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RESEARCH ARTICLE

Patterns of clozapine prescribing in a mental health service in New Zealand

Jeff Harrison · Minna Janlöv · Amanda J. Wheeler

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Abstract *Objective* To describe clozapine prescribing in a mental health service in Auckland, New Zealand and compare it with national and international treatment guidelines. *Setting* A large public mental health service for adults in Auckland, New Zealand. *Method* A retrospective cross-sectional study of all adult outpatients and stable inpatients being treated with clozapine on 31st March 2007 in one mental health service in Auckland, New Zealand. Data on patient characteristics, diagnosis, duration of illness, number of hospitalisations, legal status relating to their treatment, living situation, marital status and occupational activity were recorded from case notes. Data collected on clozapine included date of initiation, dose and duration of treatment. Prior antipsychotic use and information on all other psychotropic drugs prescribed was also collected. Data were entered into a custom-designed Microsoft Access database and analysed using SPSSv15.0. *Main outcome measures* Clozapine prescribing patterns and concordance with best practice recommendations for clozapine use. *Results* 402 adult mental health outpatients and stable inpatients were eligible for inclusion. The mean daily dose of clozapine was 383 (SD 166) mg. For those first presenting after universal government funding, the mean time between presentation and initiation of clozapine, was 2.8 (SD 1.9) years, compared to 5.7 (SD 3.3) years prior to funding. Of those presenting after universal government funding, approximately two-thirds (69.0%) had $\leq$2 trials with other antipsychotics prior to commencing clozapine; of whom the majority (62.0%) received only second-generation antipsychotics (SGA). Both the number of antipsychotic agents trialled and the time to clozapine initiation has fallen since government subsidy was introduced in 1999. Based on a analysis of annualised hospitalization rates, it appears that shortening the delay to receiving clozapine leads to fewer hospitalisations in this treatment-resistant population, although this did not achieve statistical significance in our study. *Conclusions* Contemporary management of patients with treatment resistant schizophrenia in New Zealand is broadly in line with national and international best practice guidelines. There is some evidence, based on hospitalisation rates, to support the assertion that shorter delays in accessing clozapine leads to better outcomes. This needs further evaluation using measures of clinical outcome including objective measures of functioning.

Keywords Clinical audit · Clozapine · Guidelines · New Zealand · Prescribing · Schizophrenia

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Impact of findings on practice

- Early recognition of treatment resistance and use of clozapine appears to be associated with reduced hospitalisation and, if confirmed, supports a change in practice.

- Treatment resistant schizophrenia appears to be successfully managed with clozapine monotherapy in the majority of cases.
- Contemporary management of treatment resistant schizophrenia in New Zealand is in line with national and international best practice recommendations.

Introduction

Schizophrenia is a chronic, serious and disabling mental health condition. People with schizophrenia frequently suffer significant problems with social and occupational functioning because of either positive symptoms (hallucinations, delusions, disorganised behaviour and thoughts), negative symptoms (such as amotivation and apathy) or cognitive symptoms (problems with attention or with working memory). The lifetime prevalence of schizophrenia is approximately 1.0% [1].

The goal of treatment for schizophrenia is both the relief of symptoms and the recovery of social and occupational functioning. Optimal treatment involves a range of pharmacological, psychological and psychosocial interventions [2–4]. Antipsychotic medication plays a central role in the management of symptoms, thereby supporting functional recovery. Historically treatment was initiated with agents such as chlorpromazine and haloperidol, now referred to as first-generation antipsychotics (FGAs). FGAs have a high incidence of problematic adverse effects such as extrapyramidal movement effects and hyperprolactinaemia. New agents with a lower incidence of these side-effects and evidence of increased efficacy have now become available [5]. These agents are termed second-generation antipsychotics (SGAs). Increased availability of SGAs such as risperidone, olanzapine and amisulpiride has resulted in a move away from FGAs and to earlier use of SGAs [2–4].

