the first-generation long-acting injectables (FGLAIs) is well established (Johnson, 2009). An early meta-analysis by Davis et al. (1994) suggested a significant superiority of LAI formulations over oral medications. Tiihonen et al. (2011) reported that LAI formulations were associated with a 50%–65% reduced rehospitalisation rate (adjusted hazard ratio [HR], 0.36; 95% CI, 0.17–0.75; $p = 0.007$) compared with identical oral APDs. A number of mirror image studies also demonstrated their efficacy in reducing relapse and hospitalisation rates (Haddad, Taylor, & Niaz, 2009). A systematic meta-review (Adams et al., 2001) reported better retention in treatment, and reduced risk of relapse and rehospitalisation on LAIs.

There have also been some quite contradictory results. Even though several meta-analyses claimed the superiority of LAIs over oral APDs (Kishimoto et al., 2013; Leucht et al., 2011; Velligan & Sajatovic, 2013), a summary of Cochrane reviews and two large-scale studies did not demonstrate this (Kishimoto et al., 2012; Rosenheck et al., 2011). A systematic review and meta-analysis (Leucht et al., 2011) of RCTs, which specifically compared outcomes in patients treated with oral APDs and those treated with LAIs, reported that even though LAIs were more effective in reducing relapse and rehospitalisation rates, there was no significant difference in adherence rates between oral APDs and LAIs. This study estimated that there was a 10% absolute reduction in relapse rates associated with the use of LAI formulations compared with the oral regime (22% vs. 33%, $p = 0.0009$).

The use of LAI antipsychotics has started to decline however, since the introduction of oral SGAs (Barnes & Curson, 1994; Callaly & Trauer, 2000; Johnson & Wright, 1990; Shah, 1991). In addition to the stigma associated with 'old' LAIs and clinicians' attitudes towards prescribing LAIs, the role of aggressive marketing, claims of better tolerance and less severe side effects of oral SGAs are also contributing factors to this reduction, In contrast to FGLAIs, SGLAIs (second-generation long-acting injectables) were only introduced in 2006. Since then, three different SGLAIs have become available and widely used: risperidone, paliperidone and olanzapine. A prospective study reported that LAI risperidone was well tolerated by patients and led to more treatment adherence than oral risperidone (Weiden et al., 2009). Another study (Lindenmayer, Khan, Eerdeken, Van Hove, & Kushner, 2007) showed that LAI risperidone was safe and well tolerated after 12 months of treatment in schizophrenia patients. In an open, randomised controlled six-month study, long-acting risperidone was superior to zuclopenthixol depot for a subsample of schizophrenia patients with comorbid substance abuse (Rubio et al., 2006).

Other studies of large samples (Lambert et al., 2011; Olivares, Rodriguez-Martinez, Burón, Alonso-Escolano, & Rodriguez-Morales, 2008; Olivares et al., 2009) showed improvement on global measures, such as the Clinical Global Impression and the Global Assessment of Functioning. Similarly, studies have been published on paliperidone (Alphs, Bossie, Sliwa, Ma, & Turner, 2011; Gopal et al., 2011; Pandina et al., 2011) and olanzapine long-acting injections (Kane et al., 2010; Lauriello et al., 2008).

The evidence is still limited in comparison with the evidence for FGLAIs. A meta-analysis of RCTs on the efficacy and safety of SGLAIs (Fusar-Poli, Kempton, & Rosenheck, 2013) concluded that SGLAIs have superior efficacy to placebo on psychotic symptoms but found no evidence of superiority over oral APDs. Most RCTs, however, have shown better adherence and reduction of relapses and rehospitalisation on SGLAIs (risperidone and olanzapine mainly, in absence of comparative data on aripiprazole LAI).

However, the SGLAIs are more expensive. Even though a better side-effect profile has been claimed for this group, the side effects when prescribed over the long term have not yet been explored. Data comparing FGLAIs and SGLAIs are also sparse (Brissos, Veguilla, Taylor, & Balanzá-Martinez, 2014). Therefore, more studies are required in this area in order to provide guidance for clinicians.

Frequent relapses usually occur during the first years of illness; therefore, the efficacy of LAIs in first-episode schizophrenia patients is a crucial area to explore. There is evidence for a decreased rate of relapse with LAIs compared with oral APDs in the early phase of schizophrenia (Brissos et al., 2014), but current guidelines have a conservative position at this stage (more details on guidelines are given in the clinical guidelines review in Section 2.4).

There are some concerns that LAIs may be related to excessive dosing and risk of increasing side effects (such as TD). A study by Arnold et al. (2004) did not support this

concern that use of LAIs is associated with higher prescribed antipsychotic dosages compared with oral APDs. Also, LAIs cannot easily be translated into oral chlorpromazine equivalent dosages (the usual method for comparing different types and routes of APDs), a problem that may affect outcome because of low or excessive dosing in the absence of clear guidelines to direct the clinician (Valenstein, Copeland, Owen, Blow, & Visnic, 2001).

There is also not enough evidence available yet to support the use of LAIs over oral APDs. RCTs may not be ideal for this situation, if we think non-adherence is a deliberate act, because patients participating in RCTs are more likely to be willing to take treatment. In RCTs, usually patients who are willing to listen to a lengthy explanation of the trial, provide consent and show up for appointments, are likely to be recruited, but those who miss appointments and are less cooperative are likely to be excluded from the study recruitment procedure (Kishimoto et al., 2012). Subjects in RCTs may consist of patients with better treatment adherence and lower illness severity. So, patients in RCTs may not be representative of the patient group for whom clinicians would routinely choose LAIs. Extrapolating results from RCTs in this area may therefore affect generalisability.

It is also difficult to demonstrate differences between oral medications and LAIs in short-term studies. Kane, Kishimoto and Correll (2013a, 2013b) mentioned that studies lasting two years would have substantially more likelihood of detecting a difference than those lasting only one year. Therefore, given the main advantage of LAIs in addressing non-adherence, the differences between oral and LAI formulations are better evaluated in naturalistic long-term studies (Schooler, 2003). Observational effectiveness studies are more suitable for this group (Kane et al., 2013a) because of the inclusion of more representative samples, use of pragmatic variables and routine treatment conditions in real-world clinical settings.

In view of the above discussion on different types and routes of antipsychotics, it has become clear that the effectiveness of a medication is a combination of its efficacy and tolerability. Given the dilemma and contradictory evidence on efficacy when comparing two types and two routes of antipsychotics, the best evaluation of the effectiveness of any compound should include an assessment over a lengthy observational period in a real-world setting. To maximise the effectiveness, treatment options need to be considered in relation to the clinical circumstances of the individual patient (Barnes, 2011).

It is also important to take into account when considering effectiveness of an intervention, that because of the heterogeneity of both the presentations and outcome, it is difficult to predict the individual vulnerability for patients with schizophrenia and related disorders. Such a vulnerability may influence the overall individual course of the disorder and response to intervention, including the readmission risks (Olesen & Mortensen, 2002). Even though a wide range of variables have been examined as possible predictors of outcome in schizophrenia, due to heterogeneity of the disease, identifying a single characteristic, clinical symptom or sign that is strongly associated with long-term prognosis has been difficult.

2.3 Other Clinical Variables (Patient Characteristics, Compulsory Admission, Duration of Inpatient Admission, Dosages of Antipsychotic Medications and Clinician Characteristics) and Treatment of Schizophrenia

2.3.1 Patient demography

Medical literature and guidelines worldwide have also focused on the effect of patient characteristics (age, gender and ethnicity) when considering treatment of schizophrenia and related disorders. The pharmacokinetics and pharmacodynamics of APDs differ in men and women. Genetics, age, height, weight, lean fat ratio, diet, exercise, concurrent disease and presence of other drugs all contribute to APD response (Seeman, 2004).

In general, women require lower doses compared with their male counterparts. However, clinical practice guidelines (CPGs) do not differentiate between male and female patients. Ageing increases total body fat and there is a decrease in intracellular water and protein binding; also, drug metabolism decreases (Seeman, 2004). Therefore, gender and age need to be taken into account when prescribing APDs. In addition, studies have shown that adherence rate is poor in ethnic minorities and in younger patients (Valenstein et al., 2004).

Many of the early studies have also found antipsychotic doses and prescribing rates for high potency FGAs and LAIs to be higher in ethnic minority groups (Citrome, Levine, & Allingham, 1996; Price, Glazer, & Morgenstern, 1985; Walkup et al., 2000). Studies, mainly from the USA, have shown that African-American patients were less likely than Caucasian patients to receive SGAs, even after controlling for demographic and service-use characteristics (Kuno & Rothbard, 2002; Valenstein et al., 2001; Wang, West, Tanielian, & Pincus, 2000). Therefore, studies are suggesting ethnic influences on the treatment decision (Arnold et al., 2004; Daumit et al., 2003). Another study (Walkup et al., 2000) reported that these variations could not be explained by differences in clinical severity. However, after controlling for method of administration, the impact of race was reduced to non-significance in this specific study.

Several studies (Kuno & Rothbard, 2002; Valenstein et al., 2001; Wang et al., 2000) found that African-Americans were less likely than white patients to be prescribed SGAs. After adjusting for clinical and demographic variables, African-American men were also prescribed LAI medication at discharge more frequently than African-American women and white men and women. A recent study by Puyat et al. (2013) on racial and ethnic disparities in the use of antipsychotic medication conducted a systematic review and meta-analysis of the published evidence. They did not find any significant differences

among African-Americans (OR = 1.01, CI = 0.99–1.02) compared with Caucasian patients. Among those who received antipsychotic treatment, ethnic minorities were consistently less likely to be treated with newer antipsychotics. However, there are also studies that have raised concerns that other factors likely to be affecting prescribing practice have not been considered in some of the studies that focused on ethnicity. Pharmacokinetic differences between ethnicities and drug metabolism (e.g., poor metabolisers) differences need to be explored further before making any conclusion.

Some of these concerns have been also raised in the NZ context. There are increasing concerns about the inequalities in overall health outcome in NZ and the increased rate of admission to psychiatric units for Māori and Pacific people compared with NZ Europeans (Abas et al., 2003; Wheeler, Robinson, & Robinson, 2005). One study (Wheeler, Humberstone, & Robinson, 2008) aimed to compare APD prescribing in schizophrenia for ethnic groups over 4.5 years. In this specific study, data were collected from the clinical files of three mental health catchment areas in Auckland, NZ. The conclusion was that most baseline differences in antipsychotic prescribing between ethnic groups were resolved over time.

Some of the other relevant clinical variables, among many, that are believed to be important in the treatment of schizophrenia, and thus outcome, are compulsory admission status under the Mental Health Act (MHA), dosages of antipsychotics, number of previous admissions and length of hospitalisation (Breier, Schreiber, Dyer, & Pickar, 1991; Olfson, Ascher-Svanum, Faries, & Marcus, 2011). Some literature also explores the role played by clinicians, especially variation in prescribing patterns and the effect of this on outcome (Hamann et al., 2004).

2.3.2 *Mental Health Act*

Involuntary admission under mental health legislation is one of the most discussed topics in psychiatry. According to a study by Swartz et al. (1999), “Public concern is heightened due to rare but tragically violent acts by severely mentally ill individuals who are found to be non-adherent to treatment” (p. 1968). However, this is not the only reason why involuntary admission and treatment still exists in psychiatry. The goal of involuntary admissions under the MHA is to provide standards for the rights of people with mental health conditions (Katsakou & Priebe, 2006). This is to ensure treatment of vulnerable people with mental illness when capacity to make decisions is impaired because of symptoms of mental illness. The involuntary hospital admission has been a part of psychiatry for more than 200 years. It is now practised more or less throughout the world, but the frequency of involuntary admissions, as well as the rules and regulations for involuntary treatment, still differ significantly between countries.

Mental health legislation however, faces criticism from the human rights perspective. Debate continues about the usefulness of MHA and long-term outcome, i.e., is the outcome better than if the same patients were not coerced into treatment? Despite history of utilising coercion since the late 18th century (Burns et al., 2013), there is little research available on the potential long-term effects of involuntary admission. The evidence for its effectiveness on rehospitalisation and treatment adherence is also equivocal (Dawson & Romans, 2001). One specific study in Israel concluded that involuntary first admission might be an important factor in assessing whether patients are likely to be readmitted involuntarily but had no effect on readmission rates (Fennig, Rabinowitz, & Fennig, 1999). Another larger study (Sanguineti, Samuel, Schwartz, & Robeson, 1996) concluded that involuntary admission with a diagnosis of schizophrenia is a predictor for readmission.

Concerns also have been raised in NZ from the Office of the Director of Mental Health (Ministry of Health, 2014), as well as in other parts of the world, regarding a higher rate of compulsory admission for ethnic minorities and patients with schizophrenia (Edmonds, Williams, & Walsh, 2000; Wheeler et al., 2005). A UK study (Bhui et al., 2003) reported similar concerns regarding the use of mental health legislation. Therefore, evidence on the long-term effects of involuntary admissions and subsequent rehospitalisation would provide guidelines for clinicians to ensure proper utilisation of such a method.

There have been debates on ethical justification and best practice. A systematic review (not specifically focused on patients with schizophrenia) reported that a significant number of patients were admitted on an involuntary basis. Even though they showed clinical improvement, patients did not feel retrospectively that the admission was justified or beneficial (Katsakou & Priebe, 2006). In addition, a study by Swartz et al. (1999) stated that “a brief period of court-ordered treatment may actually have no effect, or even an adverse effect (i.e., by further antagonizing the individual forced to comply with treatment), while providing little benefit” (p. 1974). A recent study with two-year follow-up data also did not show any significant effect of involuntary admission on the number of admissions and LOS in hospital (Castells-Aulet et al., 2015). Most studies from the USA, the UK and Germany suggest that the rate of compulsory admission depends not only on clinical factors such as diagnosis but also, largely, on social factors. Therefore, regional variation has been well documented.

NZ’s mental health legislation is based to an extent on the United Kingdom (UK) Mental Health Act 1983. The Mental Health (Compulsory Assessment and Treatment) Act 1992 in NZ provides a comprehensive framework for mental health treatment for a person experiencing a serious mental illness. The MHA treatment order can be an inpatient order

or a community treatment order. Inpatient treatment orders can be in place initially for five days following an admission and then require a review. The review is to decide the need for continuing compulsory treatment for a further two weeks. Generally, after this period, a responsible psychiatrist can request a community treatment order, which requires a judicial review. The condition of the community treatment order is that the patient takes prescribed medications and attends regular follow-up assessments. It also requires that a mental health practitioner consult with the patient and family.

As regards to diagnosis, almost all investigators have concluded that patients with schizophrenia are more readily admitted against their will than other patients (Riecher-Rössler & Rössler, 1993). One explanation could be that this is due to frequent relapse because of nonadherence to medications in young people with schizophrenia. In view of the number of concerns and significant variation in practice, studies are required to identify the predictors of involuntary admissions and outcome. This would require both quantitative and qualitative data on this group. Variations in the definition of mental disorder and variations in the criteria for involuntary admission, including focus on social dangerousness around the world, are also important contributing factors when it comes to decision making. In addition to patient related factors, service related factors are important, which includes availability of community support, resources, as well as culture of the place or hospital. Increasing evidence also shows that poverty and unemployment increase the risk of involuntary admission (Høyer, 2008) and political emphasis on public safety has also been a motive for an increasing rate of coercion for people considered as dangerous and mentally ill. Therefore, due to multifactorial reasons, there is no easy answer when it comes to outcome. Identifying associations between MHA and sociodemographic variables as well other clinical variables may however help to identify

specific subgroups that benefit from treatment under the MHA. This may help to reduce the rate of involuntary admission and treatment locally.

2.3.3 Length of hospitalisation

Hospitalisation is one of the costliest interventions for this group of patients, and the effect of recurrent hospitalisation is devastating for both the patient and the caregiver. The duration of hospital admissions has also been a focus of research. Psychiatric hospitalisation tends to be indicated now largely to provide a safe environment for persons considered to be suicidal, homicidal or otherwise dangerous (Masters, Baldessarini, Öngür, & Centorrino, 2014). This shift has been encouraged by the deinstitutionalisation movement as well as by increased expectations of the effect of modern treatment, mainly of antipsychotic medications. Another motivation is to limit costs, as duration of hospitalisation is the major contributor in this respect.

The evidence about the effects of shorter LOS on clinical and functional outcomes and readmission rates is, however, inconclusive and not necessarily predicted by the severity of symptoms (Rocca et al., 2010; Warnke, Rössler, & Herwig, 2011). A retrospective study concluded that although short hospital stays are common, approximately 40% of psychiatric inpatients are rehospitalised within one year of discharge (Thompson, Neighbors, Munday, & Trierweiler, 2003). The high readmission rate may be partially due to the trend towards brief initial hospitalisations.

Other studies (Appleby, Desai, Luchins, Gibbons, & Hedeker, 1993; Kirshner, 1982; Schneider & Ross, 1996) concluded that patients hospitalised for a shorter period were significantly more likely to return within 30 days after discharge when compared with those treated for longer periods. This may be due to inadequate preparation for discharge and ineffective links to outpatient care. The mean LOS has been considered 28 days with

a range between 15 and 30 days (Appleby et al., 1993; Kirshner, 1982; Schneider & Ross, 1996).

Length of stay does not depend on a single factor and therefore it is difficult to comment on how long is too long, or how short is too short. Aftercare is also an important factor—establishment of good aftercare services may reduce both length of stay and rehospitalisation which are both resource-intensive. A recent study reported that the length of hospitalisation averaged 13.2 days among patients with a variety of severe psychiatric illness and was strongly associated with the level of post-discharge care. Schizophrenia again came across as an important predictor for prolonged hospitalisation, as was lower functional status (lower GAF scores) (Masters et al., 2014).

Most studies have not found a consistent relationship between diagnosis and rehospitalisation. Some studies have reported an association between higher rehospitalisation rates and a diagnosis of schizophrenia, whereas others have reported higher rates of rehospitalisation among patients who have a diagnosis of substance abuse or dependence or who have a chronic psychiatric disorder with an affective component (Thompson et al., 2003).

There are three types of factors implicated in LOS: clinical factors, treatment factors and factors linked to the care system. In addition, the need for rehousing or placement frequently leads to delayed discharge (Tulloch, Fearon, & David, 2008). The behaviour of individual clinicians has not come across as a significant factor in prolonging patients' LOS (Huntley, Cho, Christman, & Csernansky, 1998). Therefore, developing care systems addressing the patient's specific needs could be more helpful in predicting LOS and also could be helpful for planning bed availability (Capdevielle et al., 2013).

In the NZ context, concerns have been raised regarding the higher rates of rehospitalisation for those of Māori ethnicity (Edmonds et al., 2000; Sachdev, 1989).

Previous hospitalisation was also documented in many studies as a predictor for rehospitalisation (Mortensen & Eaton, 1994; Olfson et al., 1999; Olfson, Ascher-Svanum, Faries, & Marcus, 2014).

2.3.4 Antipsychotic dosage

Another area that has been the source of debate is antipsychotic dosing. Potency equivalents for APDs are required to guide clinical dosing (Gardner, Murphy, O'Donnell, Centorrino, & Baldessarini, 2010; Gardner, Murphy, O'Donnell, Centorrino, & Baldessarini, 2014). To ensure a 'level playing field', studies that compare APDs' efficacy require objective measures for the dosage of APDs. The earliest method for determining equivalents, developed by Davis (1974), was based on double blind studies reported in the literature that used chlorpromazine as a comparator (Andreasen, Pressler, Nopoulos, Miller, & Ho, 2010). This provided data about comparable dosage and identified dose ratios in relation to 100 mg of chlorpromazine. This method has been used by many studies over the years to compare efficacy and also to address side effects.

However, questions have been raised regarding the consensus of opinion for chlorpromazine equivalents (CPZE), a commonly used tool for comparing dosages.

CPZE was used to estimate the efficacy equivalence between APDs, referring to the dose of an APD in mg/day that was as effective as 100 mg/day of chlorpromazine (Patel, Arista, Taylor, & Barnes, 2013). However, CPZEs are primarily based on dopaminergic blockade and not on a drug receptor profile for cholinergic, serotonergic or histaminergic systems, so this could affect the conversion of SGAs, and therefore the dose and potency would not always be linear.

Similar concern was raised because of the discrepancies between the oral equivalents of LAIs (Atkins, Burgess, Bottomley, & Riccio, 1997). Values per drug are ambiguous in

nature, and an up to threefold variation in CPZE values has been reported (Rijcken, Monster, & Brouwers, 2003).

Other methods used for calculation of the dose of antipsychotics are percentage of British National Formulary (BNF) maximum and defined daily dose (DDD), and studies have been carried out investigating the coherence between these methods. One study (Nose et al., 2008) showed a high degree of coherence between the three methods, whereas another study found a great discrepancy and recommended further research (Rijcken et al., 2003). The ambiguity has become more of a problem since SGAs with different receptor profiles started to dominate treatment. Therefore, CPZE values might not be accurate for SGAs (Dewan & Koss, 1995). Subsequently, Woods (2003) developed an equivalency table based on the methodology of Davis (1974). A recent study, however, reported that for CPZE the coherence was strongest for FGAs (Gardner et al., 2010).

Review of the antipsychotic treatment of schizophrenia and other clinical variables highlights the fact that prompt administration of effective antipsychotic treatment that patients adhere to is important for good symptom control and for reducing relapse (Juckel et al., 2014). However, the discussion also highlights the fact that real-life outcome is variable. A number of patient factors, medication factors and illness factors need to be examined to improve the outcome for people with schizophrenia and related disorders.

It is widely thought that demographic factors, individual vulnerability, comorbid substance abuse, previous hospitalisation, premorbid adjustment, medication non-compliance and lack of efficacy and effectiveness of antipsychotic medications are some of the important variables that contribute to high frequency of hospital admission (Lauronen et al., 2007; Novick et al., 2010).

2.4 Clinical Practice Guidelines

In everyday practice, clinicians face the challenge of selecting the most appropriate treatment; such clinical decisions require an understanding of the empirical research evidence on medication efficacy. CPGs have been developed to bridge the gap between existing practice and current evidence derived from research.

Despite more than 50 years of psychopharmacological research on APDs (Stein, Lerer, & Stahl, 2012), there is still insufficient evidence-based data for choice to be made among the at least 50 antipsychotic medications available worldwide. Before the introduction of SGAs, the decision as to which antipsychotic to choose was relatively simple. A recently published study by Leucht et al. (2013) using data from published RCTs concluded that the straightforward classification of first generation and second generation is not helpful and that there are differences in efficacy between antipsychotics.

However, because of the ongoing dilemma regarding the efficacy and effectiveness of individual antipsychotics (FGAs/SGAs), clinicians face a daily challenge in their clinical practice when deciding on the suitability of any antipsychotic for patients with schizophrenia and related disorders. One way to evaluate real-world prescribing of antipsychotic medications is to compare the trend with published guidelines.

In view of a reduced likelihood of promoting APD-induced parkinsonism, most guidelines released before 2009 recommend SGAs as first-line treatment for patients with schizophrenia and related disorders. The NICE (2009) guidelines and PORT (2009) guidelines have taken into consideration the recent controversy between FGAs and SGAs. The PORT recommendation stated “in light of the comparable efficacy and variable risk of side effects among the different FGAs and SGAs, a straightforward recommendation for preferential use of SGAs over FGAs for first-line treatment of acute

positive symptoms is not currently warranted” (Kreyenbuhl, Buchanan, Dickerson, Dixon, & Schizophrenia Patient Outcomes Research Team, 2010, p. 94).

The PORT recommendation is the use of antipsychotic medications, other than clozapine and olanzapine, as first-line treatment for persons with schizophrenia experiencing their first acute episode. The NICE (2009) guidelines also acknowledged the recent evidence for comparable efficacy of FGAs and SGAs for treating schizophrenia. The RANZCP (2005) and APA (2004) guidelines recommended oral SGAs as a preferred first-line choice in view of the concerns regarding EPS and TD.

The recently published RANZCP guidelines (Galletly et al., 2016) also recommended SGAs except olanzapine as a first-line treatment for first-episode psychosis and mentioned olanzapine as a second-line agent if there is no response to first-line treatment.

In general, acute phase treatment guidelines and algorithms do not differ much, but guidelines and algorithms are more diverse regarding maintenance treatment (Gaebel et al., 2011; Moore, Covell, Essock, & Miller, 2007; Takeuchi, Suzuki, Uchida, Watanabe, & Mimura, 2012). There is noticeable correspondence between guidelines in many of the recommendations.

According to a review by Gaebel et al. (2011), all existing guidelines recommend oral APD as the preferred option but in case of patients’ preference or adherence problems, LAI is recommended. All guidelines recommend two adequate trials (of 6–8 weeks, within the effective dose range) of different antipsychotics (with at least one SGA) for treatment-resistant patients, before initiating clozapine. All guidelines recommend different psychosocial interventions.

There is also consensus regarding recommended dosages; generally, lower doses are recommended for first-episode patients. The dosage range recommended is between 300 and 1,000 CPZE of antipsychotics. Almost all guidelines recommend lower dosages for

the first episode, between 300 and 600 CPZE dosages. Daily doses of FGAs lower than 300 mg CPZE were found to be inadequate for optimal treatment and doses above 940 mg CPZE produced no better responses than 540–940 mg CPZEs (Kaplan & Sadock, 1988, pp. 1591–1626).

The newer guidelines also acknowledge that CPZE is more appropriate for FGAs and have mentioned dosage ranges for individual SGAs rather than CPZE. However, for research purposes, for head-to-head studies and for the provision of clear guidelines for clinicians, equivalent dosage is important.

The greatest disparities are regarding the duration of treatment. The guidelines that have addressed the issue recommend maintaining antipsychotic treatment for at least a year for the first episode and for two years up to indefinitely for multi-episode patients (Gaebel et al., 2011). The RANZCP (2016) guidelines recommended continuing treatment for two to five years for first-episode psychosis.

After reviewing the available evidence and treatment guidelines (Hasan et al., 2012), the World Federation of Societies of Biological Psychiatry (WFSBP) stated in their summary statement that FGAs and SGAs are both effective in the treatment of first-episode schizophrenia and due to the reduced risk of inducing neurological side effects, the first-line use of SGAs in first-episode schizophrenia patients is recommended (Hasan et al., 2012). The treatment decision should be guided by the effectiveness and the side-effect profile of the antipsychotics and should be made individually for each patient.