Approximately 30% of patients with schizophrenia do not respond, or only partially respond, to standard antipsychotic (FGA or SGA) treatment [6]. This is commonly termed treatment-resistant schizophrenia (TRS). TRS is defined as the persistence of symptoms, together with poor social and/or occupational function, despite an adequate trial of at least two antipsychotics. Clozapine is an SGA agent used in the management of treatment-resistant schizophrenia, having shown significant efficacy advantages over other first- and second-generation antipsychotics [7–10]. Like other SGAs, clozapine has a lower risk of extrapyramidal effects compared to FGAs. However, clozapine has the potential to cause serious acute and chronic side-effects including agranulocytosis, neutropenia, myocarditis and cardiomyopathy, and constipation including bowel obstruction. Clozapine is also associated with weight gain and metabolic changes in lipid metabolism and glucose tolerance requiring careful monitoring and follow up [11, 12]. Due to these often rare but important adverse effects, its product licence in New Zealand, as in most other countries, restricts its use to those patients with TRS [13, 14].

In addition to the immediate need to control symptoms that are affecting a patient's ability to function, there is evidence that the time taken to achieve a treatment response in schizophrenia is related to long-term clinical outcome, with those stabilised earlier having better outcomes [15]. Practice guidelines to improve the treatment of schizophrenia have been developed in many parts of the world. A recent World Health Organisation/World Psychiatric Association (WHO/WPA) review of these guidelines, [16] identified three high quality guidelines from the National Institute for Health and Clinical Excellence [17], the American Psychiatric Association [2], and the Royal Australian and New Zealand College of Psychiatrists [3]. Each of these guidelines, along with other well-recognised national and international guidelines from around the world, recommend that patients should be considered for treatment with clozapine as soon as there is documented failure to respond to treatment with at least two adequate trials of antipsychotics, at least one of which should be an SGA [18–21]. However, each of the three guidelines cited above define an adequate trial differently, with treatment durations ranging between 4 and 6 weeks (APA) and 6–8 weeks (NICE and RAZNCP). For the purposes of this study an adequate trial is defined as at least six weeks treatment with an adequate dose (30–600 mg chlorpromazine equivalents/day).

In addition to those with TRS, clozapine is recommended in some guidelines for use in patients who experience neuroleptic malignant syndrome or tardive extrapyramidal side-effects on other antipsychotics [19]; who are deemed to be at high-risk of suicide [3, 18, 19, 21]; or who exhibit persistent aggressive behaviours [18, 21]. It is important to note that clozapine is licensed for suicidal ideation only in the USA.

Although clozapine has been registered in New Zealand since early in 1993, its use—along with other SGAs—was somewhat limited until February 1999. Prior to that date, patients could be treated in the community with clozapine, but only where funding was diverted from funding intended for inpatient treatment. As a result, access to these treatments varied throughout the country and was dependent on decisions made on a patient-by-patient basis by different health boards. In February 1999, in an attempt to improve patient access, full government prescription subsidy was extended to cover the use of clozapine and other SGAs in the community.

Aim

The aim of this study was to describe the prescribing of clozapine in a cohort of stable mental health patients under the care of the mental health services of a large public mental health service in Auckland, New Zealand.

Method

The study was a retrospective, cross-sectional study of all adult mental health patients prescribed clozapine under the care of a large public secondary care mental health service, as at 31st March 2007. The service is part of the largest District Health Board (DHB) in New Zealand, covering a large area and serving a population of approximately half a million people; approximately 12% of the population of New Zealand [22]. In New Zealand, the overwhelming majority of psychiatric services are provided through the public sector. There is only one private psychiatric hospital and whilst a minority of patients with serious mental illness may see psychiatrists or psychologists privately all acute and crisis care is delivered through the public system.

Patients were identified from the Clozapine Monitoring Service (CMS) database managed by Novartis NZ Ltd. The Novartis brand of clozapine was the only product available in New Zealand as at 31st March 2007 and registration with the CMS was mandatory for all patients prescribed clozapine, irrespective of whether care was delivered in the public or private system.

Patients excluded from the audit were those inpatients in the first 18 weeks of clozapine treatment, those inpatients who were admitted acutely unwell (e.g. following a period of non-compliance), those who moved out of the DHB area, and those who died.