For multi-episode patients, the WFSBP stated that all SGAs and FGAs can be considered as treatment options (Hasan et al., 2013). The WFSBP stated that antipsychotics (FGAs and SGAs) are effective in relapse prevention, and FGAs and SGAs do not show general differences in reducing symptoms with long-term treatment.

The NICE (2009) guidelines summarised the treatment choices by saying treatment should be guided by the side-effect profile of the drug, patient's experience and response with certain antipsychotics and potential interaction.

Existing guidelines for schizophrenia and available evidence also recommend antipsychotic monotherapy (Barnes & Paton, 2011; Tandon, Belmaker, et al., 2008).

However, antipsychotic polypharmacy (the co-prescription of more than one antipsychotic for an individual patient) is a relatively frequent phenomenon.

Antipsychotic polypharmacy has increased over the years and is prescribed to 25% of outpatients and more than 50% of inpatients with schizophrenia in the USA, and to 13%–90% of patients internationally (Chakos et al., 2006). This is despite unequivocal evidence of the risks of this strategy, and of benefits not generally considered adequate to warrant a recommendation for its use in routine clinical practice (Barnes & Paton, 2011).

Treatment resistance is a clinical problem faced by psychiatrists in day-to-day practice. It affects the choice of antipsychotics and may increase the use of more than one antipsychotic (Correll, Rummel-Kluge, Corves, Kane, & Leucht, 2009). One-fifth to one-third of people with schizophrenia are considered to have treatment-resistant illness. So there is an increasing trend towards antipsychotic combination treatment or antipsychotic polypharmacy with a prevalence rate between 27% and 60% (Millier et al., 2011). The combination of FGAs and SGAs is the most common combination (Ganguly, Kotzan, Miller, Kennedy, & Martin, 2004; Ito, Koyama, & Higuchi, 2005). Despite this trend, few RCTs with a good study design have been conducted to evaluate the efficacy of combining strategies (Freudenreich & Goff, 2002) and the majority of the studies have reported increased side effects with polypharmacy (Correll, Frederickson, Kane, & Manu, 2007; Faries, Ascher-Svanum, Zhu, Correll, & Kane, 2005). The reported rate of antipsychotic polypharmacy in CATIE studies was as low as 5% (Chakos et al., 2006).

Some studies examined specifically augmentation of clozapine with another antipsychotic but the results were not consistent (Anil Yagcioglu et al., 2005; Paton, Whittington, & Barnes, 2007). Another review stated that, despite some positive data, there is currently no biological or evidence-based rationale why combinations should be superior to monotherapy (Goodwin et al., 2009).

Another form of polypharmacy in patients with schizophrenia or related disorders is co-prescription of other psychotropic medications such as antidepressants, mood stabilisers, sedative-hypnotics, anxiolytics and anticholinergics (Millier et al., 2011). The indication could be augmentation, treating comorbid conditions or treating side effects. CATIE reported in their study that 38% were on antidepressants, 18% on anxiolytics, 16% on sedative-hypnotics and 15% on anticholinergic medications (Chakos et al., 2006). The rate of mood stabiliser use was only 19% in the CATIE sample.

In the European Schizophrenia Outpatient Health Outcome (SOHO) study, concomitant medication use ranged from 5% to 29% for anticholinergics, 8% to 23% for antidepressants, 22% to 37% for anxiolytics and 7% to 19% for mood stabilisers (Haro et al., 2007). This study concluded that the use of certain antipsychotics (olanzapine, quetiapine, clozapine) may be associated with less use of concomitant medications (Novick et al., 2005).

The existing guidelines and algorithms do not provide a great deal of direction on the use of adjunctive psychotropic medications. The recent RANZCP guideline (Galletly et al., 2016) also highlighted the concern regarding an increase in mortality on antipsychotic–mood stabiliser combinations. However, all guidelines encourage treatment of comorbid conditions. Concomitant psychiatric medications and polypharmacy is also an important risk factor for clinically relevant adverse drug reactions (Novick et al., 2005).

Existing guidelines recommend clozapine for treatment-resistant schizophrenia after two failed trials on adequate dosages of antipsychotics (one should be SGAs). However, the practice varies across the globe. Approximately 20%–30% of patients with schizophrenia are treatment resistant; evidence internationally suggests only a modest fraction of them are being treated with clozapine (Moore et al., 2007). It has been consistently underutilised in the USA, the UK, Canada, NZ and Australia (Warnez & Alessi-Severini, 2014).

However, recent studies from Australia and NZ suggest a change in practice: clinicians have started prescribing clozapine earlier (Malalagama, Bastiampillai, & Dhillon, 2011) and the rate of prescription is increasing (Wheeler, Feetam, & Harrison, 2014).

2.5 Theory–Practice Gap

The gap between research and practice is well-documented in many areas of health care (Glasgow & Emmons, 2007). The concern is whether the concept of ‘hierarchy of evidence’ may have contributed to the idea that ‘real-life’ studies are not as legitimate as RCTs (Nordon et al., 2016). A definition of evidence based medicine (EBM) provided in a publication stated “EBM is the conscientious, explicit, and judicious use of current best evidence in making decisions about the care of individual patients” and RCT “has become the gold standard for judging whether a treatment does more good than harm” (Nordon et al., 2016, p. 78). These concepts also contribute to this ongoing ‘research-practice gap’ and support the idea that ‘real life observational studies are providing distorted view on real effect of medications’.

Keeping in mind the conflicting points of view with regard to the efficacy and effectiveness of different types and routes of antipsychotics for relapse prevention, evidence from real-life data might help bridge the efficacy–effectiveness gap.

CPGs are just one piece in a larger jigsaw of evidence for decision making (Barley, Pope, Chilvers, Sipos, & Harrison, 2008). Part of a clinician's decision making depends on knowledge acquired from training, or from personal experience and interaction with colleagues, patients, opinion leaders and pharmaceutical representatives. A study by Barley et al. (2008) concluded that guidelines are only a component of the knowledge psychiatrists might use when making decisions about management of schizophrenia and therefore simple dissemination of guidelines will not change practice. This also partly explains the reason for the ongoing theory–practice gap.

Clinicians might simply not follow guidelines because of a number of concerns such as ‘CPGs are not applicable for the patient group in their day-to-day practice’, ‘they represent a cook-book approach’, ‘there are time and organisational constraints’ and ‘the culture of the organisation does not foster their use’ (Barley et al., 2008, Casey, 2013). Overall, not many studies have examined the variations among individual clinicians in prescribing antipsychotics for schizophrenia and it is described as a complex process that can be influenced by a number of factors at the patient, provider and system levels (Davis, Yee, & Millar, 1994). Understanding of the multi-faceted routes of such variation is the key to success in bridging the gap between theory and practice.

Clinicians need to understand what different treatments really achieve or do not achieve. There may be multiple reasons for the failure of health research findings to translate into practice (Glasgow & Emmons, 2007). Patient selection has been identified as one of the main culprits for inconsistent findings. One concern is that clinical trials have included patient cohorts that are not truly representative of the patients these medications would be used for in ordinary practice (Fleischhacker & Goodwin, 2009). The traditional RCT design does not always represent routine clinical practice. As per a recent article focused on ‘efficacy–effectiveness gap’ (Nordon et al., 2016), “the concept of pragmatism holds

that the lack of generalizability has led to the research practice gap and any direct dissemination of evidence arising from clinical trials into clinical practice might be inadequate, therefore the generation of real-life evidence on the impact of drugs is becoming increasingly recommended” (p. 78).

Data from real-life settings therefore could be compared with RCT findings under rigorous conditions. This would facilitate the process of developing guidelines, to ensure the practice of actual evidence-based medicine. In order to meaningfully advance the treatment outcome, it is essential to adopt a rigorous hypothesis-testing approach and to utilise appropriate methods. It is worthwhile to mention that the results of observational studies usually reflect the patterns of practice, and can be considered more meaningful to evaluate effectiveness (Millier et al., 2011). For example, the SOHO study (Haro et al., 2007) was a three-year prospective observational study on antipsychotic treatment outcome and highlighted the need for large-scale observational study in schizophrenia.

RCTs do not necessarily provide the final answer to treatment effectiveness, and other real-world experiences (observational, non-randomised studies) have a role in quantifying effectiveness (D’Agostino, 2007). The limited generalisability of RCTs has been explained more in recent times. RCTs do not always guarantee a high degree of internal validity (i.e., design and conduct must eliminate the possibility of bias). The internal validity of RCTs may be compromised because of differential refusal or high drop-out rates, initial group differences despite randomisation, subversion of randomisation, non-compliance with treatment protocols, and cross-over between treatment conditions. They can almost certainly compromise external validity (i.e., generalisability); therefore, they can pose important limitations on translating findings to common practice.

Policy debates increasingly require information that is directly generalisable to community patient samples. So, despite limitations due to lack of randomisation, the

main goal of observational studies is to determine how treatment is applied in actual practice and thus maximise external validity. The SOHO (Schizophrenia Outpatient Health Outcome) study particularly highlighted the role of well-designed, large observational studies in order to overcome difficulties that arise while interpreting study findings (Haro et al., 2007).

A study by Concato and colleagues (Concato, Shah, & Horwitz, 2000) specifically challenged the hierarchy of study design in clinical research. After examining the same topic for both RCTs and observational studies, this study stated, “the popular belief that only RCTs produce trustworthy results and that all observational studies are misleading, does a disservice to patient care, clinical investigation and the education of health care professionals” (p. 1892). The following quote helps to explain why we need different types of studies to ensure practice is based on ‘best available evidence’, not always on ‘best possible evidence’ in many areas: “Conceptualizations of evidence need to include, but also go beyond, that from tightly controlled RCTs” (Glasgow & Emmons, 2007, p. 417).

In contrast with efficacy trials, practical trials have several advantages and provide information that aid decision makers during their day to day practice. Practical trials encourage heterogeneity in contrast to efficacy trials and usually reflects more of the complexity and context of the real world. In order to bridge the theory–practice gap and to improve outcomes for patients with schizophrenia and related disorders, therefore, there is an ongoing need for observational studies with long-term follow-up. Appreciating and integrating multiple types of evidence would increasingly help us to address this theory and practice gap.

SECTION 3: AIMS AND HYPOTHESIS

3.1 Study Aims

The purpose of this observational (non-interventional) study, based on real-life data, is to describe and follow a broadly defined clinical population diagnosed with schizophrenia or a related disorder. The specific aims are as follows:

- 1) To investigate the **antipsychotic choice** on discharge of patients treated for schizophrenia or related disorders at three public hospitals in New Zealand; selected because they differed in geography, population size and ethnic mix.
- 2) To compare that **observed practice** with published clinical **practice guidelines** for the treatment of schizophrenia or related disorders.
- 3) To explore the **associations** between prescribing patterns and both patient and clinician characteristics.
- 4) To examine the **associations** between index discharge variables and subsequent two-year **rehospitalisation rates** and **hospital bed days** in this cohort.

3.2 Hypothesis

3.2.1 *Null hypothesis*

Patient characteristics, clinician characteristics, and type, route or dosage of prescribed antipsychotics would not have any effect on the outcome, as quantified by rehospitalisation for relapse and/or mean cumulative hospital bed days during subsequent hospitalisation.

3.2.2 Specific research questions for statistical analysis

For discharged patients with a diagnosis of schizophrenia or a related disorder:

1.1. Do patient characteristics (age, gender, ethnicity) and other clinical variables (compulsory admission, duration of hospital admission, clinician characteristics) predict the antipsychotic prescribing patterns (type, route, dosage) on discharge?

1.2. Do patient characteristics and other clinical variables predict the duration of index hospital admission or discharge under compulsory treatment (MHA)?

1.3. Are there differences in the numbers or characteristics of those discharged on conventional/first-generation (FGA) antipsychotics as compared with second-generation (SGA) antipsychotics?

1.4. Are there differences in the numbers or characteristics of those discharged on oral antipsychotics compared with those prescribed long-acting injectable antipsychotics (LAIs)?

In the two years following the index discharge:

2.1. Is there a statistical relationship between the rate of rehospitalisation and the prescribed antipsychotic medications (FGA vs. SGA, oral vs. depot/LAIs) on discharge?

2.2. Is there an association (statistical relationship) between the duration of subsequent hospitalisation and antipsychotics (FGA vs. SGA, oral vs. depot/LAIs) prescribed on discharge?

2.3. Do discharge variables (age, gender, ethnicity, compulsory admissions, duration of index admission, clinician characteristics) influence outcome (rehospitalisation and mean hospital bed days during subsequent admissions)?

SECTION 4: METHODOLOGY

4.1 Study Design

The research intended to address the aims and hypotheses presented in Chapter 3. To answer these questions, the clinical records of an unselected, consecutive series of inpatients were included from the inpatient discharge data of the district health boards (DHBs) of three regions (Waikato, Lakes and Tairāwhiti).

Waikato DHB serves a population of 377,335 people and the ethnic mix has more Māori (22%) than the national average (15.4%). Lakes DHB covers a population of 103,175 people and the population tends to be younger than the national average, especially for those aged 19 and under. The Lakes region also has a higher proportion of Māori (35%). Tairāwhiti DHB provides service to 46,698 people and the population mix tends to be much younger than the national average, again with a higher proportion of Māori (48.9%) compared with the national average.

Each of these services provides inpatient and outpatient care and delivers a multidisciplinary team service (inpatient and outpatient) throughout its respective region. These public hospitals use a coding system for diagnosis, based on the ICD Version 10. This is a standard diagnostic tool for epidemiology, health management and clinical purposes and is used to monitor the incidence and prevalence of diseases. ICD-10 was endorsed by the Forty-Third World Health Assembly in May 1990 and came into use from 1994. This study included the diagnosis of schizophrenia or related disorders (schizophrenia, schizotypal disorder, delusional disorders, brief psychotic disorder, shared psychotic disorder, schizoaffective disorders, other psychotic disorders not due to a substance or known physiological condition, unspecified psychosis not due to a substance or known physiological condition) coded as F20 to F29 under ICD-10.

The most efficient way to capture a representative sample was considered to be use of a cross-sectional study design and observation of the outcome (rehospitalisation rates and subsequent hospital bed days following the index discharge) of this sample over a two-year period, by utilising the national mental health database, known as PRIMHD (the Programme for the Integration of Mental Health Data). This approach was preferred over other study designs because it was believed an observational study would provide data from unselected cohorts in the real-world setting, and would help to address the gap between efficacy and effectiveness.

The distinction between the impact of an intervention under ideal conditions (efficacy) and in routine clinical practice (effectiveness) is critical in interpreting clinical trials. Also, schizophrenia in most cases is a lifelong illness, where longer-term follow-up is necessary to comment on outcome. The observational study design therefore allowed a two-year follow-up period and inclusion of a larger sample size to increase the power of the study, which could have been an obstacle if RCT had been favoured.

Clinician characteristics in this study were obtained by written request to ensure reliable information either from the clinicians or from service managers in the absence of clinicians (some clinicians were practising overseas at the time of data collection).

4.2 Participants

The study cohort comprised 451 patients with a diagnosis of schizophrenia or related disorders (ICD-10, F20–29) discharged from inpatient units in three NZ regions (Waikato, Lakes and Tairāwhiti) between July 2009 and December 2011 (Dey et al., 2016a).

4.2.1 Inclusion and exclusion criteria

The study inclusion criteria covered almost all patients with comorbidities and acute risk issues, discharged during the specified period:

- aged 18–75
- discharge diagnosis of schizophrenia or related disorders, i.e., documented in the discharge summary and coded in the F2 (ICD-10) category, irrespective of risk, legal status and comorbidities
- on antipsychotics at the time of the index discharge

Exclusion criteria were applied to those who were diagnosed with:

(1) intellectual disability, (2) substance induced psychosis, (3) psychosis due to organic causes (head injury, delirium, dementia) and (4) psychosis due to other general medical conditions on discharge.

These diagnostic categories were not included because the treatment would vary according to the very nature of those specific conditions, and the majority of patients with schizophrenia or related disorders receiving treatment from adult mental health services of public hospitals usually do not have these diagnoses as their primary conditions.

4.2.2 Sample size and power calculation

A power calculation was undertaken to ensure minimising of type 2 error (the error of failing to observe a statistically significant difference between two groups when in reality a difference does exist). Commonly used power is 80%, i.e., there is an 80% probability of detecting a difference if one exists and 20% chance of a false negative result.

Sample size in a study is dependent on multiple factors: alpha value (level of significance, normally 0.05), power (ranges between 80 and 95%), variance of population (the greater the variance, the larger sample size required) and effect size.

Therefore, to ensure sufficient statistical power of finding significant differences in rehospitalisation rate between those discharged on SGA and FGA, power calculations in this study were undertaken based on the literature review. Locally, the study by Wheeler

et al. (2008) was determined to be the best available data for the basis of power calculation because of its large sample size ($n = 4821$), inclusion of patients with diagnosis of schizophrenia and it also contained the demographic information and proportion of patients on different types of antipsychotics (types, administration route and dose) at three local DHBs.

Based on the Wheeler study, the current study assumed that 80% of the patients would be discharged on SGAs (Wheeler et al., 2008). In accordance with the assumptions, this would amount to 240 exposed patients and 60 non-exposed. On the basis of international literature (in absence of robust local data) on outcome data, it was assumed that 30% of patients discharged on SGAs would be rehospitalised compared with 50% of patients discharged on FGAs (Conley et al., 1999; Werneck, Hallak, Nakano, & Elkis, 2011).

Using the above proportions and a level of significance of 0.05 (95% CI), the statistical power of the study with 300 patients would be 84%. It was estimated that 80%–90% of patients with schizophrenia or related disorders would likely meet the study inclusion criteria. The census of adult mental health services in 2009/10 (Mental Health and Addiction: Service use 2009/10, published February 2013), reported that 54% of all patients were male and a higher percentage of youth (15–24 years) were seen by secondary services. The total Māori rate was almost 1.5 times higher than other ethnic groups, with a higher age-standardised rate compared with other ethnicities.

Therefore, recruitment of a sample of sufficient size as determined by the power calculations was achievable. In terms of demography, all three regions included in this study had a higher percentage of Māori compared with other parts of NZ's North Island. The achieved sample size for this study was 451 after excluding 14 because of duplication or absence of follow-up data.

4.2.3 Recruitment and data collection

The initial tasks were to gain permission from the Northern Y Regional Ethics Committee and to communicate with staff (clinical director and service managers) for each site.

The role of ethics committees in observational studies is to safeguard the rights and interests of participants, promote high-quality research for the well-being of society and ensure awareness of ethical principles. Ethics committee approval facilitates ongoing access by the researcher to necessary information for the study. This includes accessing the National Health Index (NHI) and index discharge dates for the patients with a discharge diagnosis of schizophrenia or related disorder (ICD codes F20–29) and information on subsequent hospitalisations. Ethical approval was granted (NTY/12/exp/026) by the committee following a formal application.

In order to facilitate the data collection process, initial discussion was held with Waikato Hospital's mental health staff. This was achieved by written requests and a brief presentation of the research topic to small groups of staff. Once staff were informed about the research, a process was agreed upon to identify eligible patients from clinical records. Wherever possible, the researcher attended meetings with staff to provide an overview of the research.

At an early developmental stage of this research, the researcher had discussed the research methodology with the representative of the Te Puna Oranga service (cultural facilitator for Māori ethnicity) at Waikato Hospital. This discussion included an introduction to the research methodology and the probable outcome this study would be addressing. This meeting provided helpful feedback and no concerns were raised regarding the process.

The research methodology was subsequently presented to both Lakes and Tairāwhiti DHB representatives and at a local conference (Auckland) of the Royal Australian and New Zealand College of Psychiatrists. These presentations allowed the researcher to further refine the process and methodology. The inclusion of three sites ensured a mixture of different ethnicities and a larger sample size, thus increasing the generalisability of the results. Ethics committee approval was granted for the two other sites (Lakes and Tairāwhiti).

Promotion of the study was further achieved by including the staff of the medical records department of each service. Each service required an individually tailored approach, which was agreed upon by the service managers and clinical directors before progressing. Searches of both manual record files and electronic databases were conducted to ensure breadth and precision in data collection.

The study's researcher was involved directly in the data collection process for all three sites. To reduce the chance of delay and variation, the researcher completed the data collection for two sites (Waikato and Lakes DHB). Wherever necessary, the researcher attended meetings and encouraged discussions with clinicians and service managers to explain the process and the aim of the study. The data from Tairāwhiti was obtained with the help of a local clinician, with whom regular meetings were held to ensure the consistency of the process. As a result of this consultative process, data collection for individual site was completed within the expected time frame.

Consent from the participants was not a requirement because the study was observational only, did not include any direct involvement with patients and did not influence or change the treatment course of the patients. Years of postgraduate experience and country of postgraduate training were obtained from individual clinicians and service managers

(some clinicians were not working with the respective service at the time of data collection), following a written request from the researcher.

The following information on index discharge was extracted from clinical records:

- demographic information—age, gender, ethnicity of patients;
- diagnoses documented on discharge;
- date of index discharge;
- presence or absence of the Mental Health (Compulsory Assessment and Treatment) Act, 1992;
- duration of index admissions (hospital bed days);
- prescribed antipsychotics on discharge—generic name, types (FGAs/SGAs), routes (oral/LAIs), dosages (converted to CPZEs);
- other prescribed psychotropic medications on discharge (sedative-hypnotics, antidepressants, mood stabilisers, anticholinergics);
- Information on discharging clinicians (country where they had received their postgraduate qualification and years of postgraduate experience as psychiatrists);
and
- duration of previous admissions: hospital bed days in the 24 months prior to the index admissions.

To ensure the availability of outcome data extending over two years, the Ministry of Health (MOH) statistician was also consulted and provided with an outline of the methodology and expected timeframe. It was agreed by both parties that PRIMHD would be available for the outcome data on this cohort .

Four different groups of outcome measure were obtained from PRIMHD:

- crisis contact (MOH code T01);
- crisis and planned respite (MOH codes T05 and T30);
- rehospitalisation and inpatient bed days (MOH codes T02, 03, 04);
- community follow-up (MOH codes T36 and 42).

4.3 Statistical Analysis

Processing and analysis of the data were performed using the Statistical Package for the Social Sciences (SPSS) PC version 20.0. Categorical variables were expressed as absolute numbers and percentages and continuous variables as mean \pm standard deviation (*SD*) and 95% CI for normally distributed data.

Descriptive statistics were used to describe the sample characteristics. Statistical differences between groups were investigated with the chi-square test or the Fisher's exact tests (for small numbers) for categorical variables. A *p* value of < 0.05 was considered statistically significant. Kaplan–Meier graphs were used to examine the risk of relapse over time. Multivariate regression analyses were performed to explore associations between variables.

Univariate regression analyses estimated the effects of independent variables on rehospitalisation bed days. Hazard ratios (HRs) from a time-dependent regression analysis were used to describe the likelihood of rehospitalisation after adjusting for each variable in univariate analyses. Coefficient indicated the estimated change in average bed days for a change in category of the indicated predictor variable.

4.4 Method of Analysis

The analysis was divided into two stages.

4.4.1 Part 1

Based on discharge information extracted from patient records (see Section 4.2.3), the first part of the analysis sought to examine the prescribing pattern of antipsychotics and other psychotropic medications on discharge, in order to compare the trend with existing guidelines for the treatment of patients with schizophrenia, and subsequently to examine the associations between prescribing patterns and patient and clinician characteristics.

For the analysis, demographic variables included gender, age and ethnicity. The age range in this study was 18–75 years and was divided into three age groups, 18–24 years, 25–49 years and 50–75 years. This was for a number of reasons. Seventeen is generally the upper-age cut-off in most published studies of child and adolescent psychosis and is usually the lower cut-off for adult psychosis studies and clinical services (Rabinowitz, Levine, & Häfner, 2006). The onset of schizophrenia is usually in adolescence and early adult life, coinciding with the developmental stage of incomplete social maturation (Galletly et al., 2016) and this may result in a disrupted vocational and developmental trajectory. The onset of schizophrenia after 60 years is also usually rare and nearly all such cases are women. Adult mental health services of most public hospitals in NZ usually provide service to patients up to the age of 65. In the case of a pre-existing history of mental illness, some services continue to provide support until the mid-seventies, in the absence of any other diagnosed age-related condition such as dementia.

Ethnicity was divided into Māori (the indigenous people) and non-Māori (including NZ European, Pacific Island, Asian and other ethnicities). This was in view of the small number of other ethnicities apart from NZ European and Māori and in order to simplify the analysis. No subgroup analyses were planned.

Diagnoses were divided according to ICD-10 codes F20–29 and analysed separately. The analyses did not differentiate between first episode or chronic illness, but most patients in this study were representative of patients with chronic illness.

Antipsychotics were divided according to types (FGAs and SGAs) and routes (oral, LAIs, oral and LAIs, two oral APDs), and polypharmacy was considered the prescription of two or more APDs (oral and LAIs and two or more oral antipsychotics). FGAs and SGAs were also analysed separately as oral FGAs and SGAs and LAI forms of both first- and second-generation APDs. Antipsychotic dosages were converted to CPZE irrespective of types and routes to facilitate comparison of dosages. Information on other psychotropic medications was also explored and compared in order to provide an insight into the prescribing pattern. Even though evidence is limited on concomitant use of other psychotropic medications (antidepressants, mood stabilisers, sedative hypnotics and anxiolytics) in patients with schizophrenia or related disorders, their use due to lack of efficacy of antipsychotic medications or partial response is not uncommon practice (Chakos et al., 2006).

Admission under the mental health legislation consisted of both inpatient and community treatment orders and these were not distinguished in the analyses. For the purpose of analysis, it was divided into presence (yes) or absence (no) of MHA. The duration of index admission was divided into three weeks or less and more than three weeks. This is an arbitrary division assumed on the basis of the average duration of inpatient stay in most hospitals. Previous admission duration was divided into two similar groups: three weeks or less and more than three weeks.

CPZEs were divided into three groups: 300 mg or <, 301 mg to 600 mg and > 600 mg.

This division was in view of the existing guidelines for treatment of schizophrenia.