Data was collected from patient files, including both paper and electronic records. Information was extracted from medical and nursing assessments, clinical summaries, case reviews and discharge summaries, medication charts and copies of prescriptions. Data was entered into a custom-built Microsoft Access database. A data collection manual was produced and specific training on data collection procedures was provided. Initially data collection was supervised to ensure that data was collected consistently. In addition, weekly review was carried out with researchers to resolve problems with missing or contradictory information. Data cleaning and supplementary data collection to collect missing data was undertaken.

Data collected included sociodemographics, clinical characteristics and pharmacological treatments. Sociodemographic data included patient demographics (gender, age and ethnicity), occupational activity, relationship status and living arrangements. Data collected on clinical characteristics of the patients included their diagnoses (Axis I-III of the DSM-IV [1]), year of first presentation of a mental health problem to any treatment provider, number of psychiatric hospitalisations and their legal status under the Mental Health Act [23]. The patient's psychiatric admission history was verified with the National Health Events Database, accessed via the DHB.

Data on medication included the date of initiation, dose of clozapine on 31st March 2007, and the use of other antipsychotics both currently and historically i.e. number and type (SGA, FGA) of trials prior to starting clozapine. Where another antipsychotic was co-prescribed with clozapine the start date and reason for co-prescription was also recorded. Details of other co-prescribed medications (antidepressants, mood-stabilisers, side-effect medication, sedatives/hypnotics) were also collected, including whether they were prescribed regularly or "if required" (prn). The data on psychotropic co-prescribing is not reported in this paper.

All doses were recorded as total daily doses. Patients that had discontinued clozapine for longer than 12 weeks before being re-initiated were considered to have undergone a failed trial with another agent and the new clozapine start date was recorded. As described above, an antipsychotic trial was defined as at least 6 weeks of therapy with an adequate dose of antipsychotic (defined as 300–600 mg chlorpromazine equivalents/day) [24]. If the same antipsychotic was used on more than one occasion only one trial of that particular antipsychotic was counted.

Given the international consensus, reflected in the guidelines discussed above and the evidence of better patient outcomes with earlier symptom control, this paper reports on the gap between first presentation and initiation of clozapine. Data on the number of antipsychotics trialled prior to clozapine use is reported. Comparison of these data with the published literature and with best practice guidelines is discussed. Finally, the effect of the time to treatment with clozapine in patients with TRS on admission rates prior to and after clozapine inititation is explored.

Data was analysed using SPSS software (SPSS 15.0; SPSS Inc. Chicago, IL. USA). Frequency tables were constructed to provide counts of categorical data and descriptive analysis were undertaken for all data. Statistical differences between groups were investigated using χ^2 tests, *t*-tests and ANOVA, as appropriate. Correlations were explored using Pearson or Spearman correlations, as appropriate. In order to explore the influence of different variables on hospitalisation rates, as a marker of patient outcome, a logistic regression model was built using increase or decrease in hospitalisation rate as the dichotomous dependent variable. The independent variables

included in the model were age at first presentation, ethnicity, gender, gap between first presentation and initiating clozapine and admission rate prior to receiving clozapine. Statistical significance for all tests was defined as a p value less than or equal to 0.01 in order to correct for multiple testing.

The study received approval from the New Zealand Health and Disability Ethics Committees Northern X Regional Ethics Committee (Ref: NTX/07/79/EXP).

Results

There were 461 patients registered with the Clozapine Monitoring Service in March 2007. 59 patients were excluded: three because they were hospitalised and acutely unwell; one who was hospitalised and in the first 18 weeks of clozapine treatment; 25 who were not taking clozapine as at 31st of March 2007; 27 who moved out of the DHB area; and three who were deceased. A total 402 patients were included in the analysis: 343 outpatients and 59 stable inpatients.

Sociodemographics

Table 1 describes the sociodemographics for this cohort. The mean age was 39.7 years (range 19–84 years) and nearly three-quarters (72.8%) of patients were male. More than half of the cohort self-identified as being of New Zealand European ethnicity (56.7%) and one-quarter (23.6%) identified themselves as New Zealand Māori (indigenous people).