Rather than considering it as a continuous variable, this grouping was considered because

it would be easy for clinicians to interpret. Most existing guidelines recommend a dosage between 300 and 600 mg and higher dosages for multi-episode patients (up to 1,000 mg). Dosages more than 1,000 mg are usually considered high dosage and dosages below 300mg are considered not therapeutic.

Eighteen different clinicians treated this cohort. For analysis, the clinicians were divided into three groups on the basis of their postgraduate experience: 1–10 years, 11–20 years and more than 21 years. This was an arbitrary division. There are not many studies focused on clinician characteristics even though this is considered an important variable in many studies. Therefore, clinician characteristics were seen as a relevant and important clinical variable to address prescribing differences in clinical settings in ‘real-world practice’.

Clinicians with less than 11 years’ experience are usually graduates with reasonable experience but still developing and consolidating their practice. Their clinical experience in psychiatry could be considered as long enough to allow comparison with more experienced clinicians. Clinicians with more than 11 years’ experience but less than 20 years’ experience, usually have both theoretical and practical experiences, and clinicians experienced beyond 21 years may be more likely to be influenced by their customary individual choices rather than by evidence pointing to other choices. For the purpose of further analysis, four different groups were also created depending on the country of postgraduate training.

4.4.2 Part 2

The second part of the analysis examined the associations between the outcome information (rehospitalisation for relapse and hospital bed days, crisis contact and community follow-up) and discharge variables, plus the duration of previous hospital admissions in the two years prior to index admissions.

More extensive analysis focused on rehospitalisation (occurring within 12 months and 24 months following index discharge). Crisis contact, crisis and planned respite, and community contacts were also analysed to examine the percentage of patients requiring those types of contacts within 12 months and by 24 months following index discharge.

SECTION 5: RESULTS

5.1 Part 1

A total of 451 patients met the inclusion criteria: 286 from Waikato, 85 from Lakes and 80 from Tairāwhiti districts. This sample exceeded the number required by the pre-study power calculation.

5.1.1 Patient demography (age, gender and ethnicity)

See Table 1 summarising the patient demography of the cohort.

Table 1. Patient demography

Demographic	<i>n</i>	%
Age group		
18–24 years	88	20
25–49 years	289	64
50–75years	74	16
Gender		
Male	290	64
Female	161	36
Ethnicity		
Māori	269	60
Non-Māori	182	40

The study population was 64% males (see Figure 1) with a mean age of 35 years ($SD = 11.7$). Mean age was 40 years ($SD = 12.9$) in females. As can be seen in Figure 1, males predominated in both younger age groups (77% of those aged 18–24 years, 65% of those aged 25–49 years) and females were more common in the over 49 age group (54%).

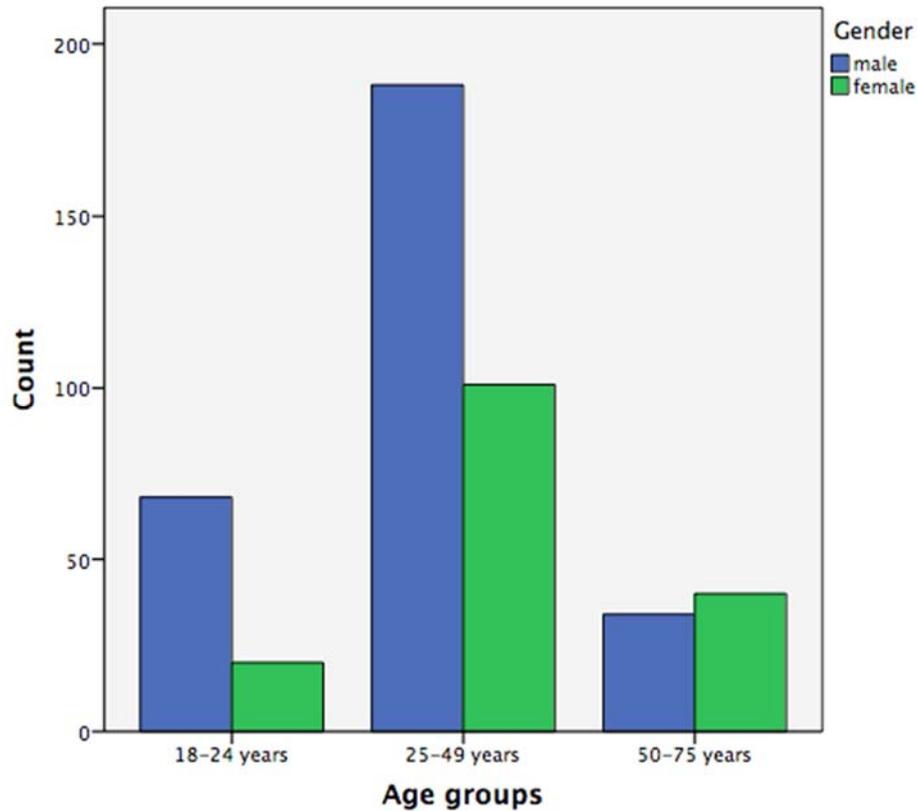


Figure 1. Age group by gender

Five different ethnic groups were identified in the sample: NZ European, Māori, Pacific Islands, Asian and others. The sample consisted of 60% Māori, 35% NZ European, 3.6% others, 1% Pacifica and 0.4% Asian. The mean age of Māori patients was 35 years ($SD = 11.7$) and non-Māori was 40 years ($SD = 13.1$).

For further analysis, patients were pooled into two ethnic categories (see Figure 2): Māori (indigenous population of NZ) and non-Māori (non- indigenous, predominantly European/Pakeha). The ethnicity of one patient was unknown and this patient was excluded from further analyses. As seen in Figure 2, **Māori** were particularly predominant in the younger age groups ($n = 237$, **67%**), while there were more **non-Māori (55%)** in the **over 49** age group.

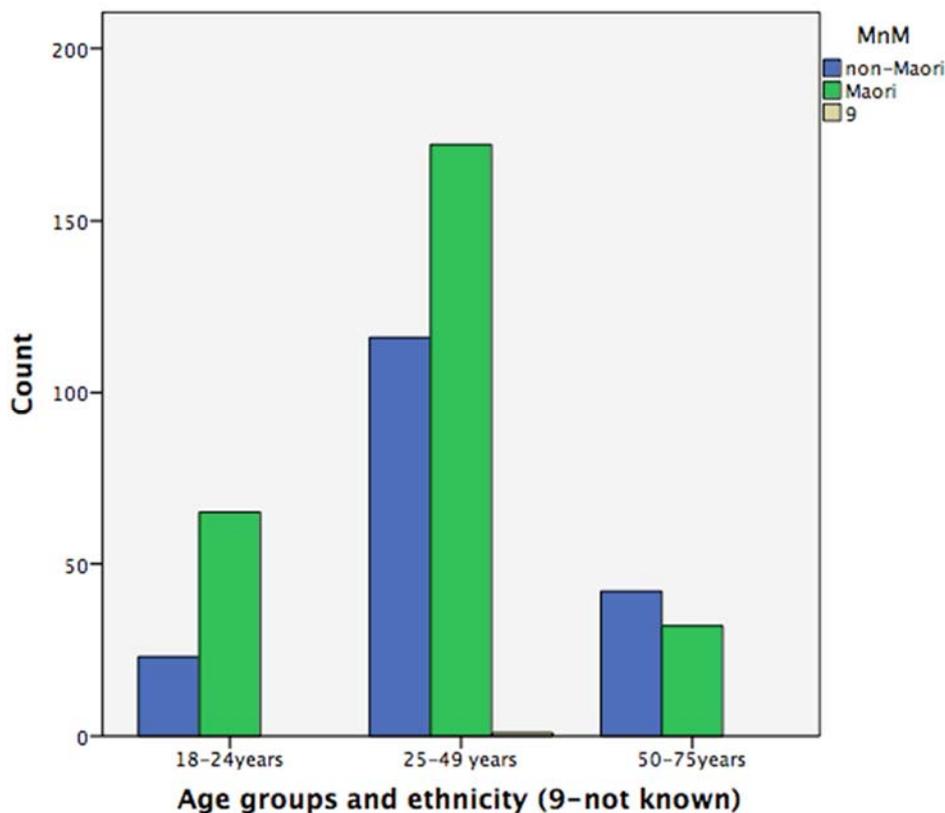


Figure 2. Age groups and ethnicity

5.1.2 Diagnosis

Schizophrenia was the most common diagnosis (**76%**) followed by **schizoaffective disorder** (**21%**). The remainder included delusional disorder, acute and transient psychotic disorder, brief psychotic disorder, psychotic disorder not otherwise specified (NOS) and unspecified non-organic psychosis.

When analysed by age, **85.2%** (75/88) of the younger age group (**18–24**) had **schizophrenia** and only **10.2%** ($n = 9$) had **schizoaffective disorder**. In the **25–49** years group, **75.0%** ($n = 217$) had **schizophrenia** and **20.4%** ($n = 59$) had **schizoaffective disorder**. Of the **over 49** years group, **66.2%** ($n = 49$) had **schizophrenia** and **33.8%** had **schizoaffective disorder**. In relation to gender, **83.1%** ($n = 241$) of the **males** had a diagnosis of **schizophrenia** and **14.1%** ($n = 41$) had **schizoaffective disorder**. Sixty-two per cent (**62.1%**, $n = 100$) of the **females** had a diagnosis of **schizophrenia** and **32.3%** (n

= 52) had **schizoaffective** disorder. Among **Māori** patients, **45%** had a diagnosis of **schizophrenia**, **12% schizoaffective disorder** and **3% others** (see Figure 3). Among non-Māori patients, 30% had a diagnosis of schizophrenia, 9% schizoaffective disorder and 1% others.

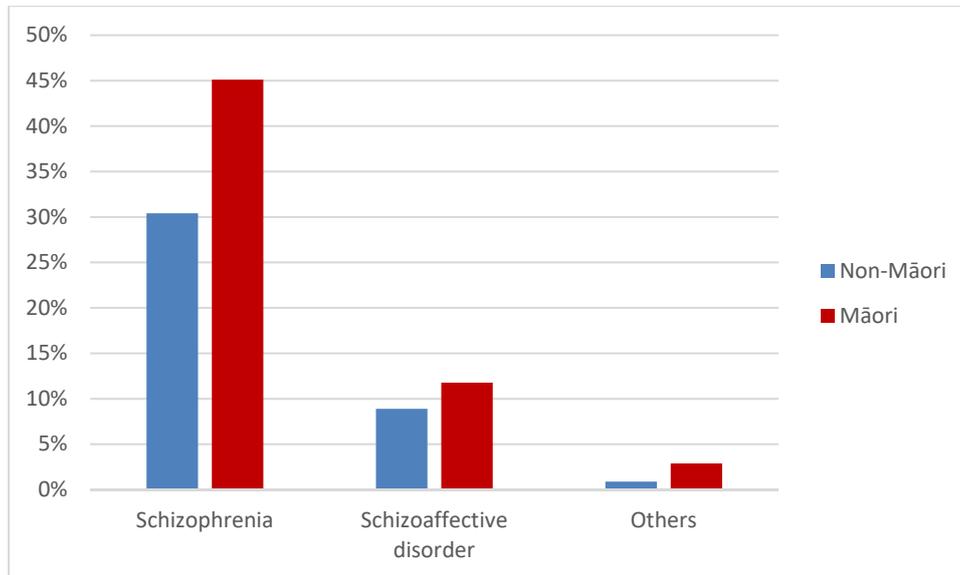


Figure 3. Histogram of diagnosis by ethnicity

5.1.3 *Mental Health Act*

At the time of discharge from their index admission, **47%** of patients were under the **Mental Health Act** (Compulsory Assessment and Treatment Act 1992) and **53%** were legally **‘informal’**. The ‘MHAs’ consisted of both inpatient and community treatment orders, which were not distinguished in the analyses.

Forty-six (**52.3%**) patients in the **under 25** years ($n = 88$) group (18–24 years) were under the MHA; 127 (**43.9%**) patients of the **25–49** years group ($n = 289$) and 39 (**52.7%**) patients of the **over 49** (50–75years) group ($n = 74$) were under the MHA. The difference between the groups was not significant.

Out of 290 **males**, 139 (**47.9%**) were under the **MHA** and 73 (**45.3%**) of 161 **females** were under the **MHA**. Overall, **47%** of **Māori** patients were under the MHA ($n = 269$).

As shown in Table 2, rate of compulsion did not vary significantly by age, gender, ethnicity or diagnostic subcategory.

Table 2. Patient demographics, diagnosis and compulsory treatment status

Characteristic	Rate of treatment compulsion	
	<i>n</i>	%
Age groups (<i>n</i>)		
18–24 years (88)	46	52
25–49 years (289)	127	44
50–75 years (74)	39	53
Gender (<i>n</i>)		
Male (290)	139	48
Female (161)	73	45
Ethnicity (<i>n</i>)		
Māori (269)	126	47
Non-Māori (182)	86	47
Diagnosis (<i>n</i>)		
Schizophrenia (341)	166	49
Schizoaffective disorder (93)	39	42
Others (17)	7	41

Note. Rates of compulsory treatment, including both inpatient and community treatment orders, did not vary according to the listed predictor variables, viz. age groups: $\chi^2 = 3.03$, $df = 2$, $p = 0.22$; male vs. female: $\chi^2 = 0.184$, $df = 1$, $p = 0.68$; Māori vs. non-Māori: $\chi^2 = 0.007$, $df = 1$, $p = 0.93$; schizophrenia vs. schizoaffective disorder: $\chi^2 = 1.08$, $df = 1$, $p = 0.29$.

5.1.4 Duration of index admission

The mean **LOS** for the whole sample was **26 days** ($SD = 32.0$). Of the 451 patients, **60.8%** ($n = 274$) spent between 1 and 21 days (**3 weeks or <**) in hospital and **39.2%** stayed **more than three weeks**. Most patients (37.5%) stayed between 8 and 21 days.

Table 3 presents the relationship between average LOS (in days) and patient demography and MHA.

Table 3. Mean length of stay in days and patient characteristics

	LOS in days (<i>SE</i> *)	CI*
Age group		
18–24 years	34 (3.9)	26.8–42.1
25–49 years	23 (1.8)	19.0–26.3
50–75 years	27 (3.2)	20.4–32.8
Gender		
Male	24 (1.9)	20.6–27.9
Female	28 (2.5)	23.0–33.0
Ethnicity		
Māori	26 (2.1)	21.9–30.2
Non-Māori	25 (2.03)	21.1–29.0
MHA		
Yes	36 (2.8)	30.5–41.7
No	16 (0.99)	14.3–18.2

Note. LOS = length of stay; *SE* = standard error; CI = 95% confidence intervals; MHA = Mental Health Act.

The younger age group (**18–24 years**) spent more days (**mean of 34 days**) in hospital than the other two age groups ($p = 0.0001$). Analyses by gender or ethnicity did not show any significant differences. For patients under the **MHA** it was **36 days** ($SD = 41.3$) compared with **16 days** ($SD = 15.3$) for the legally **informal**. That difference was statistically significant ($p = 0.0001$).

When duration of stay was divided into three weeks or more and less than three weeks for the purpose of analysis to address shorter or longer LOS, **50%** of the younger age group (**18–24 years**) stayed **more than three weeks** compared with **34.6%** of the **25–49 years** group and **44.6%** of the **over 49 years (50–75 years) group** (as shown in Table 4). The differences between the younger age group and 25–49 years group was statistically significant ($p = 0.01$).

Table 4. Duration of index admission in relation to patient characteristics

Variables	1–3 weeks	> 3 weeks
Age groups		
18–24 (<i>n</i> = 88)	44 (50.0%)	44 (50%)
25–49(<i>n</i> = 289)	189 (65.4%)	100 (34.6%)
50–75 (<i>n</i> = 74)	41 (55.4%)	33 (44.6%)
Ethnicity		
Māori	168 (62.5%)	101 (37.5%)
Non-Māori	105 (58%)	76 (42%)
Gender		
Male (<i>n</i> = 290)	184 (63.4%)	106 (36.6%)
Female (<i>n</i> = 161)	90 (55.9%)	71 (44.1%)
MHA		
Yes (<i>n</i> = 212)	90 (42.5%)	122 (57.5%)
No (<i>n</i> = 239)	184 (77.0%)	55 (23.0%)

Note. MHA = Mental Health Act.

As shown in Table 4, the differences between the two genders and between ethnicities were not statistically significant. **Patients of Māori ethnicity had shorter admission (3 weeks or less) than non-Māori** (see Table 4). In contrast, more patients (**57.5%**) under the MHA spent **more than three weeks** during index admission, compared with only **23.0%** of **informal** patients and the difference was significant ($p = 0.0001$).

5.1.5 Regression analysis for length of stay during index admission:

After adjusting for other variables (gender, ethnicity, MHA, CPZE, duration of previous admissions), **age had an effect on the duration of index admission** (see Table 5).

Table 5. Regression analysis results for length of stay adjusted for age, ethnicity, gender, Mental Health Act, chlorpromazine equivalents

Variables	Coefficient ^a (days)	CI	<i>p</i> value
25–49 years vs. 18–24 years	-10.9	-18.2 to -3.7	0.003
50–75 years vs. 18–24 years	-10.8	-20.4 to -1.2	0.03
Female vs. male	4.5	-1.43 to 10.4	0.13
Māori vs. non-Māori	-0.9	-6.6 to 4.9	0.77
MHA vs. informal	18.8	13.24 to 24.40	0.000

Note. CI = confidence interval; MHA = Mental Health Act. ^aCoefficient indicates estimated change in bed days for a change in category of the indicated predictor variable. For example, patients in 25–49 years age group spent 11 fewer days in hospital than those under 25 (18–24 years).

Patients in the age range of **25–49 years** and **50–75 years**, each spent around 11 days less in hospital than the younger age group (18–24 years). Although females spent around five days more than males, the difference was not statistically significant. There was no statistically significant difference between Māori and non-Māori patients. Those subject to **compulsion (MHA)** spent, on average, **19 days more ($p < 0.001$)** in hospital than voluntary patients. This effect was not modified by gender or ethnicity.

5.1.6 Antipsychotics prescribed on discharge

Complete medication lists were obtained for each patient from the discharge summaries. For the purpose of analysis, information was coded as primary antipsychotic medications, other prescribed psychotropic medications (mood stabilisers, antidepressants), sedative-hypnotics and anti-cholinergic medications.

Irrespective of route, 324 (**71.8%**) of the subjects were prescribed **SGAs**, 73 (**16.2%**) **FGAs** and 54 (**12%**) received **both**. More than three-quarters of the patients (**79%**) were prescribed **oral SGAs**, while only **5%** received **oral FGAs**. Table 6 shows the frequency of the discharge prescription of the different types of antipsychotics. The routes of administration are summarised in Table 6.

Table 6. Prescribing frequency of different antipsychotics at discharge

Oral APD	<i>n</i> (% of total of 451)
Olanzapine	138 (30.6%)
Risperidone	101 (22.4%)
Clozapine	90 (19.9%)
Other SGA ^a	32 (7.1%)
Quetiapine	28 (6.2%)
Haloperidol	20 (4.4%)
Other FGA (trifluoperazine)	9 (2.0%)
Long-acting injectables	
Risperidone consta	78 (17.3%)
Zuclopenthixol	35 (7.8%)
Flupenthixol	35 (7.8%)
Haloperidol	33 (7.3%)
Olanzapine	1 (0.2%)

Note. APD = antipsychotic drug; SGA = second-generation antipsychotic; FGA = first-generation antipsychotic. ^aOther SGAs = amisulpride, ziprasidone, aripiprazole.

Olanzapine (31%) was the most commonly prescribed oral SGA and haloperidol (4%) was the most commonly prescribed oral FGA. A higher percentage of **Māori than non-Māori (24% vs. 13%)** were prescribed clozapine ($p = 0.007$).

Table 7 summarises the frequency of different routes of APDs prescribed on discharge for this cohort. A quarter of the patients were prescribed LAI preparations of FGAs, while **17.5%** were given **SGA LAIs**. Of the 193 patients on LAIs as monotherapy or as polypharmacy (in combination with an oral APDs), 59% were on FGAs. Only one patient among 451 was on olanzapine LAI (olanzapine LAI was not funded by Pharmac New Zealand at that time). Apart from risperidone LAI, no other SGA LAIs were available in NZ during that time period. The prescribed FGLAIs were mainly haloperidol, zuclopenthixol and flupenthixol. Only 11 patients were prescribed other types of FGAs. These LAIs were prescribed either as monotherapy or in conjunction with oral antipsychotics.

Table 7. Prescribed frequencies of different routes of antipsychotics

Routes of APD	<i>n</i> (% = 451)
Oral (monotherapy)	230 (51.0%)
LAI (monotherapy)	69 (15.3%)
Oral + LAI	124 (27.5%)
Oral + Oral	28 (6.2%)

Note. APD = antipsychotic drug; LAI = long-acting injectable.

5.1.7 Antipsychotics and other variables

1) Demography

1.1) Routes (Oral, LAI, combination of APDs)

Age groups:

- a) The 18–24 years group ($n = 88$): 51 (**58.0%**) patients were on **oral antipsychotic** as a monotherapy; 10 (**11.4%**) had only **LAI**s; 24 (**27.3%**) had a combination of **oral and LAI**s; three (**3.4%**) had **two oral** APDs.
- b) The 25–49 years group ($n = 289$): 144 (**49.8%**) patients were on a single **oral APD**; 48 (**16.6%**) had **LAI**s; 78 (**27.0%**) had a combination of **oral and LAI**s; 19 (**6.6%**) had **two oral** APDs.
- c) The 50–75 years group ($n = 74$): 35 (**47.3%**) were on a **single oral** agent; 11 (**14.9%**) had **LAI**s; 22 (**29.7%**) had a combination of **oral and LAI**s, six (**8.1%**) had **two oral** APDs.

None of the differences between age groups were statistically significant.

Gender:

- a) Of 290 males, 146 (**50.3%**) had **oral APD** as monotherapy; 44 (**15.2%**) had a single **LAI**; 83 (**28.6%**) were on a combination of **oral and LAI** and 17 (**5.9%**) had **two oral APDs**.
- b) Of 161 females, 84 (**52.1%**) had a single **oral APD**; 25 (**15.5%**) had **LAIs**; 41 (**25.5%**) had a combination of **oral and LAIs**; 11(**6.8%**) had **two oral APDs**.

None of the differences between genders were statistically significant.

Ethnicity:

LAIs were prescribed more to Māori patients, either as monotherapy or in combination with oral antipsychotics, but the differences did not reach statistical significance (see Table 8).

Table 8. Ethnicity and routes of antipsychotics prescribed

Ethnicity	Oral	LAI	Oral + LAI	Two oral APDs	Total
Māori	132 (49.1%)	45(16.7%)	77(28.6%)	15 (5.6%)	269 (100%)
Non-Māori	97 (53.6%)	24 (13.3%)	47 (26.0%)	13 (7.2%)	181(100%)

Note. LAI = long-acting injectable; APD = antipsychotic drug.

1.2) Types: First- and second-generation antipsychotics

Age groups:

- a) The 18–24years group: **SGAs** were prescribed to 75 (**85.2%**) of patients ($n = 88$). Only five (**5.7%**) of them were on **FGAs**.
- b) The 25–49 years group: 200 (**69.2%**) patients ($n = 289$) were prescribed **SGAs**; 53 (**18.3%**) had **FGAs**. The differences between the 18–24 years group and the 25–49 years group in prescriptions of SGAs ($p = 0.002$) and FGAs ($p = 0.003$) were statistically significant. **The younger group was prescribed more SGAs than the 25–49 years age group.**

- c) The 50–75 years group: Forty-nine patients (**66.2%**) in the over 50 group ($n = 74$) had **SGAs** and 15 (**20.3%**) had **FGAs**. The differences between patients aged 18–24 and those aged over 49 in prescription of **SGAs** ($p = 0.005$) and **FGAs** ($p = 0.007$) were statistically significant.

Gender:

Among the 290 males, 208 (71.7%) had **SGAs** and 46 (15.9%) had **FGAs**. Out of 161 females, 116 (72.0%) had **SGAs** and 27 (16.8%) had **FGAs**. The differences between the genders were not significant.

Ethnicity:

Of the **Māori** patients, 192 (**71%**) were prescribed **SGAs** and 42 (**15.6%**) received **FGAs**; 132 (**72.9%**) **non-Māori** patients had **SGAs** and 30 (**16.6%**) had **FGAs**. There were no statistically significant differences in prescribing of **SGAs** and **FGAs** by ethnicity.

1.3) Types and routes

Tables 9 and 10 summarise the prescribing pattern of oral and LAIs (**FGAs** and **SGAs**) according to patient demography.

Table 9. Prescribing pattern of oral second-generation and first-generation antipsychotics

Characteristics	Oral SGAs (n, %)	Oral FGAs (n, %)
Age groups		
18–24 years (n = 88)	78 (88.6%)	0
25–49 years (n = 289)	222 (76.8%)	17 (5.9%)
50–75 years (n = 74)	57 (77.0%)	6 (8.1%)
Gender		
Male (n = 290)	229 (79.0%)	15 (5.2%)
Female (n = 161)	128 (79.5%)	8 (5.0%)
Ethnicity		
Māori (n = 269)	212 (78.8%)	11 (4.1%)
Non-Māori (n = 181)	145 (80.1%)	11 (6.1%)

Note. SGA = second-generation antipsychotic; FGA = first-generation antipsychotic. $p = 0.02$ (oral SGAs: 18–24 vs. 25–49 years); $p = 0.02$ (oral FGAs: 18–24 vs. 25–49 years); $p = 0.06$ (oral SGAs: 18–24 years vs. 50–75 years) $p = 0.008$ (oral FGAs 18–24 vs. 50–75 years)

The differences by gender and ethnicities in prescribing of oral SGAs and FGAs were not statistically significant.