Approximately three-quarters (72.4%) of the cohort were single and 43.0% had no form of regular occupational activity. Nearly two-thirds (63.9%) did not live independently, the majority either living with relatives (27.6%) or in supported accommodation (21.4%).

Table 1 Patient sociodemographics

$N = 402$	Number of patients (%)
Gender	
Male	292 (72.6%)
Female	110 (27.4%)
Age (years)	
Mean(SD)	39.7 (11.47)
Median (range)	38 (19–84)
Ethnicity	
European	228 (56.7%)
Maori	95 (23.6%)
Pacific nation	54 (13.4%)
Asian	17 (4.2%)
Other	8 (2.0%)
Relationships	
Single	291 (72.4%)
Living as married	26 (6.5%)
Divorced/separated/widowed	85 (21.1%)
Occupational activity	
Employment full-time	39 (9.7%)
Part-time occupational activity[a]	104 (25.9%)
Student	9 (2.2%)
Homemaker	4 (1%)
Retired	15 (3.7%)
Other (inpatient/prison)	58 (14.4%)
None	173 (43.0)
Living situation	
Independent	145 (36.1%)
Alone	76 (18.9%)
With partner	23 (5.7%)
With others	46 (11.4%)
With relatives	111 (27.6%)
Supported accommodation[b]	86 (21.4%)
Other[c]	60 (14.9%)

[a] Part time occupational activity includes: part time employment, supported employment or any other occupational activity. [b] Supported accommodation includes; a group home situation shared by mental health patients in which the placement is determined by mental health services. [c] Other includes: prison, hospital, forensic unit

Clinical characteristics

The mean time since first contact with a treatment service was 17.7 years. The overwhelming majority (96.5%) of patients had a diagnosis of schizophrenia or schizoaffective disorder. The remaining 3.5% of patients were being treated primarily for bipolar disorder and six patients for other disorders (Table 2). Nearly a quarter (22.9%) of patients had a co-morbid Axis I disorder (psychiatric disorder), two-thirds of whom (59 of 92) had a substance-related disorder. Nearly one-third of patients (31.8%) had a co-morbid Axis II diagnosis (personality disorder and/or intellectual disability) of which the overwhelming majority (113 of 128) had personality disorders. Over half (53.5%) of the cohort had physical health problems (Axis III co-morbidity), most commonly gastrointestinal disorders (22.1%) such as constipation and gastro-oesophageal reflux.

The majority (81.6%) of patients had multiple previous mental health admissions. The average number of previous admissions was eight (SD: 9, median: 6, range: 0–87). Just over one-third of patients (34.6%) were being compelled to take treatment under the provisions of the Mental Health (Compulsory Assessment and Treatment) Act [23].

Table 2 Clinical characteristics

Duration of illness (years)[a]	402
Mean (SD)	17.7 (9.83)
Median (range)	16 (1-52)
Age at first presentation	
Mean (SD)	22.6 (7.30)
Median (range)	21 (8-71)
Major Axis I diagnosis	402
Schizophrenia/schizoaffective	388 (96.5%)
Bipolar disorder	8 (2.0%)
Other[b]	6 (1.5%)
Comorbidity Axis I	92 (22.9%)
Substance related disorder	59 (14.7%)
Anxiety disorder	13 (3.2%)
Mood disorder	7 (1.7%)
Psychotic disorder	1 (0.2%)
Other[c]	12 (3.0%)
Comorbidity Axis II	25 (6.2%)
Personality disorder	10 (2.5%)
Intellectual disability	15 (3.7%)
Comorbidity Axis III	215 (53.5%)
Cardiac	39 (9.7%)
Neurological	27 (6.7%)
Endocrine	59 (14.7%)
Respiratory	43 (10.7%)
GIT	89 (22.1%)
Other[d]	78 (19.4%)
Previous psychiatric admissions	402
0	20 (5.0%)
1	54 (13.4%)
2–5	130 (32.3%)
6–10	106 (26.4%)
11–20	70 (17.4%)
>20	22 (5.5%)
Treated under mental health act	139 (34.6)

[a] Time elapsed between first presentation to a treatment provider and 31-March-2007