Table 10. Prescribing pattern of Long-acting injectables (FGAs vs. SGAs)

Characteristics	FGLAI (n, %)	SGLAI (n, %)
Age groups		
18–24 (n = 88)	12 (13.6%)	22 (25%)
25–49 (n = 289)	81 (28.0%)	45 (15.6%)
50–75 (n = 74)	21 (28.4%)	12 (16.2%)
Gender		
Male (n = 290)	74 (25.5%)	53 (18.3%)
Female (n = 161)	40 (24.8%)	26 (16.1%)
Ethnicity		
Māori (n = 269)	69 (25.7%)	53 (19.7%)
Non-Māori (n = 181)	45 (24.9%)	26 (14.4%)

Note. FGLAI = first-generation long-acting injectable; SGLAI = second-generation long-acting injectable. $p = 0.007$ (FGLAIs 18–24 vs. 25–49 years); $p = 0.06$ (SGLAIs 18–24 vs. 25–49 years); $p = 0.03$ (FGLAIs 18–24 vs. 50–75 years); $p = 0.18$ (SGLAIs 18–24 vs. 50–75 years)

The differences between genders and ethnicities were not statistically significant and FGLAIs were prescribed more to patients over the age of 24.

2) Mental Health Act

2.1) Routes of antipsychotic drugs

Of 212 involuntary patients, **19.8%** were prescribed **LAIs** as monotherapy and **40.1%** had only **oral antipsychotics**; **34.4%** received **combinations** of oral and LAIs, and **5.7%** had a **combination** of two oral antipsychotics. The rates were **11.3%** ($p = 0.01$), **60.7%** ($p = 0.0001$), **21.3%** ($p = 0.002$) and **6.7%** ($p = 0.69$) respectively for voluntary patients. In summary, patients under compulsion were more likely to be prescribed LAIs alone or in combination with orals.

2.2) Types of APD

Of the 212 patients **under the MHA**, **18.9%** were prescribed **FGAs** and **67.5%** were prescribed **SGAs**. Compared with this, **13.8%** of the voluntary patients were prescribed **FGAs** and **75.7%** were prescribed **SGAs**. The differences were not statistically significant.

2.3) Types and routes

Table 11 summarises the antipsychotic prescribing pattern, routes and types.

Table 11. Association between compulsory treatment and antipsychotic treatment at discharge

Antipsychotic (<i>n</i> , %)	Compulsory (%)	Voluntary (%)
Oral (230, 51%)	85 (37%)	145 (63%)
LAI (69, 15%)	42 (61%)	27 (39%)
Oral + LAI (124, 27.5%)	73 (59%)	51 (41%)
Oral + oral (28, 6.2%)	12 (43%)	16 (57%)
Oral FGA (23, 5%)	12 (52%)	11 (48%)
Oral SGA (357, 79%)	157 (44%)	200 (56%)
LAI: FGA (114, 25%)	63 (55%)	51 (45%)
LAI: SGA (79, 18%)	52 (66%)	27 (34%)

Note. Statistical comparison of compulsory vs. voluntary frequencies, all $df = 1$: oral vs. LAI monotherapy: $\chi^2 = 11.5, p = 0.0007$; oral vs. LAI + oral: $\chi^2 = 14.8, p = 0.0001$; LAI vs. LAI + oral: $\chi^2 = 0.014, p = 0.91$; oral: FGA vs. SGA: $\chi^2 = 0.303, p = 0.58$; LAI: FGA vs. SGA: $\chi^2 = 1.74, p = 0.19$. LAI = long-acting injectable; FGA = first-generation antipsychotic; SGA: second-generation antipsychotic.

Of the 212 patients, oral SGAs were prescribed to 74.1% of the involuntary and 83.7% of the voluntary patients ($p = 0.01$). Oral FGAs were prescribed to 5.7% involuntary and 4.6% voluntary patients ($p = 0.67$). The prescription rate for FGLAIs was 29.7% for involuntary patients and 21.3% for voluntary patients. The p value was not statistically significant. The prescription rate for SGLAIs was 24.5% for involuntary patients and 11.3% for voluntary patients. The p value was very significant (0.0003).

3) Average length of stay in days

3.1) Individual antipsychotics

Oral antipsychotics: Table 12 summarises the LOS in relation to individual oral APDs.

Table 12. Length and individual oral antipsychotics

APD	LOS (in days)	95% CI*
Risperidone	19	15.9–22.8
Olanzapine	22	18.5–25.7
Quetiapine	22	13.7–30.3
Clozapine	33	25.1–40.9
Haloperidol	27	14–41

Note. APD = antipsychotic drug; LOS = length of stay; CI = confidence interval.

LAI: Table 13 summarises the average LOS in relation to individual LAIs.

Table 13. Length of stay and individual long-acting injectables

LAI	LOS	95% CI*
Risperidone	27	21.4–32.1
Haloperidol	37	14.8–59.4
Zuclopenthixol	30	16–44.1
Flupenthixol	25	14.4–34.8

Note. LAI = long-acting injectable; LOS = length of stay; CI: confidence interval.

3.2) Routes and types

Patients on LAIs as a monotherapy and patients on FGAs irrespective of routes stayed longer compared with those on other types and routes of APDs (see Table 14).

Table 14. Average length of stay and antipsychotic drugs (types and routes)

APD	LOS in days	95% CI ^a
Oral	23	19.7–26.8
LAI	35	22.4–48.5
Oral + LAIs	24	20.3–27.8
Two orals	27	16.8–38.2
Oral SGAs	24	21.2–26.6
Oral FGAs	17	9.7–24.1
LAI: SGAs	26	21.2–31.8
LAI: FGAs	29	21.1–37.4
FGAs*	33	20.0–45.7
SGAs*	24	21.3–26.8
FGA + SGA*	25	18.4–32.0

Note. APD = antipsychotic drug; LOS = length of stay; CI = confidence interval; LAI = long-acting injectable; SGA = second-generation antipsychotic FGA = first-generation antipsychotic. ^aIrrespective of routes.

The duration of stay was subsequently divided into three weeks or less and more than three weeks for the purpose of analysis.

4) Duration of Index Admission (3 weeks or < vs. > 3 weeks)

4.1) Types and routes of antipsychotics

Table 15 summarises the duration of index admission in relation to different types and routes of chosen antipsychotics.

Table 15. Duration of index admission in relation to prescribed antipsychotics

Antipsychotics	DOIA	
1) Routes (n)	3 weeks or <	> 3 weeks
Oral (n = 230)	148 (64.3%)	82 (35.7%)
LAI (n = 69)	39 (56.5%)	30 (43.5%)
Oral + LAI (n = 124)	70 (56.5%)	54 (43.5%)
Two oral (n = 28)	17 (60.7%)	11 (39.3%)
2) Types		
Oral FGA (n = 23)	15 (65.2%)	8 (34.8%)
Oral SGA (n = 357)	218 (61.0%)	139 (39.0%)
FGLAI (n = 114)	65 (57.0%)	49 (43.0%)
SGLAI (n = 79)	44 (56.0%)	35 (44.0%)

Note. DOIA = duration of index admission; LAI = long-acting injectable; FGA = first-generation antipsychotic; SGA = second-generation antipsychotic; FGLAI = first-generation long-acting injectable; SGLAI = second-generation long-acting injectable.

Irrespective of routes, **42.5%** of patients discharged on **FGAs** stayed in hospital **more than three weeks**. Among those on **SGAs**, **38%** stayed **longer than three weeks**. There were no statistically significant differences observed for the duration of index admission by different types and routes of antipsychotics.

4.2) Individual antipsychotics

Among the **oral risperidone** group, **29%** of patients spent **more than three weeks** in hospital. In the **oral olanzapine** group, **40%** of patients spent **more than three weeks** in hospital. Ninety patients (20%) were prescribed **clozapine** (alone or in combination) and of these **47%** spent **more than three weeks** in hospital (see Table 16).

Table 16. Duration of index admission and selected oral second-generation antipsychotics (n = number of patients)

DOIA (days)	Risperidone (n = 101)	Olanzapine (n = 138)	Quetiapine (n = 28)	Clozapine (n = 90)	Others ^a (n = 32)
1–3 weeks	72 (71.3%)	83 (60.1%)	18 (64.3%)	48 (53.3%)	18 (56.3%)
> 3 weeks	29 (28.7%)	55 (39.9%)	10 (35.7%)	42 (46.7%)	14 (43.8%)

Note. DOIA = duration of index admission; ^aOthers: amisulpride, ziprasidone, aripiprazole.

The difference in the duration of index admissions between risperidone and clozapine was significant ($p = 0.01$). Half of the patients on haloperidol spent three weeks or less in hospital with no significant differences when compared with SGAs.

Among patients on **risperidone** ($n = 78$) LAIs, **55.1%** ($n = 43$) spent **three weeks or less** and **44.9%** ($n = 35$) spent **more than three weeks** during their index admission.

Among the patients on FGLAIs, **48.1%** ($n = 16$) on **haloperidol** ($n = 33$), **57.1%** ($n = 20$) on **zuclopenthixol** ($n = 35$) and **62.9%** ($n = 22$) on **flupenthixol** ($n = 35$) spent **three weeks or less** in hospital. Fifty-two per cent (**51.5%**) on **haloperidol** ($n = 17$), **42.9%** ($n = 15$) on **zuclopenthixol** and **37.1%** ($n = 13$) on **flupenthixol** spent more than three weeks in hospital. The differences were not significant statistically.

Table 17 displays the regression analysis examining the association between duration of index admission and types and routes of prescribed antipsychotics after adjusting for patient demography, compulsory status, dosage of antipsychotics after converting to CPZE and duration of previous admissions two years prior to index admissions.

Table 17. Regression analysis results for the duration of index admission and types and routes of antipsychotics

Antipsychotics	Coefficient ^a (days)	<i>p</i> value	95% CI
FGA vs. SGA	7.8 days	0.06	-0.5–16.3
LAIIs (Mono therapy or combination) vs. no LAIs	0.4 days	0.88	-5.4–6.3
FGLAIIs vs. SGLAIIs	3.6 days	0.51	-7.5–14.8
LAIIs vs. Oral monotherapy	8.2	0.12	-2.0–18.4
^a Polypharmacy (2 or more) vs. monotherapy	-3.8	0.23	-10.0–2.4
Oral SGAs vs. FGAs	4.9	0.36	-5.7–15.5
Clozapine vs. no clozapine	8.8	0.03	0.7–17.0

Note. FGA = first-generation antipsychotic; SGA= second-generation antipsychotic; LAI = long-acting injectables; FGLAI = first-generation long-acting injectable; SGLAI = second-generation long-acting injectable. ^aCoefficient indicates the estimated change in bed days for a change in category of the indicated predictor variable. For example, patients prescribed FGAs spent 8 days more in hospital compared with those prescribed SGAs. ^bPolypharmacy (combination of antipsychotics: oral and LAIs or two oral APDs), compared with monotherapy.

Chlorpromazine equivalent dosage

1.1) Mean dosage

The CPZE for the prescribed antipsychotic was within the range of **300–600 mg** for **42%** of the patients. According to existing guidelines for schizophrenia, the recommended dose range is 300–1,000 mg, and the dosage for maintenance is mentioned as between 300 and 600 mg. The **mean CPZE** for the total sample was **489.7 mg** ($SD = 314.4$).

There were no significant differences in mean dosages between age groups. The mean dosage was **474.6 mg** ($SD = 280.8$) for the younger age group (**18–24**), **498.6 mg** ($SD = 302.6$) for the **25–49** years group and **472.6 mg** ($SD = 391.1$) for the **over 50** group (50–75 years). There were no statistically significant differences between age groups. Females received lower dosages than males (**female vs. male = 457.90 mg vs. 507.34 mg**). The *t* test, *p* value was **0.11**. The mean dosage prescribed for **Māori** was higher at **506.61 mg** ($SD = 329.9$), compared with **465.4 mg** ($SD = 289.5$) for **non-Māori** but the difference was not statistically significant ($t = 1.36$, $df = 449$, $p = 0.17$).

1.2) Chlorpromazine equivalents dosage and length of stay

The patients on **600 mg or more** CPZE spent **34 days** ($SD = 35.0$) in hospital compared with only **21 days** ($SD = 21.3$) for those on the smaller dose of **300–600 mg** daily.

Of those ($n = 157$) who had **less than 300mg** CPZE, **35%** spent **more than three weeks** in hospital during index admission; on **300–600 mg** CPZE **34%** spent **more than three weeks**; and on **more than 600 mg**, **55%** spent **more than three weeks**. Regression analysis does not suggest any statistically significant association between the dosage and LOS during index admission (see Table 18).

Table 18. Regression analysis for chlorpromazine equivalent dosage and relationship with duration of index admission (adjusted for age, gender, ethnicity, MHA and previous admission duration)

CPZE ^a	Coefficient ^b (days)	95% CI	<i>p</i> value
300–600 mg	-6.2	-12.6–0.3	0.06
> 600 mg	5.3	-2.2–12.9	0.16

Note. CPZE = chlorpromazine equivalents; CI = confidence interval. ^aCPZE: compared with patients on less than 300 mg. ^bCoefficient indicates the estimated change in bed days for a change in category of the indicated predictor variable.

Patients on 300–600 mg CPZE spent six days less, and patients on more than 600 mg CPZE (600–1,000 mg) spent five days more in hospital than those who had received less than 300 mg CPZE during discharge.

1.3) Chlorpromazine equivalents and other clinical variables

Significant variations were noticeable for CPZE of different types and routes of APDs but patient characteristics were not associated with significant differences in dosages. Tables 19 and 20 summarise the findings for patient characteristics and antipsychotics.

Table 19. Regression for chlorpromazine equivalent dosage by patient demography (adjusted for age, gender, ethnicity, Mental Health Act, duration of index admission, previous admission duration)

CPZE	Coefficient ^a (mg/day)	<i>p</i> value	95% CI
Age group (years)			
25–49 vs. 18–24	57.0	0.14	-18.7–132.8
50–75 vs. 18–24	29.5	0.56	-70.5–129.6
Gender			
Male vs. female	59.7	0.06	-1.6–121.1
Ethnicity			
Māori vs. non-Māori	51.9	0.09	-7.7–111.6

Note. CPZE = chlorpromazine equivalents; CI = confidence interval. ^aCoefficient indicates average change in CPZE for indicated comparison of predictor variables. For example, males received an average of 59.7 mg/day more than females. Each of the variables is adjusted for all other variables.

Table 20. Regression of chlorpromazine equivalent dosage by type and route of antipsychotic treatment

Treatment	^b Coefficient (mg/day)	<i>p</i> value	95% CI
SGA ^a vs. FGA	219	< 0.001	142–297
Oral SGA vs. FGA	144	0.04	8.9–280
Oral monotherapy vs. LAI monotherapy	133	< 0.001	74.9–192
Polypharmacy vs. monotherapy	177	< 0.001	118–236
Clozapine vs. no clozapine	409	< 0.001	347–471

Note. CI = confidence interval; SGA = second-generation antipsychotic; FGA = first-generation antipsychotic; LAI = long-acting injectables. ^aIrrespective of routes. ^bCoefficient indicates average change in CPZE for indicated comparison of predictor variable. For example, patients on SGA received an average of 219mg/day more than those on FGA; similarly, patients on only oral antipsychotic, on more than one antipsychotic, and on clozapine, on average received higher dosage than those on LAI, monotherapy or not on clozapine respectively. These differences also are statistically significant.

Those under the MHA received 8 mg more than the legally informal ($p = 0.79$). Patients who spent **more than three weeks** in hospital during their **previous admissions** (within two years prior to index admission) received **101 mg more CPZE** ($p = 0.007$). Patients who spent less than three weeks received 19 mg more but this was not significant ($p = 0.65$). Both of these were compared with those who had no previous admissions. During **index admission**, patients who had **prolonged admissions (> 3 weeks)** also received

higher dosages, **92 mg more** ($p = 0.004$) than those who had a shorter admission (< 3 weeks). In summary, patients who had prolonged admission required higher dosages than those who stayed for three weeks or less.

Previous admissions (within two years prior to index admission)

This paragraph sets out to provide details on the amount of time spent hospitalised in the two years prior to the index admission and its relationship to prescribed antipsychotics on discharge during index admission. For the 230 patients on **oral antipsychotics** during the index admission, mean **LOS** during previous admissions was **14 days** ($SD = 2.5$, 95% CI = 9.5–19.3); for 69 patients only on **LAIs**, mean **LOS** was **35 days** ($SD = 11.8$, 95% CI = 11.8–58.3). The mean **LOS** was **15 days** ($SD = 2.9$, 95% CI = 9.1–20.4) for the 124 patients on a **combination of oral and LAIs** and **17 days** ($SD = 6.3$, CI = 4.9–29.6) for 28 patients who were on **two oral APDs** during index discharge. Ninety patients who were on **clozapine** during index discharge spent on average **21 days** in hospital during their previous admissions ($SD = 5.2$, CI = 10.4–30.8).

Table 21 summarises the associations between duration of index admissions and duration of previous admissions after adjusting for other variables.

Table 21. Regression analysis results for duration of index admission in relation to duration of previous admissions (adjusted for age, gender, ethnicity, MHA, CPZE)

PAD	Coefficient (days)	95% CI	<i>p</i> value
< 3weeks	-3.1	-11.1–4.8	0.43
> 3weeks	7.3	0.1–14.5	0.04

Note. PAD = previous admission duration; CI = confidence interval.

Patients who spent **more than three weeks** in hospital during their **previous admissions** also **spent seven days more** in hospital during the **index admission**, compared with patients who had not had any previous admissions.

H) Other psychotropic medications

With regard to other prescribed psychotropic medications, **20.6%** of patients were on **antidepressants** ($n = 93$), **21.5%** ($n = 97$) on **mood stabilisers**, **27%** ($n = 124$) were prescribed **sedatives and hypnotics** and **13%** ($n = 61$) were on **anticholinergic** medications. The subsequent analysis was on antidepressants, mood stabilisers and sedative-hypnotics.

1.1) Age groups

Of the age group 18–24 years, only 12 (13.6%) had antidepressants, 11 (12.5%) had mood stabilisers and 20 (22.7%) had sedative-hypnotics.

Of the age group **25–49** years, 56 (**19.4%**) had **antidepressants**, 60 (**20.8%**) had **mood stabilisers**, 86 (**29.8%**) had **sedative-hypnotics**.

Of the age group **50–75** years, 25 (**33.8%**) had **antidepressants**, 26 (**35.1%**) had **mood stabilisers**, 18 (**24.3%**) had **sedative-hypnotics**.

There were no statistically significant differences in the prescribing pattern of antidepressants, mood stabilisers and sedative-hypnotics between the younger age group and the 25–49 years group. Anticholinergic prescribing also was not influenced by patient age groups.

When antidepressants and mood stabilisers were considered, the differences with the over 50 group were significant for both the younger age groups. No statistically significant differences were observed for sedative-hypnotics prescribing patterns between groups.

For **antidepressants**, the p value was **0.01** for the **25–49** years and **over 49** groups; similarly, the difference was significant ($p = \mathbf{0.002}$) between the **younger group (18–24)** and the **over 49** group.

For **mood stabilisers**, the p value was **0.01** (25–49 vs. 50–75 years group) and **0.007** (18–24 years vs. 50–75 years group). There were no differences between the age groups when sedative-hypnotics were considered.

1.2) Gender

Of the **males**, 46 (**15.9%**) had **antidepressants**, 50 (**17.2%**) had **mood stabilisers** and 81 (27.9%) had **sedative-hypnotics**.

Of the **females**, 47(**29.2%**) had **antidepressants**, 47 (**29.2%**) had **mood stabilisers** and 43 had **sedative-hypnotics** (28.3%).

The difference between the two genders was significant for both antidepressants and mood stabilisers. **Females** were prescribed more **antidepressants** ($p = 0.001$) and **mood stabilisers** ($p = 0.004$). Anticholinergic prescribing patterns did not show any difference.

1.3) Ethnicity

Of Māori, 47 (17.5%) had antidepressants, 51 (19.0%) had mood stabilisers and 68 (25.3%) had sedative-hypnotics.

Of non-Māori, 46(25.4%) had antidepressants, 46 (25.4%) had mood stabilisers and 55 (30.4%) had sedative-hypnotics.

Māori were prescribed **fewer antidepressants** ($p = 0.04$); there were no differences in the prescribing rate for mood stabilisers, sedative-hypnotics or anticholinergics between ethnicities.

Mean length of stay

Table 22 presents the findings for LOS in relation to other psychotropic medications.

Table 22. Mean length of stay in relation to other psychotropic medications

Sedatives	LOS in days (CI)
Yes	20 (12.30–28.17)
No	24 (21.34–27.22)
Antidepressants	
Yes	37 (26.83–47.49)
No	23 (20.05–25.13)
Mood stabilisers	
Yes	38 (27.90–48.97)
No	22 (19.73–24.42)
Anticholinergics	
Yes	38 (24.37–52.64)
No	24 (20.97–26.18)

Note. LOS = length of stay; CI = confidence interval.

The patients on antidepressants, mood stabilisers and anticholinergic medications spent more days in hospital than those who did not receive the other psychotropic medications. The patients who received sedatives and hypnotics spent less time in hospital during their index admission than patients on other forms of psychotropic medications in addition to antipsychotic medications. The *p* value was **0.001** for those who had **antidepressants** and **mood stabilisers** compared with those without the psychotropic medications.

Clinician characteristics

The patients in this cohort were treated by 18 different clinicians. Among the 451 patients, clinicians with **11–20 years’** experience treated the most ($n = 268$, **59%**), followed by those who had **more than 21 years’** experience ($n = 93$, **21%**). Clinicians with **1–10 years’** experience treated 75 patients (**17%**). There was no information available on two clinicians because they were no longer working in NZ at the time of the data collection. One clinician declined to provide information. These three clinicians treated 15 patients (3%).

NZ- and Australian-trained clinicians treated the most patients ($n = 148$, **33%**), followed by **UK-trained** clinicians ($n = 117$, **26%**). Clinicians whose postgraduate training was from **India** treated **19%** of patients ($n = 86$). **Twenty-two** per cent ($n = 97$) were treated by clinicians trained elsewhere.

Clinician characteristics and other clinical variables

1.1) Patient demography

Clinicians with **less than 11 years'** experience treated fewer patients from the younger age group (18–24 years) and more (**75%**) from the **25–49 years** group. **Sixteen per cent** of patients under their care were from the over 50 group (**50–75 years**). This is in comparison with clinicians with 11–20 years' experience, and those with more than 20 years' experience (see Table 23).

Table 23. Patient characteristics by length of clinicians' experience

Patient demography	1–10 years ($n = 75$)	11–20 years ($n = 268$)	21+ years ($n = 93$)
Age group	<i>n</i> (%)	<i>n</i> (%)	<i>n</i> (%)
18–24	7 (9.3%)	61 (22.8%)	19 (20.4%)
25–49	56 (74.7%)	162 (60.5%)	59 (63.4%)
50–75	12 (16.0%)	45 (16.8%)	15 (16.1%)
Gender			
Male	47 (62.7%)	170(63.4%)	63 (67.7%)
Female	28 (37.3%)	98 (36.6%)	30 (32.3%)
Ethnicity			
Māori	42 (56%)	167 (62.3%)	54 (58.1%)
Non-Māori	33 (44%)	101 (37.7%)	38 (40.9%)

No significant differences were observed between clinicians whose training was in different countries when age group and gender were considered. The NZ- and Australian-trained doctors treated almost equal numbers (52.0%) of Māori and non-Māori; **UK-trained** doctors treated more **Māori (65.8%)** patients than **non-Māori (34.2%)**. The difference between these two groups was significant ($p = 0.02$). Indian-trained doctors

treated 55.8% Māori and 44.2% non-Māori. The **doctors from elsewhere** treated **67.7% Māori** and **32.3% non-Māori** ($p = 0.02$ for NZ- or Australian-trained doctors and doctors from elsewhere). Therefore, more Māori patients were treated by clinicians trained in the UK and elsewhere (USA, Europe, South Africa) than non-Māori patients.

1.2) Diagnosis

Thirteen per cent (**12.9%**) of patients with a diagnosis of **schizoaffective disorder** were treated by clinicians with **more than 21 years'** experience. The clinicians with **less than 11 years'** experience treated **27%** of patients with a discharge diagnosis of schizoaffective disorder and clinicians with **11–20 years** of experience treated **22%** of patients with schizoaffective disorder. Most patients treated by clinicians had a diagnosis of schizophrenia with no significant differences between clinicians with variable experience.

UK-trained clinicians treated the maximum number of patients with **schizophrenia** (109 of 117, **93%**) in contrast to those who were trained in **NZ or Australia (66%)** and **India (56%)**.

1.3) Duration of index admission

Forty-four per cent (**44%**) of patients treated by clinicians with **1–10 years'** experience spent **more than three weeks** during index admission; the case was the same for **35%** of patients treated by **clinicians with 11–20 years'** experience and **43%** of patients for clinicians with **more than 20 years'** experience.

Country of training did not influence duration of index admission: **42%** of patients treated by clinicians trained in **NZ and Australia** spent **more than three weeks** during index admission, as did **33%** of patients treated by clinicians trained in the **UK**; **49%** of

patients treated by clinicians trained in **India** and **34%** of patients treated by **clinicians trained elsewhere** similarly spent more than three weeks during index admission.

1.4) Mental Health Act

There were 212 patients treated under the MHA. Clinicians with **1–10 years'** experiences and **more than 21 years'** experience treated **56%** of the patients under the MHA, as compared with clinicians with **11–20 years'** experience who treated **41% of patients under the MHA.**

Clinicians whose postgraduate training was in **NZ/Australia** treated **48%** of the patients under the **MHA**, clinicians trained in the **UK** treated **43%**, clinicians with postgraduate qualification from **India** treated **55%** and clinicians **trained elsewhere** (USA, South Africa, Europe) treated **44%**. The differences did not reach statistical significance.

1.5) Previous admissions

Clinicians with **more than 21 years'** experience treated more patients (**73%**) who **did not have any** previous admissions, compared with **65%** of patients treated by clinicians with **less than 11 years'** and **62%** treated by clinicians with **11–20 years'** experience.

1.6) Antipsychotic prescribing pattern

Tables 24 and 25 summarise the prescribing pattern of antipsychotics in relation to clinician characteristics.