[b] *Other*: delusional disorder, depression, dementia, substance-induced psychosis, post traumatic stress disorder (PTSD)

[c] *Other*: cognitive disorder: dementia. Pervasive development disorder, somatoform, paedophilia

[d] *Other*: oncological, skin or other physical disorders

Clozapine prescribing

The mean daily dose of clozapine was 390 mg (SD: 162.4, range 50–900 mg/day). The use of a second antipsychotic was uncommon (10.4%). In the majority of cases ($n = 37/43$) the documented reason for prescribing a second agent was to augment treatment. Risperidone was the agent most commonly used for augmentation (Table 3).

235 patients (58.5% of the cohort) presented to mental health services prior to clozapine being licensed in New Zealand in 1993. A further 96 patients (23.9% of the cohort) presented between 1993 and 1999 when, as described above, clozapine was only available for use at the discretion of individual health boards. Seventy-one patients (17.7% of the cohort) presented since government funding for community became available in 1999. Figure 1 shows the time from first presentation to clozapine initiation for those patients who presented after 1990, thereby including data on a small number of patients (15 patients, 3.7%) who were treated with clozapine prior to it being licensed in 1993. There is a statistically significant correlation ($p < 0.01$, 2-tailed Spearman correlation) between the year of first presentation and the delay before starting clozapine for all groups, including those patients whose first presentation to mental health services was after 1999, when clozapine became widely available and nationally funded. This indicates a trend towards reduced time before initiating clozapine in patients presenting more recently.

All patients in this cohort received at least one trial with an adequate dose of another antipsychotic prior to starting clozapine. The mean number of trials was 3.5 (SD = 1.5; median = 3; range = 1–10). Seven patients (1.7%) received only one trial with another antipsychotic before initiating clozapine, 120 patients (29.9%) received two antipsychotic trials, the remaining 275 patients (68.4%) received three or more trials prior to receiving clozapine. In the cohort of patients who presented on or after the funding change in 1999 ($n = 71$), 2 patients (2.8%) received only one antipsychotic agent prior to initiating clozapine, 45 patients (63.4%) received two trials pre-clozapine and 24 patients (33.8%) received three or more.

Figure 2 shows the mean number of antipsychotics and the mean number of FGA, SGA and depot antipsychotic agents per patient grouped by the year of first presentation to a treatment service for those patients presenting after 1990. There is a statistically significant correlation between year of first presentation and the total number of antipsychotic trials, as well as FGA, SGA and depot antipsychotics trialled per patient ($p < 0.01$ for all comparisons, 2-tailed Spearman's correlation). This reflects a shift towards fewer antipsychotics trialled and also reflects a greater likelihood of using two trials of SGAs prior to initiating clozapine in patients presenting more recently.

In patients presenting since 1993 total and annualised mental health hospitalisation rates pre- and post-clozapine were calculated. Patients were included in the cohort if they had a pre-clozapine hospitalisation, had been on treatment with clozapine for ≥3 years (thereby allowing a reasonable period in which hospitalisations may accumulate), and had

Table 3 Antipsychotic treatment characteristics

	Number of patients (%)	Mean daily dose(SD) mg/day	Median daily dose (range) mg/day
Clozapine	402 (100%)	390 (162.4)	350 (50–900)
Concomitant antipsychotic treatment	42 (10.4%)		
Risperidone	24 (6.0%)	3.0 (2.3)	2.0 (1–10)
Quetiapine	8 (2.0%)	296.9 (264.7)	200 (75–800)
Haloperidol	7 (1.7%)	3.4 (1.5)	4 (1–5)
Others[a]	3 (0.7%)	–	–
Antipsychotics trialled prior to clozapine	**Number of patients (%)**	**Mean number of trials (SD)**	**Median number of trials (range)**
Oral first-generation (FGA)	295 (73.4%)	1.54 (1.29)	1 (0–5)
Oral second-eneration (SGA)	271 (67.4%)	1.19 (0.99)	1 (0–4)
Depot antipsychotics	230 (57.2%)	0.81 (0.83)	1 (0–3)
All antipsychotics	402 (100%)	3.53 (1.55)	3 (1–10)