Table 24. Prescribed antipsychotics (types and routes) and clinicians' characteristics

Antipsychotics	1–10 years (<i>n</i> = 75)	11–20 years (<i>n</i> = 268)	21+ years (<i>n</i> = 93)
	Oral FGA	3 (4.0%)	12 (4.5%)
Oral SGA	62 (82.7%)	205 (76.5%)	72 (77.4%)
FGLAI	17 (22.7%)	68 (25.4%)	28 (30.1%)
SGLAI	14 (18.7%)	49 (18.3%)	14 (15.1%)
FGA	9 (12.0%)	48 (17.9%)	15 (16.1%)
SGA	55 (73.3%)	194 (72.4%)	61 (65.6%)
	NZ/AUS (<i>n</i> = 148)	UK (<i>n</i> = 117)	India (<i>n</i> = 86)
Oral FGA	6 (4.1%)	3 (2.6%)	4 (4.7%)
Oral SGA	119 (80.4%)	96 (82.1%)	63 (73.3%)
FGLAI	37 (25%)	28 (23.9%)	23 (26.7%)
SGLAI	21 (14.2%)	21 (17.9%)	22 (25.6%)
FGA	21 (14.2%)	16 (13.7%)	17 (19.8%)
SGA	107 (72.3%)	8673.5%	61 (70.9%)

Note. FGA = first-generation antipsychotic; SGA= second-generation antipsychotic; FGLAI = first-generation long-acting injectable; SGLAI = second-generation long-acting injectable.

Oral FGAs were more often prescribed by clinicians with more than 20 years' experience. They also prescribed more FGLAIs. Clinicians having been trained elsewhere did not influence the prescribing pattern compared with clinicians trained in NZ, Australia, the UK or India.

Table 25. Routes of antipsychotics and clinicians' postgraduate experience

Antipsychotic	1–10 yrs	11–20 yrs	21+ yrs
Oral	38 (50.7%)	138 (51.5%)	43 (46.2%)
LAIs	8 (10.7%)	49 (18.3%)	11 (11.8%)
Oral + LAI	23 (30.7%)	68 (25.4%)	31 (33.3%)
Oral + Oral	6 (8.0%)	13 (4.9%)	8 (8.6%)

Note. LAI = long-acting injectable.

With regard to country of training, clinicians trained in **India** treated **41.9%** of patients on oral antipsychotics (as monotherapy). Those trained in **NZ or Australia** treated **53.4%** and clinicians trained in the **UK** treated **52.1%** of patients on oral monotherapy.

Among patients on LAIs, **20.9%** of patients under doctors trained in **India** had LAIs; similarly, **12.8%** of patients of **NZ- or Australian-**trained doctors, **14.5%** of patients of **UK-**trained doctors and **15.5%** of patients of **doctors trained elsewhere** had LAIs. There were no significant differences observed between doctors trained in different countries when polypharmacy was considered.

Clinicians with **1–10 years'** experience and **more than 21 years'** experience prescribed more clozapine (**23%**) compared with clinicians with **11–20 years'** experience (**18%**). Clinicians trained in the **UK** prescribed more clozapine (**30%**) than those who were trained in **Australia or NZ (15%), India (11%)** and **other countries (24%)**.

1.7) Chlorpromazine equivalent dosages of antipsychotics

Tables 26 and 27 summarise the association of CPZE and clinicians' experience.

Table 26. Chlorpromazine equivalents and clinicians' experience

CPZE	1–10yrs (<i>n</i> = 75)	11–20 (<i>n</i> = 268)	21+ (<i>n</i> = 93)
< 300 mg	24 (32.0%)	100 (37.3%)	29 (31.2%)
300–600 mg	33 (44.0%)	106 (39.6%)	45 (48.3%)
> 600 mg	18 (24.0%)	62 (23.1%)	19 (20.4%)

Note. CPZE = chlorpromazine equivalents.

There were no significant associations observed between clinicians' experiences and the prescribed CPZE.

Table 27. Chlorpromazine equivalents and clinicians' country of training

CPZE	NZ/AUS (<i>n</i> = 148)	UK (<i>n</i> = 117)	India (<i>n</i> = 86)	Others (<i>n</i> = 97)
< 300 mg	52 (35.1%)	32 (27.4%)	37 (43.0%)	34 (35.1%)
300–600 mg	65 (43.9%)	49 (41.9%)	32 (37.2%)	44 (45.4%)
> 600 mg	31 (20.9%)	36 (30.8%)	17 (19.8%)	19 (19.6%)

Note. CPZE = chlorpromazine equivalents.

Again, no statistically significant associations were observed between clinicians' characteristics and CPZE dosage.

1.7) Prescribing pattern of other psychotropic medications

Forty-four per cent of patients (33 out of 75) under the care of clinicians with **less than 11 years'** experience were on **sedative-hypnotics**. Fewer patients (**28%** and **32%** respectively) under the care of clinicians with **11–20 years'** experience and **over 21 years'** experience were prescribed sedative-hypnotics.

Clinicians with **less than 11 years'** experience prescribed **antidepressants** to **33%** (25 out of 75) of patients under their care. Clinicians with **11–20 years'** experience prescribed antidepressants to **20%** and clinicians with **more than 21 years'** experience prescribed antidepressants to **12%** of patients under their care. So there is a trend for those with increasing years of experience to prescribe fewer antidepressants.

More antidepressants were prescribed by clinicians trained in **NZ/Australia (32%)**, followed by doctors trained in **India (30%)** and **other parts of the world** (in this study, South Africa, USA and Europe, **16%**). Clinicians trained in the **UK** prescribed antidepressants only to **4%** of patients.

Clinicians with **1–10 years'** experience prescribed **mood stabilisers** to **33%** (25 out of 75) of patients under their care. Those with **11–20 years'** experience prescribed mood stabilisers to **22%** (58 out of 268) and clinicians with **more than 21 years'** experience prescribed to **9%** (8 out of 93) of their patients.

With regard to country of training, clinicians trained in the **UK** prescribed mood stabilisers to **8%** of their patients (9 out of 117), those trained in **India** prescribed them to **31%** (27 out of 86) and clinicians with their training in **NZ or Australia** prescribed them to **32%** (48 out of 148) of their patients.

In summary, clinicians with more than 20 years' experience and clinicians trained in the UK prescribed fewer antidepressants and mood stabilisers than others.

5.2 Part 2

In the second part of analysis, the occurrence and duration of rehospitalisation was examined in relation to discharge variables (Patient demography, duration of index admission, discharge diagnoses, compulsory treatment status, prescribed psychotropics at discharge, treating psychiatrists' years of experience and country of training) and previous admission duration (within two years prior to index admissions). Antipsychotic dosages were converted to CPZE.

Of the 451 patients, **39% ($n = 177$)** were rehospitalised **within one year** and **44% ($n = 199$) within two years** following their index discharge. Of the 199 patients rehospitalised, 59 (**29.6%**) patients were admitted **within 30 days of discharge** (13% of the total), 60 patients (30.2%) were hospitalised between one and six months, and 58 patients (29.1%) between 6 and 12 months. Only 11.1% ($n = 22$) of the rehospitalisations occurred during their second year.

Sixty per cent ($n = 273$) of the total cohort ($n = 451$), had crisis contact within two years; 97% ($n = 438$) had community follow-ups, with a gradual decline in rate after the first month. Of those who had **crisis contacts** ($n = 273$), for 75 (**27.5%**) patients, this was **within one month** of the index discharge, for 101 patients (**37.0%**) between **one and six months**, and for 66 patients (**24.2%**) between **six and twelve months**. So most of the crisis contact occurred within the first six months following index discharge. Only **11.4%** of the crisis contacts occurred during the **second year**.

In addition, for **community follow-up**, the maximum contacts, **81.7%** ($n = 358$ out of 438), occurred in the **first month**, 57 (**13%**) occurred between **one and six months** and 17 (**3.9%**) occurred between **six and twelve months**. The rate then dropped to 1.4% ($n = 6$) during the second year.

5.2.1 Relationship between rehospitalisation rate and index discharge variables

1.1) Age group

Table 28 highlights the **lower rehospitalisation** rate for those **over age 49**. See also

Figure 4.

Table 28. Rehospitalisation and age groups

Age groups	RH (within 12months) <i>n</i> = 177(%)	RH (by 24 months) <i>n</i> = 199 (%)
18–24 (<i>n</i> = 88)	35 (39.8%)	40 (45.5%)
25–49 (<i>n</i> = 289)	121 (41.9%)	136 (47.1%)
50–75 (<i>n</i> = 74)	21 (28.4%)	23 (31.1%)

Note. RH = rehospitalisation.

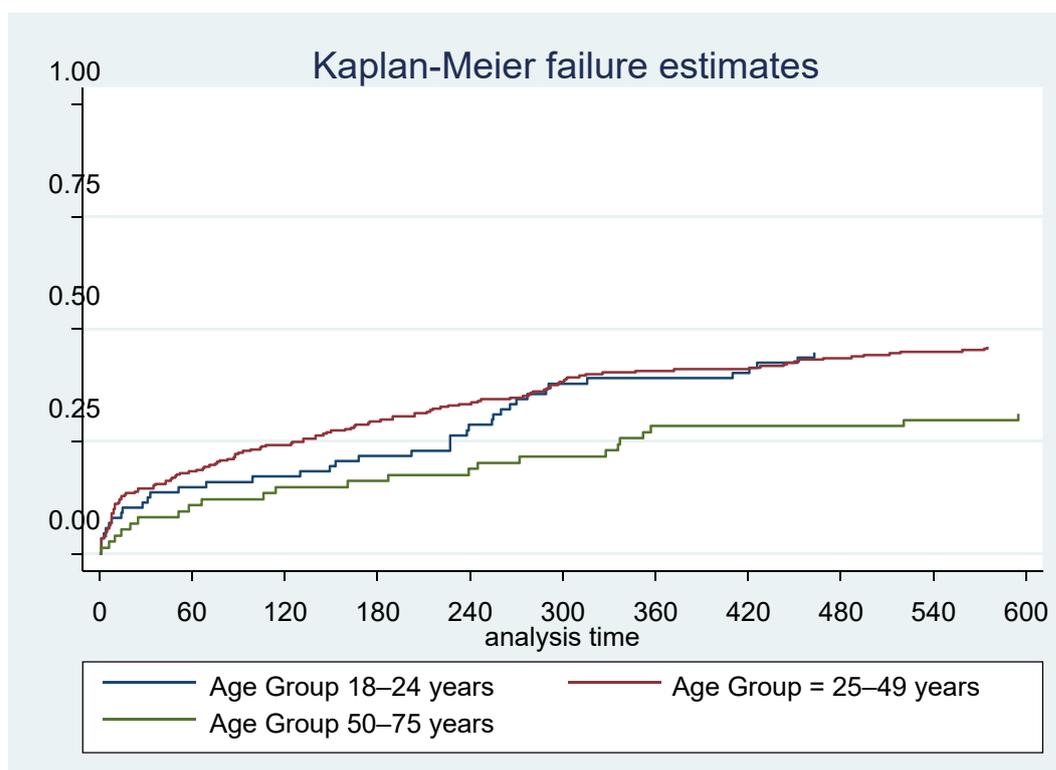


Figure 4. The rehospitalisation rate for different age groups

1.2) Gender

There were no statistically significant differences in rehospitalisation rate between males and females. **Forty-four per cent** (*n* = 127) of **males** were rehospitalised within **two**

years of index discharge compared with 45% ($n = 72$) of females. The trend was similar for the first 12 months (male = 38% and female = 41%).

1.3) Ethnicity

Figure 5 shows the (Kaplan–Meier curve) rehospitalisation rate over the two-year period displayed by ethnicity.

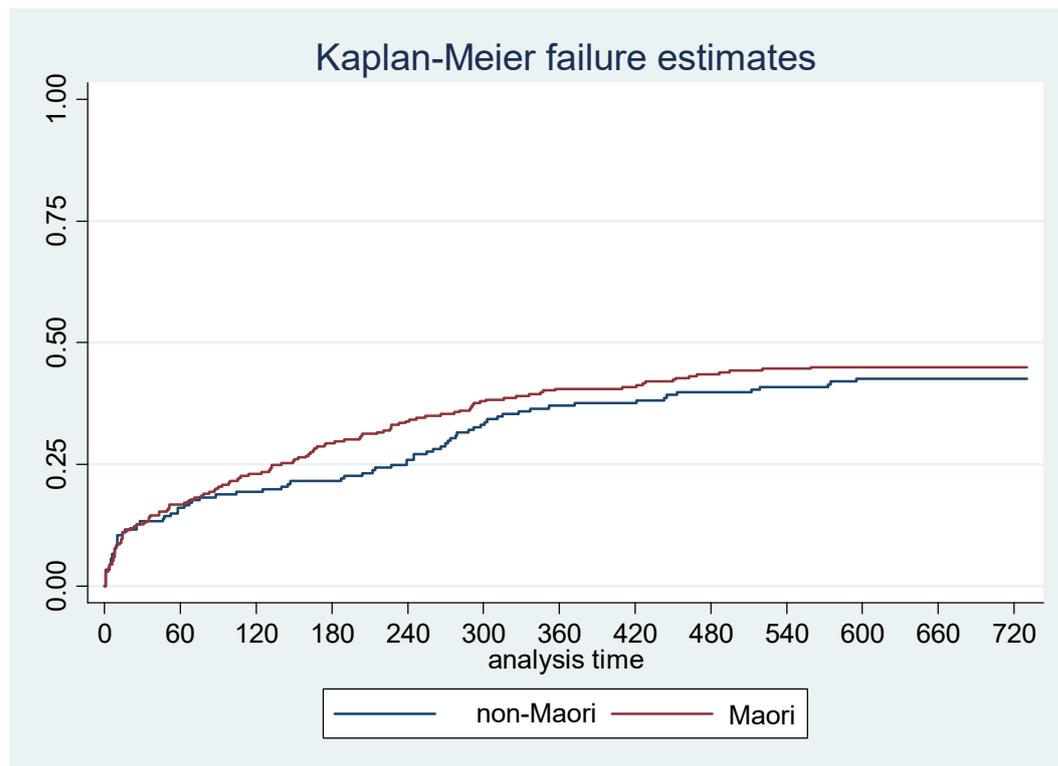


Figure 5. Rehospitalisation rate by ethnicity

Figure 5 shows no significant differences observed until 80 days following index discharge. From 80 days onward, Māori were more likely to be rehospitalised; that trend continued up to the end of two years, but the difference was not statistically significant. The differences in rehospitalisation rate between ethnicities within 12 months ($p = 0.49$) and by 24 months ($p = 0.63$) were not statistically significant.

1.4) Mental Health Act and rehospitalisation

The differences in rehospitalisation rate were more apparent within 12 months after discharge ($p = 0.07$). By completion of the two-year follow-up period, the significance of the differences between the two groups dropped to $p = 0.18$.

Table 29. Rehospitalisation in relation to the Mental Health Act

MHA	RH (within 12 months)	RH (by 24 months)
Yes ($n = 212$)	93 (43.9%)	101 (47.6%)
No ($n = 239$)	84 (35.1%)	98 (41.0%)

Note. MHA = Mental Health Act; RH = rehospitalisation.

1.5) Diagnosis and rehospitalisation

Those patients with a diagnosis of **schizophrenia** were more likely to be hospitalised (**44%**) within two years of index discharge than those diagnosed as suffering from **schizoaffective disorder** (**40%**). However, the differences were not statistically significant. The trend was similar within the first year of discharge (40% for schizophrenia and 34% for schizoaffective disorders). For the other diagnoses (psychotic disorder NOS, delusional disorder, acute and transient psychotic disorder, brief psychotic disorder, unspecified non-organic psychosis), the admission rate was higher ($n = 12/17$, 70%) by 24 months and was 59% within 12 months of discharge.

1.6) Index admission duration and rehospitalisation

Of the 274 patients who had a **shorter stay** (3 weeks or less) during their index admission, rehospitalisation rate was **46.3%** ($n = 127$) within **12 months** and **50.7%** ($n = 139$) by **24 months**. Of the 177 patients who stayed **more than three weeks** in hospital during index admission, **28%** ($n = 50$) were admitted within **12 months** and **34%** ($n = 60$) were admitted by **24 months**. The differences in rehospitalisation rate between the less than three weeks and the more than three weeks groups was statistically significant ($p = 0.0001$ for 12 months and $p = 0.0005$ for 24 months).

1.7) Antipsychotics and rehospitalisation

Table 30 summarises the rehospitalisation rate.

Table 30. Rehospitalisation in relation to types and routes of prescribed antipsychotics

APDs	RH (within 12 months)	RH (by 24 months)
Types and routes		
Oral FGA (<i>n</i> = 23)	8 (34.8%)	9 (39.1%)
Oral SGA (<i>n</i> = 357)	135 (37.8%)	152 (42.6%)
SGLAI (<i>n</i> = 79)	29 (36.7%)	33 (41.8%)
FGLAI (<i>n</i> = 114)	42 (36.8%)	49 (43.0%)
FGA (<i>n</i> = 73)	26 (35.6%)	30 (41.1%)
SGA (<i>n</i> = 324)	129 (39.8%)	144 (44.4%)
FGA + SGA (<i>n</i> = 54)	22 (40.7%)	25 (46.3%)
Only routes		
Oral APD (<i>n</i> = 230)	95 (41.3%)	106 (46.0%)
LAI (<i>n</i> = 69)	28 (40.6%)	32 (46.4%)
Oral + LAI (<i>n</i> = 124)	43 (34.7%)	50 (40.3%)
Two oral (<i>n</i> = 28)	11 (39.3%)	11 (39.3%)

Note. APD = antipsychotic drug; RH = rehospitalisation; SGLAI = second-generation long-acting injectable; FGLAI = first-generation long-acting injectable; FGA = first-generation antipsychotic; SGA = second-generation antipsychotic; LAI = long-acting injectable.

The rates of rehospitalisation were not significantly different for any antipsychotic type or method of administration. More specifically, the differences in rehospitalisation were not significant between oral FGAs and SGAs, between first- and second-generation LAIs, between different routes of antipsychotics or when polypharmacy (combination of oral and LAIs or combination of two oral antipsychotics) were prescribed.

1.8) Chlorpromazine equivalent dosage and rehospitalisation rate

There were no statistically significant differences observed between the three different groups of CPZEs (see Table 31).

Table 31. Chlorpromazine equivalent dosage of prescribed antipsychotic medications and rehospitalisation rates

CPZE dosage	RH (1–12 months)	RH (1–24 months)
≤ 300 mg (<i>n</i> = 157)	62 (39.5%)	71 (45.2%)
301–600 mg (<i>n</i> = 190)	78 (41.1%)	84 (44.2%)
601–1,000 mg (<i>n</i> = 74)	26 (35.1%)	31 (41.9%)
> 1,000 mg (<i>n</i> = 30)	11 (36.7%)	13 (43.3%)

Note. CPZE = chlorpromazine equivalents; RH = rehospitalisation.

1.9) Other prescribed psychotropics

The rehospitalisation rate did not vary when different psychotropic medications were considered (see Table 32).

Table 32. Other psychotropic medications and rehospitalisation rate

Psychotropic	RH (1–12months)	RH (1–24months)
Antidepressant (<i>n</i> = 93)	34 (36.6%)	39 (41.9%)
Mood stabiliser (<i>n</i> = 97)	35 (36.1%)	42 (43.3%)
Sedative-hypnotic (<i>n</i> = 124)	50 (40.3%)	56 (45.2%)
Anticholinergic (<i>n</i> = 61)	25 (41.0%)	26 (42.6%)

Note. RH = rehospitalisation.

1.10) Clinician characteristics

Clinicians who had **more than 21 years** of experience treated 93 patients, **50%** of whom were rehospitalised. Forty-four per cent (**44%**) of patients treated by clinicians with **11–20 years’** experiences (> 21 years vs. 11–20 years, $p = 0.28$), and **35%** of patients treated by clinicians with **less than 11 years’** ($p = 0.04$, > 21 years vs. 1–10 years) experience were readmitted within two years ($p = 0.18$ for 11–20 years vs. < 11 years). None of these differences were statistically significant.

The rate of rehospitalisation within two years - NZ/Australia: 40% ($n = 60/148$); UK: 48% ($n = 56/117$); India: 42% ($n = 36/86$); Others: 47% (46/97)- did not vary according to country of clinician postgraduate training.

Summary: Table 33 summarises the findings for discharge variables (mentioned above) before describing the likelihood of rehospitalisation after adjusting for other variables (regression analysis).

Table 33. Discharge variables and rehospitalisation within two years

Variables (<i>n</i> , %)	Number hospitalised (%)
Age group	
18–24 (<i>n</i> = 88, 20%)	40 (46%)
25–49 (<i>n</i> = 289, 64%)	136 (47%)
50–75 (<i>n</i> = 74, 16%)	23 (31%)
Gender	
Male (<i>n</i> = 290, 64%)	127 (44%)
Female (<i>n</i> = 161, 36%)	72 (45%)
Ethnicity	
Māori (<i>n</i> = 269, 60%)	121 (45%)
Non-Māori (<i>n</i> = 181, 40%)	77 (43%)
Compulsory treatment	
Yes (<i>n</i> = 212, 47%)	101 (48%)
No (<i>n</i> = 239, 53%)	98 (41%)
Duration of index admission	
< 3 weeks (<i>n</i> = 274, 61%)	139 (51%)
> 3 weeks (<i>n</i> = 177, 39%)	60 (34%)
Antipsychotic treatment	
FGAa (<i>n</i> = 73, 16%)	30 (41%)
SGAa (<i>n</i> = 324, 72%)	144 (44%)
Combined FGA+ SGAa (<i>n</i> = 54, 12%)	25 (46%)
LAI alone (<i>n</i> = 69, 15%)	32 (46%)
Oral alone (<i>n</i> = 230, 51%)	106 (46%)
Combined LAI + oral (<i>n</i> = 124, 28%)	50 (40%)
Clozapine (<i>n</i> = 90, 20%)	30 (33%)
Total CPZE, mg/day	
< 300 (<i>n</i> = 157, 35%)	71 (45%)
300–600 (<i>n</i> = 190, 42%)	84 (44%)
> 600 (<i>n</i> = 104, 23%)	44 (42%)
Clinician characteristics	
Years of experience	
1–10 (<i>n</i> = 75, 17%)	26 (35%)

Variables (n, %)	Number hospitalised (%)
11–20 (n = 268, 59%)	118 (44%)
> 21 (n = 93, 21%)	47 (51%)
Country of training	
NZ/Australia (n = 148, 33%)	60 (41%)
UK (n = 117, 26%)	56 (48%)
India (n = 86, 19%)	36 (42%)
Others (n = 97, 22%)	46 (47%)

Note. FGA = first-generation antipsychotic; SGA= second-generation antipsychotic; LAI = long-acting injectable; CPZE = chlorpromazine equivalent. ^aIrrespective of route.

5.2.2 Hazard ratio (HR) for rehospitalisation

HRs convey a type of relative risk; in this study, they convey the risk of rehospitalisation within a particular time. Regression analysis was used to obtain the HRs and their CIs.

Table 34 highlights the association (HR) between patient demography, compulsory admission and rehospitalisation rate after adjusting for other discharge variables.

Table 34. Hazard ratio in relation to patient characteristics

Variables	HR	p value	95% CI
Age group in years			
25–49 vs. 18–24	0.96	0.82	0.67–1.38
50–75 vs. 18–24	0.47	0.007	0.28–0.81
Gender			
Female vs. male	1.25	0.15	0.92–1.69
Ethnicity			
Māori vs. non-Māori	1.005	0.97	0.75–1.35
MHA vs. no MHA	1.29	0.06	0.98–1.71

Note. HR = hazard ratio; CI = confidence interval; MHA = Mental Health Act.

Patients over 49 (50–75 years) were approximately half as likely to be rehospitalised than were those under 25. Figure 6 highlights the differences in rehospitalisation rate according to age-group in years, following the index discharge.

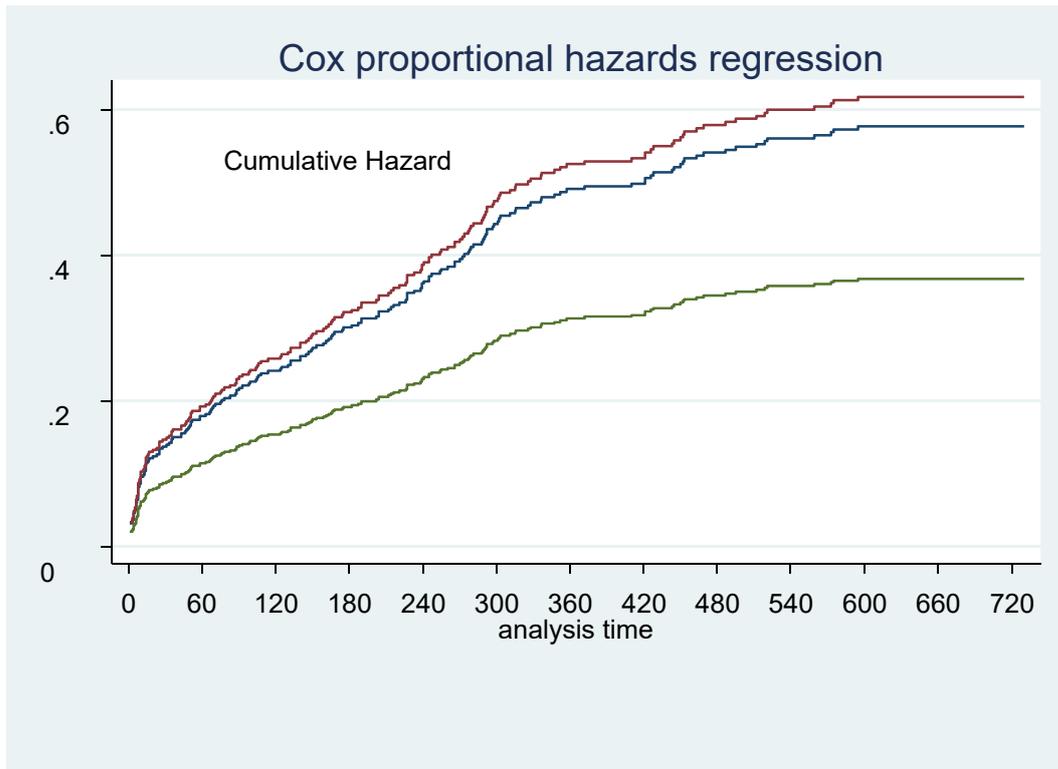


Figure 6. Age groups and rehospitalisation over two years. Blue = 18–24 years; red = 25–49 years; green = 50–75 years.

Females were 25% (see Table 34) more likely to be rehospitalised than their male counterparts but the difference did not reach statistical significance ($p = 0.15$). There were also no statistically significant differences between non-Māori and Māori patients ($p = 0.97$). Patients under compulsory treatment appeared more likely (HR = 1.29, 95% CI = 0.98–1.71, $p = 0.06$) to be rehospitalised than voluntary patients.

Patients who had **longer (> 3 weeks)** index admission were 47% less likely (HR = 0.53, 95% CI = 0.39–0.72, $p = < 0.0001$) to be rehospitalised than those who stayed three weeks or less.

Table 35. Rehospitalisation (hazard ratio) in relation to types and routes of prescribed antipsychotics

Type/Route	HR	<i>p</i> value	95% CI
FGA vs. SGA ^a	0.88	0.55	0.60–1.31
LAI ^b vs. no LAI	0.82	0.19	0.60–1.10
FGLAI vs. SGLAI	0.97	0.89	0.59–1.59
LAI vs. oral monotherapy	0.89	0.44	0.67–1.18
Polypharmacy vs. monotherapy	0.80	0.15	0.59–1.08
Oral SGA vs. FGA	1.30	0.47	0.63–2.68
Clozapine vs. no clozapine	0.60	0.01	0.41–0.89

Note. HR = hazard ratio; CI = confidence interval; FGA = first-generation antipsychotic; SGA = second-generation antipsychotic; FGLAI = first-generation long-acting injectable; SGLAI = second-generation long-acting injectable. ^aIrrespective of routes. ^bMonotherapy or combination with oral.

After adjusting for other variables, apart from **clozapine** ($p = 0.01$) there were no significant differences in rehospitalisation for different types and routes of antipsychotics. Rehospitalisation rates did not vary by antipsychotic dosage ($p = 0.98$ for 300–600 mg CPZE vs. < 300 mg, $p = 0.54$ for > 600 mg vs. < 300 mg) or co-prescription of other psychotropics (e.g., antidepressants, mood stabilisers, anticholinergics, sedative-hypnotics).

Patients treated by psychiatrists with more than 20 years' experience were 82% more likely to be rehospitalised than patients of clinicians with less than 11 years of experiences (HR = 1.82, 95% CI = 1.13–2.95, $p = 0.01$). This effect persisted after adjusting for patient age, gender, ethnicity, compulsion, duration of either previous or index admission and clinician country of postgraduate training.

However, statistical significance was lost after adjusting for types and routes of antipsychotics (HR = 1.34, 95% CI = 0.59–3.08, $p = 0.48$). It is important to mention that clinicians with more experience tended to prescribe more FGLAIs ($n = 28$, 30%) compared with clinicians with less than 11 years' experience ($n = 17$, 23%). Multivariate

analysis after adjusting for all other variables also did not show any differences in rehospitalisation when clinicians' country of training was considered.

Table 36 summarises the HRs for rehospitalisation and hospital bed days (coefficient) in relation to discharge variables (regression analysis).

Table 36. Summary of findings: Two-year rehospitalisation rates and hospital bed days

Discharge variables	Hazard ratio (95% CI) for rehospitalisation	Coefficient (95%CI) for total days rehospitalised
Age group (vs. 18–24)		
25–49	1.08 (0.76, 1.53)	-17.7(-32.3, -3.03)*
50–75	0.58 (0.35, 0.97)*	3.2 (-18.1, 24.5)
Māori vs. non-Māori	1.12 (0.84, 1.49)	4.48 (-7.63, 16.6)
Female vs. male	1.04 (0.78, 1.39)	1.68 (-10.6, 13.9)
Compulsory treatment (yes vs. no)	1.29 (0.98, 1.71)	11.5 (-0.19, 23.1)*
Duration of index admission (> 3weeks vs. < 3 weeks)	0.53 (0.39, 0.72)***	9.2 (-3.52, 22.0)
Antipsychotics		
Clozapine vs. no clozapine	0.61 (0.41, 0.89)**	20.4 (4.18, 36.6)**
FGA vs. SGA	0.89 (0.61, 1.33)	3.04 (-13.5, 19.6)
LAI vs. oral	1.04 (0.71, 1.54)	3.82 (-13.0, 20.6)
CPZE (vs. 100–300 mg)		
300–600 mg	1.00 (0.73, 1.38)	2.84 (-10.6, 16.3)
> 600 mg	0.89 (0.61, 1.29)	5.77 (-10.2, 21.7)
Clinician characteristics		
Training years (vs. 1–10 years)		
11–20 years	1.40 (0.92, 2.1)	8.85 (-9.10, 26.8)
> 20 years	1.83 (1.13, 2.9)**	16.6 (-3.64, 36.9)
Country of training (vs. NZ/Australia)		
UK	1.26 (0.87, 1.81)	-1.61 (-17.0, 13.8)
India	1.03 (0.68, 1.56)	8.4 (-9.1, 25.9)
Others	1.32 (0.89, 1.93)	9.5 (-6.8, 25.8)
Previous admission duration (vs. no admission)		
3 weeks or less	1.07 (0.72 to 1.59)	1.38 (-7.4–10.18)
> 3 weeks	1.01 (0.69 to 1.47)	0.94 (-7.06–8.92)

Note. Coefficient example: Patients prescribed clozapine during their index admission spent on average 20 days longer readmitted than others. HR = hazard ratio; CI = confidence interval; CDOIA = duration of index admission; FGA = first-generation antipsychotic; SGA = second-generation antipsychotic; LAI = long-acting injectable; CPZE = chlorpromazine equivalents. * $p < 0.05$. ** $p < 0.01$

Therefore, regression analysis showed a significant association between age group and rehospitalisation, with patients over 49 hospitalised less compared with those below 25. The association between duration of index admission and rehospitalisation rate was also statistically significant, highlighting that longer duration of index admission was associated with a reduced rate of rehospitalisation in two years' time, compared with shorter admission. Clozapine was associated with a lower rate of rehospitalisation compared with those not on clozapine, and patients treated by experienced clinicians (> 20 years) were rehospitalised more compared to patients under the care of less experienced clinicians (1–10 years).

The following sections will summarise the associations between discharge variables and hospital bed days in details. Regression analysis showed an association between hospital bed days and younger age group (18–24). Patients under the MHA as well as those on clozapine stayed longer during rehospitalisation than voluntary patients and those not on clozapine.

5.2.3 The number of rehospitalisation bed days and relationship with index discharge variables

2.1) Age, gender and ethnicity

Patients **over the age of 50** (up to 75) spent on average **51 days** in hospital, followed by the group of patients aged **18–24** with **48 days** and patients aged **25–49 years** with **30 days**. Regression analysis (adjusted for other variables) showed younger age groups (18–24) spent more days readmitted relative to the comparison group. This has been expressed as the coefficient in Table 36 (summary of findings). Coefficients indicate the estimated change in average bed days for a change in category of the indicated predictor variable.

There were no statistically significant differences in mean hospital bed days during rehospitalisation between males and females, or between Māori and non-Māori patients. **Males** spent on average **36 days** in hospital and **females 37 days**. **Māori** patients spent on average **38 days** in hospital and **non-Māori** spent **34 days**. Even after adjustment (coefficient) for age, duration of index and previous admissions, CPZE dosages and MHA, there was no difference.

2.2) Diagnosis

The mean number of hospital bed days at rehospitalisation was **37** for patients with a diagnosis of **schizophrenia** and **31 days** for **schizoaffective** disorder. Patients with other diagnoses (psychotic disorder NOS, delusional disorder, acute and transient psychotic disorder unspecified, brief psychotic disorder, unspecified organic psychosis) spent more days (mean = 42 days) in hospital. The differences were not statistically significant ($p = 0.63$).

2.3) Compulsory status (MHA)

Patients who were discharged under **compulsory status** spent on average **42 days** rehospitalised compared with **30 days** for those who were **not under compulsory status**. Regression analysis (adjusted for age group, gender, ethnicity, duration of index admission, MHA, CPZE dosages, previous admission duration) showed that those subject to compulsory treatment spent more days (11.5 days more) ($p = < 0.05$, 95% CI = -0.19 to 23.1) readmitted relative to the legally informal (see Table 36).

2.4) Duration of index admission and previous admissions (< 3 weeks and > 3 weeks)

The duration of index admissions followed a similar trend during rehospitalisation. Patients who spent less than three weeks in hospital during index admission spent on average 34 days in hospital at rehospitalisation, while those who stayed more than three

weeks at index admission stayed 43 days during rehospitalisation. Regression analysis (coefficient) did not show any statistically significant differences (see Table 36).

2.5) Antipsychotics

Table 37 summarises the association between different types and routes of antipsychotics and rehospitalisation bed days.

Table 37. Hospital bed days at rehospitalisation for different types and routes of antipsychotics

Types and routes (<i>n</i> = admitted patients)	Mean hospital bed days for those readmitted
FGAs (<i>n</i> = 30)	39
SGAs (<i>n</i> = 144)	36
FGAs + SGAs (<i>n</i> = 25)	34
Only LAIs (<i>n</i> = 32)	39
Only oral (<i>n</i> = 106)	34
Oral + LAIs (<i>n</i> = 50)	36
Two oral APDs (<i>n</i> = 11)	51

Note. FGA = first-generation antipsychotic; SGA= second-generation antipsychotic; LAI = long-acting injectable; APD = antipsychotic drug.

Overall, there were no major variations in hospital bed days based on the types and routes of antipsychotics. The patients on two oral APDs (mostly on clozapine) spent the most days rehospitalised.

Table 36 summarises the findings from regression analysis (coefficient, CI and *p* values). This did not show any statistically significant differences between FGAs and SGAs (irrespective of routes), oral and LAIs (either as single agent or in combination with oral APDs), oral FGAs and SGAs, or FGLAIs and SGLAIs. Patients on more than one antipsychotics (combination of oral and LAIs/two oral APs) spent two days less compared with those who were on monotherapy, but this proved insignificant statistically. Those who were discharged on clozapine during their index discharge spent

more days (see Table 36) in hospital during their subsequent admissions than patients not on clozapine.

2.6) Chlorpromazine equivalent dosage

Patients on CPZE dosage of **100–300 mg** of antipsychotic, spent on average **34 days** in hospital, those with **300–600 mg** spent **37 days**, those with **600–1,000 mg** spent **42 days** and patients with **more than 1,000 mg** spent **33 days** in hospital (see Table 36 for regression analysis). Regression analysis (adjusted for age, gender, ethnicity, MHA, duration of index admission and previous admissions) did not show any statistically significant differences.

2.7) Other psychotropic medications (antidepressants, mood stabilisers, sedatives and hypnotics, anticholinergics)

The mean LOS during rehospitalisation was 35 days for both antidepressants and mood stabilisers. Patients who were on regular sedatives during their index admission spent on average 48 days and those who had anticholinergic medications spent on average 59 days. Regression analysis showed patients who had received anticholinergics spent more time in hospital ($p = 0.003$, 95% CI = 9–44) during readmission but this effect was not shared by other psychotropics.

2.8) Clinician characteristics

The patients of clinicians with **1–10 years’** experience spent on average **27 days**; the duration was **36 days** for patients treated by clinicians with **11–20 years’ experience**, and **44 days** for patients under the care of **clinicians with more than 21 years’** experience. When clinician characteristics were included in the regression analysis (subsequent bed days as a continuous variable and adjusted for age, gender, ethnicity, MHA, duration of index admission, CPZE dosage, previous admission duration), there is a tendency towards patients of doctors with more than 20 years’ experience spending 17

days more in hospital ($p = 0.11$, 95% CI = $-3.64-36.9$) compared with patients of doctors with less than 11 years' experience. Patients of clinicians with 11–20 years' experience spent nine days more ($p = 0.33$, CI = $-9.10-26.80$).

With regard to country of postgraduate training, patients under the care of clinicians trained in **NZ or Australia** spent on average **33 days**; the duration was **31 days** for patients under the care of clinicians trained in the **UK**, **41 days** for clinicians trained in **India** and **43 days** for **clinicians trained** elsewhere. No statistically significant differences were observed between bed days when country of training was included in the regression analysis (see Table 36).

5.3 Summary of Results

5.3.1 Part 1

Demography and diagnoses

Of the 451 patients included in this study, 60% were Māori and 64% were male and between 25 to 49 years old. Māori were particularly predominant in the younger age group (67%). Schizophrenia was the most common diagnosis in this cohort (76%), followed by schizoaffective disorder.

Other clinical variables

a) MHA and duration of index hospitalisation: Nearly half (47%) of the patients were under MHA with no significant differences observed between age, gender and ethnicity. Most patients (61%) had stayed in hospital for three weeks or less. Regression analysis showed that the younger age group (18–24 years) and patients under the MHA spent longer in hospital compared to other age groups and voluntary patients.

b) Antipsychotic prescribing pattern: The initial part of this study found that apart from increased rate (33%) of polypharmacy (prescribing two or more antipsychotics) and a

lower than recommended rate of clozapine prescription (except for Māori), antipsychotic medications, dosage and routes of administration were generally consistent with CPGs. Nearly 72% were prescribed SGAs and were mainly prescribed oral SGAs. Among oral SGAs, olanzapine (31%) was most commonly prescribed, followed by risperidone (22%), clozapine (20%) and other SGAs. Haloperidol was the commonest one among oral FGAs. A significant finding was that a higher percentage of Māori than non-Māori (24% vs. 13%) were prescribed clozapine. A quarter of patients were prescribed first generation LAIs and around 18% were on SGAs. Prescription of LAIs as monotherapy was lower (15%) than the combination of oral and LAIs (28%). There were no statistically significant differences observed between age, gender and ethnicity. The only exception was clozapine. Oral antipsychotics were prescribed more to voluntary patients compared to patients under the MHA and similarly more patients under MHA were prescribed a combination of oral and LAIs; these patterns were statistically significant. There were no statistically significant differences observed for the duration of index admission by different types and routes of antipsychotics.

c) CPZE: Mean dosage of chlorpromazine was 489.7mg. There were no statistically significant differences in dosages when age, gender and ethnicity were considered. There was also no statistically significant association observed between the CPZE dosage and LOS during index admission. However, variations were noticeable for CPZE of different types and routes of APDs. Patient on SGAs, on polypharmacy, on oral monotherapy and on clozapine received higher dosages than patients on FGAs, on monotherapy, only LAIs and not on clozapine respectively. Patients who had prolonged admission required higher dosages than those who stayed for three weeks or less.

d) Other psychotropic medications: Antidepressant and mood stabilisers were prescribed more in the over 49 group and to females. Patients on antidepressants and mood

stabilisers also spent more days in hospital compared with those not on other psychotropic medications.

e) Clinician's characteristics: FGAs were prescribed more by clinicians with more than 20 years' experience and training in different countries did not influence the prescribing pattern. Detailed statistical analysis was not carried out again for these variables, but a pattern worthwhile to mention is that clinicians with more than 20 years' experience and clinicians trained in the UK prescribed fewer antidepressants and mood stabilisers than others.

5.3.2 Part 2

Of the 451 patients, 44% were rehospitalised within two years following index discharge. Most of the rehospitalisations occurred within one year of index discharge. Even though rate of community follow-up was good (97%), maximum contact (82%) occurred in the first month, then the rate dropped slowly with only 1% having community follow-up in the second year.

None of the demographic characteristics (age, gender and ethnicity) showed any statistically significant association with rehospitalisation rate apart from a lower hospitalisation rate for the over 49 age group. Similarly, shorter hospital stay during index admission was associated with increased rehospitalisation rate, and rehospitalisation rate was lower for patients on clozapine compared with those not on clozapine. Another finding that is worthwhile to mention is an increase in rehospitalisation rates for patients treated by a psychiatrist with more than 20 years' experience. However, after adjusting for types and routes of antipsychotics, this significance was not apparent anymore. As mentioned previously, this group were also prescribed more first generation antipsychotics. Patients under compulsory treatment and patients on clozapine spent more

days in hospital during rehospitalsiation when compared with voluntary patients and patients not on clozapine.

SECTION 6: DISCUSSION AND CONCLUSIONS

6.1 Discussion

RCTs are considered to provide evidence of the highest grade when efficacy of interventions is considered in any field of medicine. They are the preferred focus for systematic reviews and meta-analyses. Even though RCTs remain the most fundamental tool in clinical research, given the gap between efficacy and effectiveness of any intervention in psychiatry, questions have been raised as to whether short-term RCTs alone, with their typically strict inclusion and exclusion criteria, necessarily provide sufficient evidence to inform guidelines for treating chronic illnesses such as schizophrenia and related disorders.

There is ongoing debate about the types of studies required to address the gap between theory and practice. It has been argued that while RCTs are essential and are the gold standard for evaluating the efficacy of clinical interventions, on their own they are insufficient to provide guidance for clinicians (Rothwell, 2005, 2006). Because of the difficulty in translating the results from a trial evaluating efficacy of interventions into clinical practice, there is a demand for studies that could enhance the internal and external validity of RCT findings, as argued by a number of authors (D'Agostino, 2007; Rothwell, 2006; Victora et al., 2004).

Both the internal and external validity of RCT findings can be enhanced by observational studies despite the 'unbiased probability statement' quality of the former (Victora et al., 2004). The probability statement requires further evidence. Observational studies, using a plausibility design, can be used to strengthen it. It has been argued that plausibility statements arise from studies that despite not being randomised, aim to make causal statements using observational designs and such causal statements may strengthen the

probability statement from an RCT (Victora et al., 2004). This highlights the importance of both experimental RCTs and pragmatic effectiveness trials in psychiatry (Hotopf, 2002). As a result, there is an ongoing need for observational studies to reflect on both the validity and the utility of efficacy-derived knowledge. A further major concern about the validity of some efficacy findings arises because of the influence of the pharmaceutical industry (Tandon & Fleischhacker, 2005; Tandon, Belmaker, et al., 2008).

Practice guidelines have been developed to improve quality of care and to assist practitioners in their day-to-day practice. These guidelines have to consider scientific (i.e., largely RCT-derived) evidence with regard to key treatment recommendations (Gaebel et al., 2005). The development of rigorous guidelines also generally requires the involvement of stakeholders (one who is involved in and affected by a course of action, such as a service provider) and consumers, in addition to psychiatric experts. A final consideration remains that most guidelines originated in more developed countries, which may limit their generalisability across the world.

Therefore, despite years of accumulating evidence on the treatment of schizophrenia and related disorders, for a variety of reasons, clinicians are still frequently reluctant to follow evidence-based guidelines. Ongoing concerns regarding stringent criteria of trials led to larger-scale studies such as CATIE (Lieberman et al., 2005), CUtLASS (Jones et al., 2006) and the three-year prospective observational study SOHO (Haro et al., 2003, 2007). The gap between day-to-day practice and guideline recommendations, however, remains a concern, because of variability in practice.

This current study is intended to address the theory and practice gap in this area by describing characteristics of the pharmacotherapeutic management and progress of a

cohort of patients with schizophrenia and related disorders, treated in public mental health facilities in NZ.

6.1.1 Aims and outcomes

The aim was, in the first instance, to compare the observed prescribing practice in this cohort with existing CPGs (PORT, NICE, RANZCP, APA) and explore the relationships between prescribing patterns and discharge variables. The second main aim was to examine any associations between variables assessed at the time of index discharge and clinical outcomes in the subsequent two years. Multiple comparisons were done (Table 36) and these were necessary to explore the effect of different variables that would later feature in subsequent discussions. Data on previous admissions within the two years prior to the index admission were also examined in view of evidence supporting previous admissions as a strong predictor of subsequent outcomes (Mortensen & Eaton, 1994; Munk-Jørgensen, Bo Mortensen, & Machón, 1991; Silva, Bassani, & Palazzo, 2009; Olfson et al., 1999, 2014).

This observational (non-interventional) study provided the opportunity to follow-up a cohort from day-to-day standard NZ practice by using the national mental health database of the MOH in NZ (PRIMHD); hence, there were no concerns regarding recall bias (which refers to a phenomenon arising from recall of events that occurred a long time ago) or drop-out. Therefore, the study results would be more reliable (internal validity) and generalisable (external validity).

The study population was recruited from socioeconomically diverse areas of NZ and included a strong representation of Māori, particularly in the more rural catchment areas. Given the nature of relapse and remission in schizophrenia and related disorders, two-year follow-ups enabled the potential evaluation of **medication effectiveness** and its **association** with the available index discharge **variables** (patient demography, clinician

characteristics, duration of index admission, presence of compulsory treatment, routes and dosages of antipsychotics, prescription of other psychotropic medications). These discharge variables were considered important to include, in view of the literature review and the researcher's clinical experiences.

The main outcomes chosen were rehospitalisation events and hospital bed days because they are among the most devastating consequences for patients and family (Thieda, Beard, Richter, & Kane, 2003). They are also quantifiable measures of the course of schizophrenia for clinicians in their day-to-day practice. Service providers often use such information to assess the cost-effectiveness of care. Identifying risk factors for rehospitalisation can also have clinical and policy implications for patient care and service planning. It is worth noting that the average length of inpatient stays for schizophrenia and related disorders exceeds that for other major psychiatric illnesses (Olfson et al., 2014).

6.1.2 Study cohort

In this study of 451 patients, the sample size was sufficiently large to give confidence that clinically significant results would be apparent. The inclusion of patients between the ages of 18 and 75 provided a representative sample of those who usually receive adult mental health follow-up across most DHBs of NZ.

Most adult mental health services across New Zealand provide care for patients up to the age of 65. In order to maintain continuity of care, it is not uncommon in day-to-day practice for people over 65 to continue follow-up with adult mental health services, until concerns arise regarding an age-related condition such as dementia. Therefore, inclusion of patients up to the age of 75 increased the opportunity to include the patient group for which clinicians usually provide care during their day-to-day practice.

The demography of this sample is also consistent with MOH NZ statistics (Ministry of Health, 2011). The MOH document reported similar gender representation as the present study (64% male, 36% female in present study; 54% male and 46% female in the MOH report). Male gender dominated in the younger age groups in the present study, again consistent with the national data and a study highlighting that males are diagnosed with schizophrenia at a younger age than are females (Angermeyer, Kühn, & Goldstein, 1990).

The present study is the first to include three different DHBs in NZ, thus allowing inclusion of a representative sample from three different regions in the North Island with different ethnic mixes. The study cohort consisted of 60% Māori with a mean age of 35. Seventy-four per cent of those under 25 were Māori (65/88). This is also consistent with the MOH report in 2014 and several NZ studies, highlighting that Māori are the most likely to be seen by mental health services among all ethnicities, and were predominately younger than non-Māori (Baxter, Kingi, Tapsell, Durie, & McGee, 2006; Dharmawardene & Menkes, 2015; Te Puni Kōkiri, 1996).

Mental health was one of the five leading causes of hospitalisation among Māori between the ages of 18 to 24. Among Māori males, the rate of hospitalisation for schizophrenia was 3.6 times higher than that of non-Māori (Robson & Harris, 2007). Given the widespread national concerns regarding the poor outcome and over-representation of the NZ indigenous population (Māori) in mental health services (Abas et al., 2003; Te Puni Kōkiri, 1996), this study sample with significant representation of Māori ethnicity allowed researchers to examine some of the concerns regarding prescribing trends, hospitalisation trends and use of the MHA in regard to Māori patients. Inclusion of rural catchment areas with an increased proportion of Māori in this study also helped to legitimise the generalisability of the findings for many parts of NZ with similar ethnic distribution. This study yet again confirms the concern that higher proportion of Māori

young males are presenting with mental health issues especially psychotic illness such as schizophrenia, compared with other ethnicities in New Zealand. This cohort with a higher proportion of Māori is therefore representative of patients hospitalised for mental health issues compared with a general population without mental health issues.

The broader inclusion criteria of this study (any discharges with schizophrenia or related disorders, including other comorbidities) also allowed inclusion of a representative group from clinicians' day-to-day practice. The analysis did not consider the comorbidities separately. However, inclusion criteria of the study reduced the possibility of excluding complex patients with various comorbidities. Most of the patients in this cohort had chronic illness with a long history of being on antipsychotic treatment. This increased the robustness of the study when the effectiveness of antipsychotics was considered. Because of its observational nature, this study helped to determine how treatment was applied in actual practice.

6.1.3 Results

Part 1

The predominant diagnosis in this cohort was schizophrenia (75.6%) followed by schizoaffective disorder (20.6%). This is consistent with other local data that reported that rates of hospitalisation for schizophrenia are high (Baxter, 2008) and schizophrenia is by far the leading cause of hospitalisation among Māori (47.9%). Therefore, the higher rate of schizophrenia and 60% of patients with Māori ethnicity in this study cohort increase the generalisability of the results to day-to-day clinical care.

Schizoaffective disorder diagnoses were more prevalent in the 25–49 years and over 49 years compared with the younger age group in this study. This is an interesting finding. A study (Abrams, Rojas, & Arciniegas, 2008) focussing on this distinct diagnosis suggested a higher frequency of schizoaffective disorder among hospitalised psychiatric inpatients.

Concerns were also raised regarding the method of diagnosis. Age of onset of schizoaffective disorder in adults appeared to have a broader range but is not much different than schizophrenia which is not consistent with this finding of increased prevalence in older age groups. However, given the ongoing debate about this specific diagnosis and uncertainty about whether schizoaffective disorder is a variant of schizophrenia or bipolar disorder, the increased prevalence in the older age group in this study highlights the ongoing concern about the validity of categorical diagnoses in psychiatry.

Involuntary admission (admission under mental health legislation) is one of the most discussed topics in psychiatry. It faces criticism in part because of concerns from a human rights perspective. Generally, the rate of implementation of compulsory treatment varies considerably among different countries, meaning there is no universally accepted rate. In the NZ context, according to a recent MOH report, use of the community treatment order (the community part of MHA) was 2.9 times higher for Māori compared with non-Māori (Ministry of Health, 2014). Several other studies raised similar concerns (Edmonds et al., 2000; Wheeler et al., 2005). The present study did not analyse inpatient and community treatment orders separately. This study's findings, however, did not show any association between mental health legislation use and ethnicity.