[a] methotrimeprazine, risperidone long-acting injection, trifluoperazine

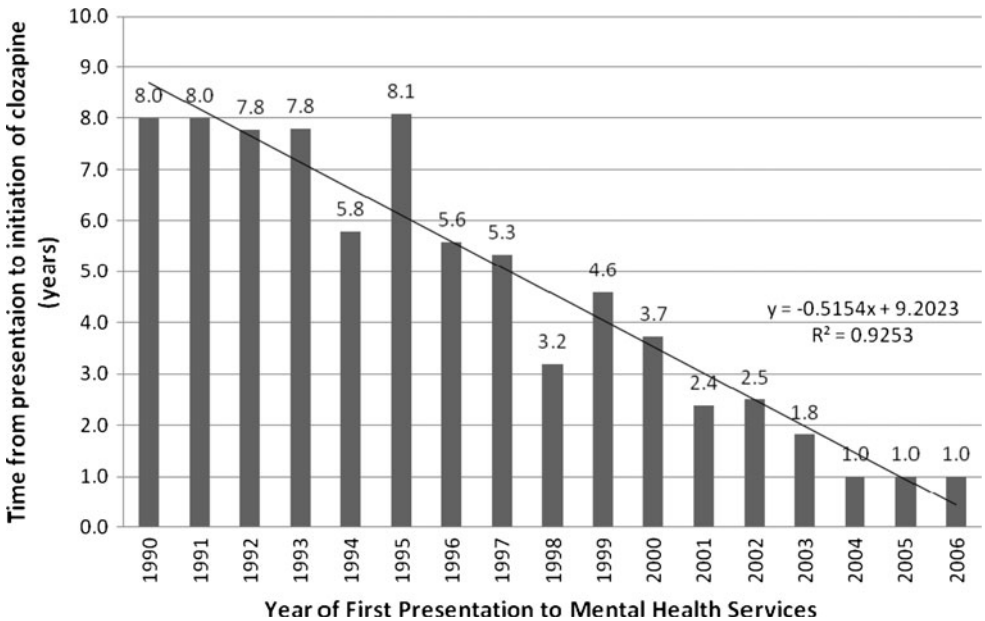

Fig. 1 Mean time to clozapine initiation by year of first presentation to treatment service

been discharged from hospital since starting clozapine. Of 97 evaluable patients, 79 (81.4%) had a reduction in hospitalisations, 17 had an increase and one patient had no change. The average number of hospitalisations pre-clozapine was 3.4 (SD = 3.2; median = 2; range = 1–20), reducing to 0.92 post-clozapine (SD = 1.4; median = 0; range = 0–8). The change in both total number and annualised hospitalisation rates was statistically significant ($p < 0.01$, Wilcoxon sign rank test). The mean relative reduction in hospitalisation rate was 45.8% (95% CI 23.5–68.1). No correlation was demonstrated between the delay from time of first presentation to initiation of clozapine and the reduction in hospitalisation rate ($p = 0.293$, Spearman).

Logistic regression was used to investigate the influence of age at first presentation, ethnicity, gender, gap between presentation and initiating clozapine and admission rate prior to receiving clozapine on a dichotomous dependent variable expressing an increase or decrease in hospitalisation rate. Whilst none of these variables reached our a priori significance threshold of $p < 0.01$ there did appear to be a relationship between a decrease in hospitalisation and age at first presentation ($p = 0.057$) and earlier initiation of clozapine ($p = 0.040$).

Discussion

This study presents a comprehensive review of the use of clozapine in a large cohort of community patients and stable inpatients.