Compulsory treatment use in this study showed no differences also according to gender and age group. Forty-seven per cent (47%) of this cohort was under the MHA, compared with an earlier NZ study (Wheeler et al., 2005) which reported 62% involuntary admission. International literature suggests the rate of voluntary versus compulsory admissions varies greatly from one country to another. The rate also varies between different locations in the same country (Salize, Dressing, & Peitz, 2002).

The evidence for the effectiveness of coercive elements on subsequent treatment outcome is equivocal (Dawson & Romans, 2001; Kisely, Campbell, & Preston, 2011).

Effectiveness depends on patient factors, illness severity and desired outcome. Some early studies that showed compulsion was effective have been criticised for their methodological weaknesses, and later RCTs did not confirm their findings; therefore, the results remain debatable. RCTs, however, are difficult to conduct in this area because they require one group to be excluded from legal statute and also raise questions about whether the improvement observed in some studies was due more to the intensive follow-up that group received than to the compulsion itself. Therefore, large-scale observational studies addressing this debatable issue might help clinicians in their daily practice.

Of greatest significance to this project is that debate continues on the type of antipsychotics that should be prescribed as first-line treatment. Variation in practice exists across the world, nationally and regionally, and sometimes even among clinicians in the same hospital. The current study's findings show, however, that prescribing trends for types of antipsychotics (prescription of higher rate of oral SGAs, increased polypharmacy and lower prescribing rate of clozapine) are no different in the three public hospitals in NZ analysed in the study, despite different ethnic mixes and the inclusion of patients with comorbidities, with or without compulsion.

A selective review and comparison of schizophrenia guidelines across the world (Gaebel et al., 2011) reported notable correspondence of many of the recommendations. With regards to antipsychotic choice, the RANZCP 2005 (McGorry et al., 2005) and APA 2004 (Lehman et al., 2004) guidelines prefer SGAs as first-line treatment, especially in first-episode patients, whereas the newer guidelines from NICE (2010) and PORT (2010) no longer indicate such a preference. The RANZCP also published recent guidelines (Galletly et al., 2016), which recommend SGAs (amisulpride, aripiprazole, quetiapine,

risperidone, ziprasidone) except olanzapine as first-line for first-episode non-affective psychosis. Olanzapine is recommended as second-line in this guideline if there is no response after 6 to 8 weeks. All guidelines, however, recommend similar dose ranges (300–1,000 mg/day CPZE) but a lower dose for first-episode patients. It is worthwhile to remember that the estimation of CPZE, particularly for SGAs, remains problematic (Gardner et al., 2010, 2014) and therefore is an ongoing issue in clinical practice.

Given the data time span of the current study (2009–2011 cohort), the choice of prescribed antipsychotics (APDs), dosage and route of administration are generally consistent with existing clinical guidelines, apart from the increased rate of polypharmacy (more than one APD) and lower rate of clozapine prescription. The overall alignment with guidelines in this study suggests concordance between theory and practice.

Nearly three-quarters (72%) of patients were discharged on SGAs irrespective of the route of administration, and fewer than one in six (16.2%) were discharged on FGAs, with approximately 12% discharged on a combination of these. The prescription rate of SGAs was higher in the younger age group compared with those aged 25–49 years and those over 49. The trend for higher rates of FGAs in patients over 49 is likely to be a reflection of illness chronicity. Gender and ethnicity did not influence prescribing patterns.

More than three-quarters (79%) of patients in this study were prescribed oral SGAs, compared with only 5% oral FGAs. The prominence of olanzapine (30.6%) in nearly one in three patients does not, however, align with guidelines published in recent years by PORT, NICE (2010) and RANZCP (2016). Olanzapine has been discouraged as a first-line drug because of concerns regarding metabolic syndrome and obesity (Kreyenbuhl et al., 2010).

Adherence has long been reported as one of the main causes of relapse and rehospitalisation in schizophrenia and related disorders, in addition to lack of efficacy of antipsychotics (Morken, Widen, & Grawe, 2008; Patel & David, 2005). LAIs are one of the clinical strategies to address adherence (Schooler, 2003). All existing guidelines have discouraged the use of LAIs as a first-line treatment; the usual recommendation is that if the patient prefers the injectable over the oral route, then an LAI may be used first-line. Therefore, the lower rate (15.3%) of LAI monotherapy in this study is not surprising and suggests that this is still reserved for reducing covert non-adherence in patients. In contrast to the predominance of oral SGAs, only one in five patients (18%) were prescribed SGLAIs, which is most likely a reflection of the limited availability (only risperidone was available) of SGLAIs in NZ at the time.

Risperidone LAIs were prescribed to 17.3% of patients and the prescription rate for FGLAIs was 25.3%. Haloperidol, flupenthixol and zuclopenthixol LAIs were between 7% and 8% each. This again suggests the possibility that even though, as a group, FGLAIs were prescribed more than SGLAIs, since the introduction of risperidone LAI, there is a tendency to prescribe it more, compared with conventional antipsychotic LAI formulations. The rate of LAI monotherapy in this study is consistent with international literature reporting variable prescribing rates, ranging from 15% to 80% (Manchanda et al., 2013). Future studies (after the introduction of newer LAIs) exploring the prescribing pattern of LAIs would be able to address whether clinicians tend to prescribe more SGAs than FGAs when there are options available, despite limited evidence to support the effectiveness of newer drugs compared with conventional APDs.

The prescription rate for combinations of oral and LAIs was 27.5% in this study. Overall, nearly 33% were prescribed two antipsychotics (6% for two oral antipsychotics in addition to the above combination). This is not in alignment with existing guidelines. The

CPGs do not recommend this practice (prescribing two or more antipsychotics for treating schizophrenia and related disorders) due to absence of robust evidence on the efficacy of such a combination.

One of the reasons for the increased prescription rate of combinations of oral and LAIs in this cohort, could be due to the fact that LAIs were introduced during hospitalisation for a substantial proportion of patients. They were then required to be on the oral APD for a period before the LAI's plasma level became therapeutic. However, this prescribing trend is consistent with other studies, which have reported prescribing two or more antipsychotics as a common treatment practice (10%–30%), noted across the world (Correll et al., 2009; Freudenreich & Goff, 2002).

Recent studies have reported the combination of FGAs and SGAs as the most common combination (Ganguly et al., 2004; Ito et al., 2005). The present study found that the preferred combination was oral risperidone and risperidone LAI, followed by the combination of oral olanzapine and FGLAIs. The first combination supports the suggestion mentioned above that LAIs were started in hospital and patients were discharged on both to allow the LAIs to achieve a steady state. It is unclear why the second combination was chosen in the absence of detailed information on the rationale (study limitation) but one likely explanation is that olanzapine LAI was not available or funded at the time in NZ; therefore, clinicians may have started patients on FGLAIs and oral olanzapine was prescribed in acute settings for treatment until a steady state was achieved for LAIs.

Future studies focusing on the rationale for prescribing two or more antipsychotics may be able to address this issue better. A recent article from China (Xu, 2015) has tried to shed some light on this topic. Reasons mentioned in this article for prescribing more than one APD were 'unrealistic expectations about the effectiveness and rapidity of effect of

medications’; ‘psychiatrists’ dominant position in the doctor-patient negotiations about treatment’; ‘traditional prescribing practice’, ‘profit driven nature’; ‘psychiatrists’ inadequate understanding of pharmacokinetics and pharmacodynamics of commonly used psychiatric medication’ and ‘professionals’ doubts about clinical guidelines’. Similar issues were addressed in another international study (Sernyak & Rosenheck, 2004).

Existing guidelines have also acknowledged some concerns regarding the effect of race on pharmacological treatment. Genetic differences and differences in the courses of illness, in addition to variation in practices, are thought to be the reasons for these variations. PORT (Kreyenbuhl, Zito, Buchanan, Soeken & Lehman, 2003, Kreyenbuhl et al., 2010) mentioned racial/ethnic minorities (especially African-Americans) were more likely than Caucasian patients to receive a higher dosage of APD. The APA has raised concerns that racial/ethnic minority patients with psychotic disorders are less likely to receive SGAs and more likely to receive LAIs (Lehman et al., 2004). At the same time, guidelines acknowledge the paucity of research in this area.

In NZ, similar concerns have been raised regarding the indigenous population. One local study (Wheeler et al., 2008) found that Māori had equal access to recommended antipsychotic treatment while another study reported concerns regarding use of more LAIs and excessive dosing in ethnic minorities (Metcalf, Laking, & Arnold, 2013). The current study with 60% of Māori in the cohort did not find any statistically significant differences in the prescribing trend between ethnicities apart from clozapine. The LAIs were prescribed to 45% of Māori compared with 39% of non-Māori in this cohort. In the absence of information on baseline characteristics, this study is not able to explain the reason for this trend in prescribing patterns. LAIs are usually recommended for patients with adherence problems. Therefore, this trend raises questions about whether the

adherence rate to APD is lower in Māori compared with other ethnicities. Future studies focusing on adherence rates to antipsychotics, including baseline information on patient characteristics, would be able to address this issue better than the current observational study. In this study, being prescribed more than one antipsychotic was no more evident for Māori than for non-Māori (34% for Māori and 33% for non-Māori).

The RANZCP 2016 guidelines (Galletly et al., 2016) also highlighted this issue and mentioned factors such as colonisation, poverty, racism, and higher rate and younger onset of cannabis use as important and relevant risk factors for Māori. The question remains, though, are any of these factors associated with more treatment-resistant illness, which may explain the prescribing trend, or do future studies need to focus on genetic variations and course of illness to explore association between these variables, ethnicity and prescribing trends? Given the heterogeneity of the diseases, most likely it would be a combination of multiple factors that usually affects the course and management of schizophrenia and related disorders.

In contrast, this study found significant differences in prescribing trends for patients under compulsory treatment status. The rate of prescription of oral APDs was low (40%) in this group compared with the voluntary group (60%, $p = 0.001$); more LAIs (19.8% vs. 11.3%, $p = 0.01$) and combination of antipsychotics (40% vs. 28%, $p = 0.007$) were also prescribed for this group. This is consistent with findings from studies focused on involuntary patients internationally, that compulsion is required more often in difficult-to-treat patients (Lambert, Singh, & Patel, 2009, Patel et al., 2011). Increased prescription rate of LAIs in this study for patients under compulsory status suggests that LAIs are usually saved for patients with adherence issues.

Approximately 30% of patients with schizophrenia are considered treatment-resistant (Elkis, 2007) and expected to be treated with clozapine. Evidence internationally,

however, suggests only a modest fraction of treatment-resistant patients are being treated with clozapine (Moore et al., 2007). A recent study in this area highlights consistent underutilisation of clozapine in the USA, the UK, Canada, NZ and Australia (Warnez & Alessi-Severini, 2014). The present study's findings are also consistent with this (only 20% of this cohort was prescribed clozapine). The result, however, contradicts a local study (Harrison, Janlöv, & Wheeler, 2010; Wheeler et al., 2008) reporting that the prescription pattern for treatment-resistant schizophrenia in NZ (33% on clozapine) is broadly in line with national and international best practice guidelines.

Another significant finding in the current study is that despite an overall low prescribing rate of clozapine, the rate of prescription was higher (24%) and closer to the recommended range in Māori compared with non-Māori ($p = 0.007$). As mentioned above, sociocultural factors as well as illness factors (differences in disease severity) and differences in response to antipsychotics could be contributory reasons for this difference (Emsley et al., 2002). Further exploration of this trend in future would be important in order to improve outcome and that would also help to identify reasons for the variation in practice.

The dosages of antipsychotics in this study are expressed as Chlorpromazine-equivalent dosage. The mean CPZE was 490 mg in the study and did not significantly differ by gender or ethnicity. The recommended dosage range suggested by all available guidelines was between 300 and 1,000 mg CPZE, and in this study the dosages were mostly within the recommended range. Only 6.7% of patients received more than 1,000 mg, though about a third (34%) received between 100 and 300 mg. The main issue to emerge in this study regarding the CPZE was the difference in dosage when different types and routes of antipsychotics were considered.

The concept of chlorpromazine-equivalent doses has come under criticism (Gardner et al., 2014; Patel et al., 2013) already. A study by Atkins et al. (1997) explained that equivalents were based primarily on dopaminergic blockade and not on a drug receptor profile for cholinergic, serotonergic or histaminergic systems. Therefore, the conversion of SGAs into CPZE will not always be a good measure of equivalent dosage. Another concern is the discrepancy between the oral equivalent of LAI antipsychotics and the vague nature of the concept of CPZE. It is worthwhile to consider whether the method of calculating the total antipsychotic dose as a percentage of the maximum recommended dose is less confusing and ambiguous than the CPZE (Hung, 2007).

The current study's findings, therefore, did not come as a surprise. This showed significant variation in dosages when different types and routes of antipsychotics were considered. The CPZE of FGAs (irrespective of routes) was 219 mg lower than the CPZE of SGAs (irrespective of routes), and that difference was significant ($p = 0.001$, 95% CI = -296 to -141). Similarly, CPZE dosage for only LAIs was less (364 mg less) than the dosage for only oral APD ($p = 0.001$, 95% CI = -445 to -283). So, as suggested above, it needs to be recognised that the allocation of CPZE, particularly for SGAs and different routes of APDs, remains a work in progress rather than being definitive. The issue of dose equivalence remains a challenge for clinicians (Davis & Chen, 2004).

The guidelines for schizophrenia do not provide a great deal of direction on the use of adjunctive psychotropic medications. Several studies have addressed the prescription pattern of other psychotropic medications and the current study's findings are consistent with some (Buchanan, Kreyenbuhl, Zito, & Lehman, 2002), but not with others (Chakos et al., 2011). Recently published RANZCP guidelines (Galletly et al., 2016) for the management of schizophrenia and related disorders highlighted the absence of sound

RCTs evaluating the efficacy of mood stabilisers in schizophrenia, and also reported evidence of increased mortality with antipsychotic–mood stabiliser combinations.

In the current study, the rates of antidepressant and mood stabiliser use were similar (21%), whereas the CATIE study (Lieberman et al., 2005) reported lower rates of mood stabiliser (19%) compared with antidepressant use (38%). Rates of hypnotic use were slightly higher (27%) in this study compared with rates in the studies mentioned above (19% in the CATIE study). A significant difference was also observed between the two younger age groups and those over 49. The older group received more antidepressants and mood stabilisers than the other two groups, and more prominent differences were observed between those aged 18–24 and those over 49 with a p value of 0.002 for antidepressants and 0.007 for mood stabilisers. Depression in patients with a primary diagnosis of schizophrenia is well recognised. Therefore, these comparisons were thought to be clinically relevant to address. In addition to first-episode of schizophrenia, studies on prevalence of depression in established schizophrenia suggest that relapse could be a major factor in the prevalence of depression (Barnes, Curson, Liddle, & Patel, 1989). This study sample consists of an inpatient cohort and therefore the rate of depression could be higher than an outpatient sample, due to the fact that most inpatient admissions are for treatment of relapse. It is, however, not clear why older age groups were prescribed more antidepressants and mood stabilisers in this sample. Does this increased prescription rate for older patients suggest clinicians were trying numerous empirical approaches to enhance clinical response, due to limited effectiveness of antipsychotics in severe schizophrenia? (Pickar, Vinik, & Bartko, 2008). Females were also prescribed more antidepressants ($p = 0.001$) and more mood stabilisers ($p = 0.004$) than males in this study. This is consistent with the CATIE study (Chakos et al., 2006).

Mood stabilisers are commonly prescribed for individuals with an affective component to their illness and antidepressants are commonly prescribed for comorbid depression.

Therefore, the trend of prescribing more antidepressants and mood stabilisers to the over-49 group and females also raises questions regarding the presentation of illness in these groups, and whether they present with more affective components and depression. Given the recent concern (Correll, Detraux, De Lepeleire, & De Hert, 2015; Galletly et al., 2016) regarding the effect of these combinations of psychotropics on the physical health, morbidity and mortality of patients with schizophrenia and related disorders, further work exploring the rationale for the use of other psychotropics (antidepressants and mood stabilisers), particularly in older patients, would be important.

Despite outpatient facilities and community service developments, patients with schizophrenia often require hospitalisation for relapse (Lindström, Eberhard, & Levander, 2007). However, there has been a shift towards shorter psychiatric hospital stays (Masters et al., 2014; Mellsop, Lombard, Mathieson, Turner, & O'Brien, 2000), encouraged by the deinstitutionalisation movement as well as by general expectations of more efficacious modern treatment. Another motivation is to limit costs, but the evidence for benefits achieved from shorter hospital stay on readmission rates and functional outcomes is inconclusive (Rocca et al., 2010; Warnke et al., 2011). The minimal length of hospital admission for adequate treatment of severely mentally ill patients is yet to be established. The mean LOS was considered 28 days in one study, with a range between 15 and 30 days (Appleby et al., 1993, 1996). In the current study, the mean duration of index admission is consistent with the Appleby et al. (1996) study. For the whole cohort, it was 26 days and most (61%) patients stayed from one day up to three weeks; 39% stayed more than three weeks.

The youngest patient groups, those below 25 years, spent longer (average 34 days) in hospital. Regression analysis (adjusted for gender, ethnicity, MHA order, CPZE dosage, previous admission duration) also confirmed that age had an effect on hospital bed days. Patients aged 25–49 years ($p = 0.002$, 95% CI = -18.2 to -3.7) and 50–75 years, ($p = 0.02$, 95% CI = -20.4 to -1.2) spent 11 days less in hospital, as compared with the group aged 18–24 years. This is consistent with some studies (Lelliott, Wing, & Clifford, 1994; Rabinowitz et al., 2006) but contradicts others that showed that increasing age predicted longer periods of hospitalisation (Zilber, Popper, & Lerner, 1990).

Other demographic variables did not influence LOS in this study. There is no statistically significant difference observed between gender or ethnicities. This study's finding on ethnicity is not consistent with the concern (Abas et al., 2003; Abas, Vanderpyl, & Robinson, 2008) that Māori require more prolonged admission than NZ Europeans.

Those subject to compulsion stayed longer (on average 36 days compared with 16 days) than voluntary patients in hospital. Regression analysis reinforced the finding that those under compulsion spent 19 days more on average ($p \leq 0.001$) than voluntary patients. The effect was not modified by gender or ethnicity. This is consistent with the few studies (e.g., Kallert, Glöckner, & Schützwohl, 2008) that have systematically addressed this issue. MHA legislation also varies across different countries, which influences practice and outcome. The differences between the two groups also suggest the possibility of differences in course, duration and severity of illness. However, because of the observational nature of this study, it is not possible to comment on clinical reasons for these differences. A better understanding of the factors associated with increased LOS would help to develop care systems addressing patients' specific needs. Reducing the negative consequences of early discharge and providing more accurate prediction of LOS could also be helpful for planning bed availability (Capdevielle et al., 2013).

Apart from clozapine-treated patients spending significantly longer in hospital than others ($p = 0.03$, 95% CI = 0.7–17 days), regression analysis did not show any significant association between duration of index admission and different types and routes of prescribed antipsychotics. As clozapine is usually prescribed after failed trials of at least two antipsychotics for treatment-resistant patients, longer hospital stays could reflect duration and severity of the illness. However, some studies have shown different outcomes. Ahn et al. (2005) reported a reduced number and duration of hospitalisations for patients on clozapine. Most studies also reported differences in effectiveness for different antipsychotics (Haro et al., 2007; Lieberman et al., 2005) and noted the effect of other clinical variables such as adherence and illness severity on outcome.

When different dosage ranges (< 300 mg, 300–600 mg and > 600 mg CPZE) were considered, regression analysis did not show any statistically significant effect on duration of hospital bed days. The use of higher dosages, however, could be a reflection of disease severity and use of more than one antipsychotic. There is, however, a significant tendency for patients prescribed antidepressants or mood stabilisers to stay longer during index admission. This may be a reflection of patients with other comorbidities requiring longer admission. The absence of any significant differences between different CPZE dosages, when considering duration of hospitalisation in this study, is not consistent with a recent study, which reported independent associations with LOS and higher dosages of antipsychotic use (Masters et al., 2014).

Previous hospital admission duration (0, < 3 weeks and > 3 weeks) and number of previous admissions (0, 1–2 admissions or > 3 admissions) also did not show any statistically significant effect on duration of index admission in this study. Patients who had previous admissions for more than three weeks also showed a trend of staying longer during index admissions. This finding is consistent with studies highlighting the effect of

prior psychiatric hospitalisation on outcome (Callaly et al., 2011; Monnelly, 1997; Swett, 1995).

Not many studies have focused on clinicians' behaviour. In this study, even though there was a tendency for clinicians with more than 20 years' experience to prescribe more FGA and FGLAIs, clinician training experience and country of training did not have any statistically significant effect on APD prescribing patterns or the duration of index admission. Other studies that have focused on clinician characteristics (Huntley et al., 1998) are generally consistent with the current findings. For example, a study by Hamann et al. (2004) showed a similar prescribing pattern, with older clinicians up to five times more likely to prescribe FGAs. This may be a reflection of training era, when only FGAs were available, and older clinicians may require convincing evidence on the efficacy of newer APDs before changing their prescribing pattern. The trend again confirms that decision-making in this area of psychopharmacology involves multiple factors, and clinicians' characteristics are only a part of the puzzle. In the absence of a body of data on this specific matter, addressing variations among individual prescribers is at the core of initiatives to implement treatment algorithms or guidelines to promote better outcomes.

In summary, the initial part of this study found that, apart from prescribing two or more antipsychotics and a lower than recommended rate of clozapine prescription (except for Māori), antipsychotic medications, dosage and route of administration were generally consistent with CPGs. The prescription pattern was significantly different for patients under compulsion and a trend of prescribing FGAs was also observed for clinicians with more than 20 years' experience.

Part 2

The second part of the study focused on rehospitalisation and the number of hospital bed days occupied during rehospitalisation following the index discharge. This part describes the two-year progress of the same cohort, discharged from inpatient care. The two-year follow-up enables the potential evaluation of medication effectiveness.

Rehospitalisation is often a painful experience for patients with schizophrenia and for their families. Given the heterogeneous outcomes in schizophrenia, the search for correlates of rehospitalisation in schizophrenia is an important goal for minimising the risk of relapse and rehospitalisation. Single variables have limited prognostic value and often yield contradictory results, but a combination of variables predicts outcome better (Möller, Schmid-Bode, & von Zerssen, 1986). The present study found correlates of rehospitalisation to be a combination of demographic and clinical variables.

The rehospitalisation rate (44%) in this study is comparable to those of overseas studies (Herceg et al., 2008; Zhang, Harvey, & Andrew, 2011), with the majority of readmissions occurring within 12 months of the index discharge. Most studies have not found a consistent relationship between diagnosis and rehospitalisation (Thompson et al., 2003). The current study also did not find any statistically significant differences between diagnostic subcategories and rehospitalisation or LOS during rehospitalisation. However, a number of international studies have reported that a diagnosis of schizophrenia is a strong predictor of rehospitalisation, increased LOS and involuntary admission (Bernardo & Forchuk, 2001; Cuffel, Held, & Goldman, 2002).

With regard to patient factors, male gender, younger age (< 40 years) and early age of onset have all been identified as risk factors for relapse (Csernansky & Schuchart, 2002). In this study, older patients (50–75 years group) were rehospitalised less often, being 53% less likely (HR = 0.47, $p = 0.007$) to be rehospitalised than the younger age groups.

This is consistent with a study by Mortensen and Eaton (1994) that concluded that readmission risk decreased with increasing age at first schizophrenia admission, and a study by Möller et al. (1982) also reported that age of > 40 years reduced the risk of rehospitalisation. This finding may also represent progression of the disorder or a ‘rising threshold’ of hospitalisation due to the patient and others becoming familiar with managing illness in the community.

Our other findings are consistent with studies (Thompson et al., 2003; Zhang et al., 2011; Wheeler, Moyle, Jansen, Robinson, & Vanderpyl, 2011) reporting that sociodemographic characteristics generally do not influence readmission risk, apart from a higher readmission rate reported for Māori in the Wheeler et al. (2011) study. Other local studies, however, have reported that even though the rate of hospitalisation and rehospitalisation are higher for Māori, the differences are small (Abas et al., 2003; Sachdev, 1989).

In the current study, no statistically significant differences overall were observed in the rehospitalisation rate between ethnicities, but the Kaplan–Meier curve over two years showed a higher rate of rehospitalisation between 80 and 280 days for Māori compared with non-Māori; this trend (not statistically significant) continued up to the end of two years. This variation raises the important question of whether extra support would help to reduce this readmission rate, and whether addressing the intensity and frequency of community follow-up initially after the index discharge would explain this variation. The importance of assertive community follow-up in reducing rehospitalisation has been emphasised in recent studies (Systema et al., 2002; Zhang et al., 2011). The current study suggests a significant drop in follow-up after 30 days of index discharge (a drop of 79.4% within one month to 12.7% between 31 and 180 days) but it did not differ by ethnicity. Even though the total percentage of community follow-up by two years was good in this

study, the drop in rate after 30 days was significant. Future study addressing the type (crisis/routine contact) and frequency (weekly/fortnightly/monthly) of community follow-up following the index discharge might help to address the reasons for this variation.

This study did not show a statistically significant (HR = 1.29, 95% CI = 0.98–1.71, $p = 0.06$) increase in rehospitalisation rates for patients under compulsory treatment within the following two years, compared with voluntary patients. The involuntary patients spent on average a significantly longer period in hospital during the subsequent admission ($p = < 0.05$). A recent study showed increased rehospitalisation rate for patient groups under compulsory treatment (Pfiffner et al., 2014); whereas this study showed a statistically insignificant trend of increase in rehospitalisation rate for patients under compulsory treatment. A systematic literature review by Kallert et al. (2008) likewise reported that the likelihood of readmission for patients admitted involuntarily was at least as high as or higher for patients admitted voluntarily. Similarly, it reported that the LOS was at least as long as or longer for voluntarily patients. A number of other studies have also identified involuntary admission as a predictor for readmissions irrespective of diagnosis (Munk-Jørgensen et al., 1991). In contrast, some studies have not found any differences (Perlman, Kentera, Thornton, & Griffith, 1988; Steinert & Schmid, 2004). The current study did not have access to other measures of severity, such as could be provided by lifelong cohort or acuity data. The increased likelihood of readmission for patients under compulsory treatment may simply reflect illness severity and lack of adherence to APD as an outpatient with subsequent relapse requiring inpatient admission. Previous studies reported that patients on continuous antipsychotic medications had an average relapse rate of 3.5% per month (Weiden & Olfson, 1995); amounting to a one-year relapse rate of 42%, very similar to the 39% one-year rehospitalisation rate in our

study. Other studies also reported almost a similar relapse rate of 38.6% during the prospective 12-month follow-up period (San, Bernardo, Gómez, & Peña, 2013; San, Bernardo, Gómez, Martínez, et al., 2013) and 48% in two years when patients were adherent to APD (Herceg et al., 2008; Hogarty, Goldberg, Schooler, & Ulrich, 1974). Because of its observational nature, this study is not able to comment specifically on adherence issues, but the two-year rehospitalisation rate was similar (44%). Some studies, however, reported a lower rehospitalisation rate of 14.6% to 21.6% for outpatients on LAIs (Chue et al., 2005; Simpson et al., 2006). Our study did not find such an association with LAI treatment.

We found comparable rehospitalisation rates and duration between patients treated with different types and routes of antipsychotic except for clozapine. These findings are consistent with overseas studies (Kishimoto et al., 2014; Taylor, 2012). CATIE (Lieberman et al., 2005) and CUtLASS (Jones et al., 2006) are the landmark studies that initially addressed this concern and challenged the view that all antipsychotics are comparably effective. The current study's findings, therefore, are consistent with the recent literature.

However, given the debate, it is worthwhile to mention that research on this matter is ongoing. A study in 2013 again concluded (San, Bernardo, Gómez, & Peña, 2013) that SGAs were superior to FGAs in reducing relapse rate. A study by Advokat et al. (2008), with a focus on LOS and rehospitalisation rates, concluded that patients on FGAs had significantly shorter LOS than those on SGAs, but patients receiving SGAs were significantly less likely to be readmitted than patients discharged on FGAs. It thus appears that more robust evidence from both RCTs and observational studies is required to provide guidance to clinicians.

In this study, clozapine was associated with a reduced rate of hospitalisation, despite its use in treatment-resistant patients (Werneck et al., 2011), as well as longer readmissions when these were necessary. Patients on clozapine were 39% (HR = 0.61, $p = < 0.01$, 95% CI = 0.41–0.89) less likely than others to be rehospitalised within the following two years. This is consistent with many studies over the years in which clozapine stood out (Conley et al., 1999). Clozapine has been demonstrated to be superior in reducing positive and negative symptoms, and so can be associated with improvement in quality of life. Patients prescribed clozapine require more intensive monitoring initially, and this may enhance adherence.

There were also no statistically significant differences observed in rehospitalisation rate when different CPZE dosages were considered. Nor did the rehospitalisation rate vary when different psychotropic medications (other than antipsychotics, e.g., mood stabilisers, antidepressants) were considered in this study.

The negative correlation between the duration of index admission and risk of subsequent rehospitalisation is of interest, given the current emphasis on minimising admission length (Masters et al., 2014), and the inconclusive evidence of the benefit of brief admission on rehospitalisation rate (Lin et al., 2006). In contrast, a fairly recent study however did not demonstrate a significant relationship between LOS and readmission (Thompson et al., 2003). In the current study, patients who were admitted longer than three weeks during their index admission were 47% less likely (HR = 0.53, 95% CI = 0.39–0.72, $p = < 0.0001$) to be rehospitalised. This may be relevant to service planners, given the progressive reduction in average LOS in recent decades (Lin et al., 2006). It is noticeable though, that those with longer index admissions (> 3 weeks) also had longer rehospitalisations. Further study of this group is warranted to address any baseline

differences in patient or illness related factors or any differences in aftercare planning, that may help to provide guidance for clinicians.

A number of international studies have also raised concerns regarding hospitalisations of shorter duration. Apart from the deinstitutionalisation movement of the 1960s and 1970s, one reason for the shift towards briefer hospitalisation is the high expectation of the effects of modern treatment. This reason could also be economically driven and administratively enforced (Masters et al., 2014). Masters and colleagues (2014) highlighted the concern that this shift and trend towards briefer hospitalisation might lead to premature discharge of patients with severe illness who remain clinically unstable. There is a paucity of research that would enable evaluation of the benefits and risk of such changes, and evidence on the effect of shorter stays on clinical and functional outcome, as well as readmission rates, is mixed and inconclusive (Jonas et al., 2012; Tulloch, Fearon, & David, 2011; Rocca et al., 2010).

Therefore, the current study's findings reinforce concern regarding shorter hospitalisations, in view of their association with subsequent hospitalisation risk. It is important for clinicians and especially service planners to consider the risks of excessively brief hospitalisation, given there has been a gradual reduction in average LOS in recent decades, as noted.

An Australian study (Daniels, Kirkby, Hay, Mowry, & Jones, 1998) examined the rate of rehospitalisation for schizophrenia, bipolar disorder and depression over a five-year period, highlighting the number of prior admissions as a predictor of both readmission rate and duration. In addition, previous studies (Eaton et al., 1992) also have demonstrated that the greatest numbers of rehospitalisations occur within the first 6 to 12 months after inpatient discharge. Therefore, studies with a follow-up period of one to two years may show higher rates of rehospitalisation. However, when the association between

numbers of previous admissions and subsequent hospitalisations (during third and fourth year of follow-up) was explored, this study did not show any significant association (see Appendix). This is inconsistent with some previous studies (Callaly et al., 2011; Monnelly, 1997; Moss et al., 2013; Swett, 1995), but consistent with studies (Chabungbam et al., 2007; Doering et al., 1998; Lyons et al., 1997; Zhang et al., 2011) that have taken into account individual patients' risk of readmission. Individual vulnerability is important to consider and may facilitate better management of this heterogeneous disorder. Studies with a larger sample size focusing on longer follow-up periods, beyond two years, in the future, would help to better address the association between previous hospitalisations and rehospitalisations.

This study found increased rates of rehospitalisation and bed day utilisation for patients of clinicians with more than 20 years' experience. They were more likely to be rehospitalised (HR = 1.83, $p < 0.01$) than patients of clinicians with less than 11 years' experience. However, the statistical significance of the former finding was no longer apparent after adjusting for LAI APD prescribing (HR = 1.34, $p = 0.48$, 95% CI = 0.59–3.08). This highlights the differences in the prescribing of different types of LAIs, where even though not statistically significant, the experienced clinicians prescribed more FGLAIs compared with clinicians with less than 11 years' experience. In the absence of data on duration of illness, adherence rate to medications, socioeconomic conditions, comorbidities and severity of illness in patient groups, one explanation could be that FGLAIs were prescribed to the more severely ill patient groups who had required rehospitalisation due to disease severity. Another concern is that side effects such as EPSs of FGLAIs can affect quality of life and can therefore lead to poor adherence and psychosocial functioning and this may increase the chance of relapse and thus hospitalisation. Several studies that have looked at the impact of these two groups

specifically (FGLAIs vs. SGLAIs) found no apparent differences in hospitalisation (Lammers, Zehm, & Williams, 2013; McEvoy et al., 2014; Olfson, Marcus, & Ascher-Svanum, 2007; Virit, Altindag, Bulbul, Savas, & Dalkilic, 2009). Finally, the clinician's country of postgraduate training did not have any statistically significant influences on rehospitalisation.

6.2 Limitations of the Study

The results of this study need to be interpreted in the context of several limitations, some of which have been briefly referred to above. This is an observational study with a retrospective analysis; therefore, it may contain problems in adequately controlling for initial differences between treatment groups.

This study is unable to comment on some of the baseline characteristics of the cohort or on risk factors at baseline that could have explained the over-representation of Māori. For example, substance abuse, socio-economic status, unemployment, migration from rural iwi regions (the iwi/tribe is the largest of the groups that form Māori society) to European-dominated cities, and unremitting illness that is probably more severe or less treatment-responsive, greater exposure to adverse social situations and loss of traditional support, can all lead to accumulation of cases.

As this is not an RCT, unrecognised confounding factors can influence the outcome.

Although some multivariate analyses were performed, it was not possible to control for all potential confounders. The patients were categorised into different groups on the basis of the antipsychotic prescribed, but questions about adherence could not be answered with this study's design. On the other hand, use and dose of the prescribed antipsychotic in the LAI group is likely to be more reliable than that of the oral group.

The data in this study were collected prior to the introduction of some of the newer LAI SGAs (olanzapine, paliperidone, aripiprazole); therefore, more LAI FGAs were

prescribed than SGAs and the main oral FGA was haloperidol. Therefore, this does not allow a conclusive comparison of the two types of antipsychotics. Also, using CPZE for antipsychotic dosage comparison, despite being the most currently credible practice, is uncertain, particularly regarding SGAs.

Patients recruited in this study were identified by diagnostic code from a database, rather than utilising structured clinical interview or validated rating scales. Assessments of illness severity and improvement were also based on patient record reviews instead of on purpose-designed, standardised clinical interviews. However, most patients in this study were multi-episode patients with previous hospitalisation, so the diagnoses should be reasonably reliable. There was also no measure of symptom severity in our data set, which can be an important factor in considering frequency of relapse in patients with schizophrenia.

Another important limitation is the study-defined outcome criterion of psychiatric hospitalisation. This only allows consideration of patients who have required hospitalisation for relapse. The study thereby underestimates the rate of relapse and fails to include patients who had a relapse but maintained functioning and were treated in the community with intensive support. Therefore, those who were hospitalised were possibly at the severe spectrum and probable non-responders to treatment in the community. Reasons for hospitalisation may not only be relapse of psychotic symptoms; reasons might also include adverse social circumstances, risk of self-harm and lack of the availability of non-hospital options in different localities.

In this study, Mental Health Act orders include both inpatient and community treatment orders, so this does not allow for comment specifically on either type of MHA compulsion, which meant the characteristics of patients on long-term community treatment orders could not be identified.

Another, possibly minor, limitation that may affect the generalisability of this study is that the sample may be representative of only specific areas in NZ because of the different ethnic mix in these specific public hospitals and may not be representative of other parts of NZ and other countries across the world. However, the geography covered was diverse and included a solid mix of urban and rural locations, economically healthy and economically fragile areas, and a number of different iwi regions.

With regard to clinician characteristics, the differences observed in prescribing patterns and rehospitalisation rates need to be considered with caution in the absence of information on the baseline characteristics of patients and chronicity of illness for the patients treated by each group. The number of psychiatrists involved was relatively small (18) and patients were not randomly assigned.

It is also worthwhile to address the fact that when multiple measures are tested in a study, there is a possibility of inevitably finding statistically significant results due to chance.

The quality of research depends on addressing clinically relevant issues while mentioning statistical significance. If a p value is 0.0001, the chance of the significant result occurring purely by chance is significantly less compared to a p value of 0.05 (Fiese, 2002).

The results of this study more likely suggest associations between variables than conclusive evidence. While the value of the study clearly lies in the fact that it represents standard, publicly funded levels and styles of mental health care of schizophrenia in a developed nation, interpretation of its findings has to be done with the awareness that many variables likely relevant to outcome or treatment choice were not available for the analysis.

6.3 Conclusions

Relapse prevention is one of the main goals of treatment for patients with schizophrenia and related disorders for several reasons: to reduce use of hospital services and social and financial costs of providing care, and to decrease patient suffering by reducing recurrent relapses and thus hospitalisation.

Relapses can be difficult to prevent. Many studies have attempted to identify factors that could reduce rates of rehospitalisation. In recent years, in the context of ongoing debate on the effectiveness of pharmacotherapy for treatment of schizophrenia, various major trials have been performed (CATIE, CUtLASS, CAFÉ, EUFEST). These aimed to facilitate the recruitment of more representative patient samples in order to improve the generalisability of study outcomes (Fleischhacker & Goodwin, 2009).

These landmark studies notably did not identify major differences in the effectiveness of different antipsychotics. For example, the CATIE study did not find any significant differences in effectiveness between perphenazine and SGAs apart from olanzapine, which had the lowest rate of discontinuation. The CUtLASS study also highlighted that there was no disadvantage in quality of life, symptoms or cost of care in using FGAs rather than SGAs (other than clozapine). Such studies have seriously challenged the results of many industry-sponsored efficacy studies, including RCTs. By contrast, the EUFEST study of first-episode patients concluded that response and remission was higher for most SGAs compared with the FGA haloperidol. In light of this inconsistency, debate on what predicts treatment response and variation in practice continues. This confusion may contribute to the apparent gap between theory and practice, fed also by the concern that interventions proven to be efficacious may not always have been found to be effective.

The present study, therefore, is an attempt to include a more representative sample from a real-world setting. It set out to examine the association between discharge variables (correlates) and prescribed routes and types of antipsychotics and then correlates of hospitalisation by following the same cohort for two years. This two-year follow-up also provided the opportunity to comment on the effectiveness of treatment with different antipsychotic types by using rehospitalisation as an outcome—an important marker of relapse.

This study cohort with 60% of Māori also provided the opportunity to comment on some ongoing concerns regarding the high rate of compulsion and hospitalisation for the indigenous population of NZ. Reassuringly, it did not find any association between patient demography and compulsion rate. Except for clozapine, the prescribed antipsychotic pattern was not significantly associated with demography. However, given the rising concern about metabolic syndrome in this group of patients, the prominence of olanzapine is a concern, and in contrast to recent guidelines advising against olanzapine as first-line (RANZCP 2016, PORT 2010). Further examination of prescribing patterns in a few years' time would be worthwhile in view of newly published guidelines following the publication of the CATIE and CUtLASS studies in 2005 and 2006.

Even though in this cohort the rate of clozapine use was lower than recommended, the rates for Māori were higher than for non-Māori and were closer to the recommended best practice. This study was not able to identify the reasons for this variation in the absence of baseline information about the chronicity of illness and socio-economic differences. The possibility of genetic variation in the pathogenesis of disease or treatment response would be an important area to visit for future research, in addition to examining sociocultural factors. Despite ongoing issues with adherence and some promising literature regarding better outcome with LAIs, LAI monotherapy is still low in this

cohort. This is a concern but could be due to the ongoing recommendation to consider LAIs only in the case of non-adherence issues unless the patient prefers them. In contrast, despite guidelines recommending monotherapy, many patients, particularly those subject to compulsion, received more than one antipsychotic. This is in alignment with international studies and is not surprising, but worthy of further exploration in the absence of convincing evidence to support such a practice.

The significant variations in CPZEs associated with the different types and routes of antipsychotics support the existing concerns: whether comparison of structurally diverse ranges of compounds with distinct neurochemical and pharmacokinetic properties could lead to over- or under-estimation of equivalent dosages.

In summary, though, the overall adherence to clinical guidelines (dosage of antipsychotics, emphasis on oral preparations) is reassuring and the deviation from guidelines (polypharmacy, low clozapine prescription) is consistent with overseas literature.

In this study, the majority of rehospitalisations occurred within 12 months. This highlights the importance of offering intensive follow-up immediately following discharge to those vulnerable to relapse and rehospitalisation. Service providers should be encouraged to invest specifically in the first year for ensuring treatment adherence and intensive psychosocial intervention, to facilitate recovery and to reduce the rate of relapse. Further research specifically focusing on identifying patient and illness factors during this time period would also facilitate development of appropriate service provision to reduce the rehospitalisation rate. The lower rehospitalisation rates in this study for those with a longer index admission need further attention in view of the trend of shorter hospital stays. Even though rehospitalisation rates and duration were generally similar

between groups receiving different antipsychotics, clozapine was associated with better outcome, which is reassuring and consistent with overseas findings.

Further research focusing on identifying baseline patient and illness factors, with a specific focus on comorbidities, would be helpful to address the reason for increased use of clozapine in Māori and the reason for lower hospitalisation rates for those with longer index admissions. The risk of relapse and the need for rehospitalisation, the most costly treatment alternative for schizophrenia and related disorders, could probably be lessened by employing strategies derived from different types of studies with longer follow-up periods, in addition to RCTs.

Clearly, in view of the number of unexplained findings for patients with schizophrenia and related disorders, more research in this area would be important and potentially helpful. A search for robust predictors would help to develop appropriate treatment for specific subgroups and would contribute significantly to our understanding of the pathogenesis of schizophrenia and related disorders.

APPENDIX: JOURNAL ARTICLE

Short Communication

Does Previous Admission History Predict Risk of Rehospitalisation in Schizophrenia and Related Disorders?

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Abstract

Aim: To examine the association between the number and duration of previous admissions and later rehospitalisation in patients with schizophrenia.

Method: Retrospective data on previous admissions were collected for a cohort treated in three New Zealand public hospitals during 2009-2011. The total cohort (n=451) was divided into groups according to number of admissions and time spent hospitalised in the previous two years. The subsequent two year hospitalisation records were then compared between groups.

Result: Analysis found no significant associations between rehospitalisation rates and number or duration of previous admissions (hazard ratios 0.92-1.57; p values 0.06-0.79).

Conclusion: Neither number nor cumulative duration of previous hospitalisations significantly predicted rehospitalisation risk.

INTRODUCTION

Hospitalisation for relapse in schizophrenia and related disorders is generally considered detrimental to well-being and is a costly treatment option [1]. Many variables, including previous admission history, have been reported to predict readmission [1-6]. For example, an Australian study [6] examined the rate of rehospitalisation for schizophrenia, bipolar disorder and depression over 5 years, highlighting the number of prior admissions as a predictor of both readmission rate and duration. Additional factors identified as predictors of rehospitalisation include length of stay, illness severity, substance abuse, personality disorder, medical comorbidity, male gender, unemployment, involuntary first admission, and limited access to follow-up care and community support [7, 8]. Hospital admissions also have become briefer since deinstitutionalization and the evolution of community based psychiatric care [9, 10].

We previously reported the correlates of rehospitalisation for schizophrenia or related disorders in a two year follow-up study [11]. The present report uses the same cohort to examine the association between number and duration of previous admissions and subsequent rehospitalisation.

METHOD

Study Design

We examined the clinical records of an unselected series of 451 inpatients from three New Zealand (NZ) public hospitals with index discharge diagnoses of schizophrenia and related disorders between July 2009 and December 2011. The cohort has been described in detail [11,13].

Most studies report average hospital stays ranging between 15-30 days [9, 12] and a median of one readmission [14,15]. Our study [13] of this same cohort showed a mean length of stay of 26 days, 61% spending between 1 and 21 days. Accordingly, we divided the cohort into two sets of three groups, the first set according to the number of previous admissions (none, 1-2, or ≥ 3) in the preceding two years (2007-2009), the second set according to the total duration of hospitalisation during this time (none, <3 weeks, and ≥ 3 weeks). These divisions were considered to be clinically meaningful, and resulted in groups with adequate numbers for statistical comparison.

The analysis then skipped the index admission phase (shared by all), and examined the relationship of each of the

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three groups to subsequent hospitalisation over two years, until December 2013. The data on hospitalisation were extracted from the Programme for the Integration of Mental Health Data, a NZ Ministry of Health collection of psychiatric service activity and outcomes database. Details about this dataset have been described elsewhere [11,13]. Ethical approval was granted by the Northern Y Ethics Committee (NTY/12/exp/026).

Participants

The study cohort comprised patients aged 18-75 years, with discharge diagnoses of schizophrenia or related disorders (International Classification of Disease, version 10, F20-29), given by responsible clinicians during the index admission. Exclusion criteria were intellectual disability, psychoses due to substance abuse, general medical or other organic causes.

Available variables

Age, gender, ethnicity, voluntary/informal legal status, duration of admissions, and treating clinician characteristics were recorded at the time of the index discharge. Antipsychotics prescribed at that time were divided into the following groups for analysis: first vs. second generation antipsychotics (irrespective of route), oral vs. long-acting injectable (LAI) antipsychotics, and clozapine vs. no clozapine. The LAI group also included patients receiving additional oral medication. Antipsychotic dosages were converted to chlorpromazine equivalents for analysis (100-300, 301-600 and >600mg/day according to dose ranges mentioned in schizophrenia guidelines [14].

Data analysis

The relationships between the number and duration of previous admissions and later rehospitalisation were explored using the Pearson chi-square test, together with univariate and multivariate proportional hazards regression analyses. The number and length of previous admissions were considered as main predictors, and the multivariate analyses included adjustments for demographic variables, types, routes and chlorpromazine equivalent dosages of antipsychotics, length of index admission, compulsory admission status, and clinician characteristics [13]. Data were analysed using SPSS (PC version 20.0). P values <0.05 were considered significant.

RESULTS

Of the 451 patients, 64% were male, and 60% were Maori (the indigenous Polynesian population of New Zealand). Most patients (64%) were between the ages of 25-49, with 16% over 50 and 3% over 65.

Schizophrenia was the most common diagnosis (76%), followed by schizoaffective disorder (20%). The remaining 4% were diagnosed with brief psychotic disorder, acute and transient psychotic disorder, delusional disorder or psychotic disorder NOS.

At the time of index discharge more than half (n=258, 57%) of patients were taking only oral antipsychotics, including clozapine. 43% (n=193) were receiving LAIs. Most patients (n=324, 72%) were prescribed SGAs, 16% (n=73) FGAs, the remainder (12%) receiving a combination of both. Clozapine was prescribed to 90

(20%) patients (Table 1). Further details of this analysis have been described previously [13].

The two-year follow-up data (Table 2) showed that of 158 patients previously hospitalized before their index admission, 44% (69) were re-hospitalized within two years; exactly the same proportion applied to patients with no previous admissions (n=130/293). Likewise, no statistically significant differences in rehospitalisation rate were observed between patient groups with shorter or longer durations of index admission.

As shown in (Table 3), both uni- and multivariate analyses failed to detect significant associations between the numbers and duration of previous admissions and rehospitalisation rate. Multivariate analysis showed a near significant (p=0.06) trend toward increased rehospitalisation risk for those with 3 or more previous admissions. When comparisons of antipsychotic medication variables (oral vs. LAI, FGA vs. SGA, clozapine vs. no clozapine) were considered, multivariate analyses returned similar non-significant results (data not shown).

DISCUSSION

This study explores the association between number and duration of previous admissions and subsequent rehospitalisation rate for a cohort with schizophrenia and related disorders. Our findings appear inconsistent with studies reporting that frequent previous admissions predict subsequent hospitalisation [1, 5, 15-17]. On the other hand, studies that have taken into account individuals' readmission risk [18,19] have noted that number/duration of hospitalisations did not necessarily influence readmission rate. Another study [20], which considered sociodemographic and clinical factors, also failed to show an association between previous admissions and rehospitalisation rates. Individual vulnerability is important to consider and may facilitate better management of this heterogeneous disorder.

The study limitations are those inherent for observational (non-interventional) studies (Tables 2, 3). The present cohort was compiled from discharge data of three hospitals and the resulting unselected sample allowed inclusion of patients with a variety of comorbidities. Although most patients had chronic schizophrenia, we did not differentiate between first episode and chronic illness. This may influence outcome due to the fact that most readmissions occur in the first two to five years, and over

Table 1: Antipsychotics prescribed on discharge.

Class	
FGA	73 (16%)
SGA	324 (72%)
Both	54 (12%)
Route	
Oral	230 (51%)
LAI	69 (15%)
Oral plus LAI	124 (28%)
Two oral	28 (6%)
FGA: First Generation Antipsychotics	
SGA: Second Generation Antipsychotics	
LAI: Long Acting Injectables	

Table 2: Rehospitalisation rate by number and duration of previous admissions.

Patient groups	Rehospitalisation, n (%)
Number of previous admissions	
No previous admission (n=293)	130 (44%)
1-2 previous admissions (n=106)	43 (41%)
≥3 admissions (n=52)	26 (50%)
Total duration of previous admissions	
< 3 weeks (n=68)	31 (46%)
≥ 3 weeks (n=90)	38(42%)
1-2 vs. >3 previous admissions: Pearson's chi-square=1.28, df=2, p=0.53	
< 3 vs. ≥3 weeks duration of previous admissions: Pearson's chi-square=0.2, df=2, p=0.90	

Table 3: Rehospitalisation risk analysed by number and duration of previous admissions.

Patient groups	HR (95% CI) univariate analysis	P value	HR (95% CI) multivariate analysis	P value
1-2 vs. zero admissions	0.86 (0.61-1.22)	0.39	0.90 (0.64-1.29)	0.59
≥3 vs. zero admissions	1.23 (0.81-1.87)	0.34	1.57 (0.99-2.49)	0.06
brief (< 3 weeks) vs. zero admission	1.04 (0.70-1.54)	0.84	1.07 (0.71-1.61)	0.75
long (≥3 weeks) vs. zero admission	0.92 (0.64-1.32)	0.65	1.05 (0.72-1.55)	0.79

HR: Hazard Ratio
 CI: Confidence Interval
 Multivariate analysis includes adjustments for age, gender, ethnicity, compulsory status, duration of index admission, antipsychotic class (FGA vs. SGA), Chlorpromazine equivalent dose, country of training and number of years in practice of the treating doctor,

time readmission rates decline [20]. Another limitation of our analysis is that information on medication adherence and other potentially relevant baseline characteristics (substance abuse, socioeconomic status, marital status) was not available.

The cohort was selected from discharge data, therefore apart from gender and ethnicity, other baseline characteristics (compulsory admission, prescribed antipsychotics, duration of admission) were noted for the index admission only. While all of the 451 patients were hospitalised, this study considered only rehospitalisation in the two years following the index admission as outcome and the number and duration of admissions in the two years prior to the index admission as predictors. Considering rehospitalisation, the data collection period of 4 years is relevant for a chronic illness like schizophrenia. The patients hospitalised in the follow-up period therefore were effectively in their third or fourth year of follow-up. Previous studies have demonstrated that most rehospitalisation occur within the first 6-12 months after inpatient discharge [11, 21, 22]. That difference may help explain why some of the findings in this paper differ from our earlier analysis of rehospitalisation in the same cohort [11]. Our previous publication [11] concluded shorter duration of index hospitalisation is associated with increased rehospitalisation rate within two years of discharge.

CONCLUSION

This "real life" observational study combining data from a hospitalised cohort in three different geographical areas did not find significant associations between number or duration of previous admissions and subsequent rehospitalisation rate in schizophrenia.

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