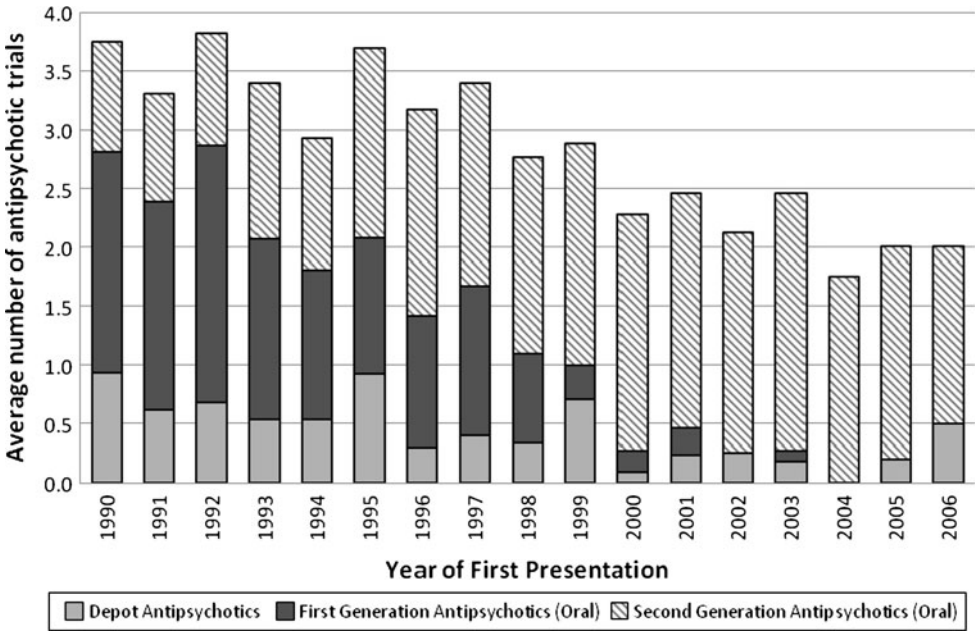

Fig. 2 Number of antipsychotics trialled prior to initiation of clozapine

The study limitations include those inherent in retrospective studies which rely on the accuracy and completeness of information recorded in clinical documents. In order to minimise this risk of reporting bias, data was collated from multiple sources. An exhaustive search of paper and electronic clinical notes as well as medication charts, monitoring databases and correspondence such as clinic letters was undertaken. Data was collected using a standardised procedure and coded according to a defined protocol. Extensive data cleaning was undertaken to minimise the amount of missing data and to resolve discrepancies between sources.

The New Zealand health system provides comprehensive government-funded health services, and therefore has low rates of private medical insurance and hence low rates of private medical care compared with other countries. The likelihood of our study having failed to identify patients suitable for inclusion is low. In addition, there was no loss to follow up. The whereabouts of all patients included in the cohort were accounted for at the ned of the study, including those who moved out of the area.

It is unclear whether our findings are applicable to similar outpatient and stable inpatient settings in New Zealand. The findings pre-1999 are unlikely to be generalisable to NZ as a whole due to the differences in availability of clozapine in the mid-to-late 1990s. Whilst it might be believed, based on the now uniform funding environment and relatively small and cohesive psychiatrist workforce in NZ, that the data on prescribing patterns and hospitalisation from a contemporary cohort of patient in this study is more widely applicable this is not proven.

As would be expected, the overwhelming majority of patients in this clozapine treatment cohort had a diagnosis of schizophrenia or schizoaffective disorder. A significant number had a secondary axis I diagnosis and a substantial minority had co-morbid personality disorder.

In line with the findings of other studies, [25, 26] our cohort was predominantly male, now in later middle-age but first presenting in their late teens or early twenties. The cohort was predominantly single, living with relatives or in supported accommodation and the majority were not in employment or undertaking other occupational activity. This reflects the effect of schizophrenia on people's social and occupational functioning. A substantial number of patients were being treated under a compulsory treatment order (Mental Health Act 1992), reflecting the serious nature of their illness.

Again, as one would expect from the literature [27, 28], many patients also had physical health co-morbidity. The most common of these were gastrointestinal (22.1%), endocrine (14.7%), respiratory (10.7%) and cardiac (9.7%) disorders. This pattern of co-morbidity is consistent with the literature; constipation is a well recognised complication of clozapine treatment, [12] and type II diabetes, respiratory problems and cardiovascular disease are well described in patients with serious mental illness [29–31].

The mean duration of illness shows that, for the cohort as a whole, most had been unwell for a long time. The number of previous admissions reflects the fact that many patients with TRS have numerous relapses requiring hospitalisation. These findings are similar to studies in China and the UK [26, 32].

Clozapine is indicated for TRS, defined as non- or only partial response to adequate trials of at least two antipsychotics (at least one of which should be a non-clozapine SGA). In this study the mean number of antipsychotics given, with an adequate trial, was 3.5. This is in accordance with the findings of Taylor et al. [32]. Whilst in Taylor's study 90% had received an SGA before first use of clozapine, only two-thirds (67.4%) of the cohort in this study had received an SGA before commencing clozapine. This difference is attributable to our inclusion of older cases, where clozapine was started before SGAs were widely available (risperidone was registered in New Zealand in 1994, olanzapine in 1996 and quetiapine in 1997). When limiting the dataset to those presenting after 1993 the data shows 93.4% of patients received one or more SGA prior to commencing clozapine. The overwhelming majority of our cohort received two or more trials of antipsychotics before commencing clozapine (97.6%) however there was a clear relationship between year of first presentation and number of treatment trials before clozapine.

In this study a clear relationship can also be seen between year of first presentation and time delay before accessing clozapine, even in the cohort of patients first presenting to mental health services after the licensing of clozapine in NZ. The average delay in using clozapine has fallen from 5.7 years in those presenting before government funding was available to 2.8 in those presenting since 1999. This compares to a mean delay before starting clozapine of five years in the study by Taylor et al. although it should be noted that the UK cohort had a shorter mean duration of illness and describes an inpatient, rather than predominately outpatient, cohort [32]. In our study the mean delay for patients presenting between 2004 and 2007 is one year or less.

This reduction in the mean delay before treatment with clozapine is reassuring. There are likely to be many factors which explain this reduction. Firstly, the change in licensing status and the availability of government funding for clozapine may have increased access. However, there was no univariate association seen between licensing status/funding status and length of delay in starting treatment with clozapine in our study. This indicates a more complex series of drivers for change. Increased clinician experience with the drug, emerging clinical trial evidence and the publication of clinical guidelines encouraging earlier use may all have played a part. Our study is unable to explain the reasons but clearly demonstrates a reduction in the delay to treatment with clozapine in patients with TRS.

When current practice in this cohort of patients is compared with guideline recommendations, there appears to be good concordance. The majority of patients received only two trials of non-clozapine antipsychotics, usually SGAs, prior to initiation and the mean delay to clozapine has reduced. This practice is in line with the three dominant international guidelines identified by the WHO/WPA review [16].

The average daily clozapine dose prescribed for this cohort was 390 mg, ranging from 50 to 900 mg/day. This is in line with treatment recommendations [2–4], and also corresponds with the findings of other reviews of clozapine prescribing both in New Zealand and in Europe [33, 34]. The dose is slightly lower than that reported in a study of American and Australian clozapine use [35]. The mean dose was also significantly lower than that reported in a study of a forensic population in Australia [36].

Whilst we accept that hospitalisation rates are a crude measure of treatment effectiveness, in the absence of prospectively collected data on symptom, functional and social outcomes as part of regular clinical practice our analysis illustrates the significant effect clozapine has on quality of life by reducing hospitalisation rates. Whilst we were unable to demonstrate a significant association between a shorter delay in receiving clozapine treatment and better outcomesin terms of reduced hospitalisation rate, there is some evidence to support this view [9, 15, 36, 37]. With only 97 patients included in the analysis our study only had 30% power to demonstrate a correlation at the 0.05 level. Data from approximately 500 patients would be required in order to achieve sufficient statistical power to test such an association.

Conclusion

Clozapine prescribing in New Zealand broadly follows national and international guidelines. Since its introduction in the early 1990s there has been an appropriate reduction in the delay before accessing clozapine for this group of patients with poorly-responsive illness. This shift to earlier use has been accompanied by a fall in the number of unsuccessful antipsychotic trials prior to considering clozapine and by a widespread move towards the use of SGAs.

This data illustrates the effectiveness of clozapine in this difficult to treat group and reassures us that patients are accessing this effective treatment in a timely fashion.

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Conflicts of interest None.

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