Clozapine Use in First-Episode Psychosis:
The Singapore Early Psychosis Intervention Programme (EPIP) Perspective

Charmaine Tang, MBBS, MRCPsych[a,*]; Mythily Subramaniam, MBBS, MHSM[b]; Boon Tat Ng, MClinPharm[c]; Edimansyah Abdin, PhD[b]; Lye Yin Poon, BSocSci (Hons), MBA[a]; and Swapna K. Verma, MBBS, MD[a]

ABSTRACT

Objective: Early symptomatic response is pertinent in improving outcomes in first-episode psychosis. One of the ways in which this may be achieved is by reducing inappropriate delays in clozapine initiation. This study aimed to examine clozapine prescribing practices among clinicians by establishing the prevalence of clozapine use, identifying baseline clinical and demographic factors that were associated with clozapine use, examining outcomes in clozapine users versus nonusers, and identifying inappropriate antipsychotic prescription patterns prior to clozapine initiation.

Methods: A retrospective study including all consecutive patients who had presented to the Singapore Early Psychosis Intervention Programme (EPIP) from April 2001 to June 2012 was conducted. Clinical and demographic data were extracted from the EPIP database. Incident cases of clozapine users were identified, and additional treatment histories were obtained from medical records. In addition to descriptive statistics, multivariate analysis was performed to identify factors associated with clozapine initiation.

Results: Data from 1,603 patients were available for baseline analyses. Of these, 69 patients (4.3%) had been prescribed clozapine. Having a younger age at onset, lack of employment, a lower Global Assessment of Functioning disability score, and a higher Positive and Negative Syndrome Scale total score at baseline were factors associated with clozapine use. After adjustment was made for confounders, clozapine users were found to have attained similar rates of remission and recovery as patients who did not use clozapine. Clozapine initiation was delayed by a mean of 19.3 weeks (SD = 27.1; range, 0–117). Prior to commencing clozapine, 29.4% of patients had received antipsychotic treatments above maximum limits, whereas 75% of patients were prescribed ≥ 3 different antipsychotics (median = 3; range, 2–7).

Conclusions: This study has confirmed that the prescribing of clozapine is low, delayed, and preceded by dosing of antipsychotic drugs above maximum limits. Identification of the factors found to be associated with clozapine use may encourage clinicians to consider clozapine sooner in relevant patients in hopes of achieving early symptomatic response.

J Clin Psychiatry 2016;77(11):e1447–e1453
dx.doi.org/10.4088/JCP.15m10063

[a]Department of Early Psychosis Intervention, [b]Research Division, and [c]Pharmacy Department, Institute of Mental Health, Singapore
**Corresponding author:* Charmaine Tang, MBBS, MRCPsych; Department of Early Psychosis Intervention, Institute of Mental Health, 10 Buangkok View Singapore 539747, Singapore (charmaine_yz_tang@imh.com.sg).

Symptomatic nonremission or treatment resistance is common in first-episode psychosis, with studies[1–8] reporting ranges between 16% and 25%. Current literature suggests that early symptomatic response is pertinent in improving remission and recovery rates.[8–10] One of the ways in which this can be achieved is by reducing inappropriate delays in clozapine initiation. Agid et al[11] implemented a standardized treatment algorithm in the First Episode Psychosis Program, with patients receiving 2 trials of 2 different atypical antipsychotics followed by a trial of clozapine as early as 25 weeks into the start of their treatment. When the clozapine-treated group was compared with the group who refused clozapine and chose to continue the same antipsychotic treatment as before, patients who received clozapine had significant improvements in Brief Psychiatric Rating Scale[12] and Clinical Global Impressions-Severity of Illness scale[13] scores, thus illustrating the importance of clozapine in the early treatment of first-episode psychosis.

The evidence as summarized in clinical practice guidelines and algorithms has established clozapine as the gold standard for treatment-resistant schizophrenia.[14–20] Beyond benefits in symptom reduction, robust large-scale studies have shown that clozapine use is associated with cognitive improvements,[21–24] increased treatment compliance,[25] substantially lower mortality,[26] and significant reduction in suicidal behavior.[27–29] Despite such overwhelming evidence, avoidance of clozapine initiation is rife in clinical practice. There is often a hesitancy to start clozapine given its side-effect profile, need for regular hematologic monitoring, and perceived position as treatment of "last resort." This was most recently demonstrated by a report from the National Audit of Schizophrenia,[30] which highlighted that patients whose illness was poorly responsive to standard antipsychotic medications were waiting too long to be started on clozapine.

This study aimed to examine clozapine prescribing practices among patients with first-episode psychosis on follow-up in the Singapore Early Psychosis Intervention Programme (EPIP). More specifically, the objectives were to establish the prevalence of clozapine use in this cohort of patients, identify baseline clinical and demographic factors that were associated with clozapine use, examine outcomes (symptomatic remission, functional remission, and recovery) at 2 years, and identify inappropriate antipsychotic prescription patterns prior to clozapine initiation.

METHODS

The EPIP is a nationwide program anchored at the only state psychiatric hospital in Singapore.[31] Patients accepted into the program are between 16 and 40 years old and have first-episode

Clinical Points

- Reducing inappropriate delays in clozapine initiation may improve outcomes in first-episode psychosis.
- This study highlights the delay and underuse of clozapine even in specialized early psychosis programs.
- The identification of various factors found to be associated with clozapine use may encourage clinicians to consider clozapine sooner in relevant patients.

psychotic disorders (defined as meeting the *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition [*DSM-IV*][32] criteria for schizophrenia, schizophreniform disorder, schizoaffective disorder, delusional disorder, brief psychotic disorder, psychotic disorder not otherwise specified, or mood disorders with psychotic features). Intensive multidisciplinary care is provided in the initial 2 to 3 years, following which patients are transferred to other psychiatric services for continued care. Psychopharmacologic treatment is based on a treatment algorithm that emphasizes the use of antipsychotic monotherapy. Clozapine is considered in patients who have failed at least 2 adequate trials of different antipsychotics, of which 1 should be an atypical antipsychotic.

Approval was granted by the relevant ethics review board. Data were obtained from the EPIP database, an on-going registry capturing clinical and demographic information prospectively. All consecutive patients who had presented to EPIP with first-episode psychosis, from April 2001 to June 2012 inclusive, were included in this study.

Sociodemographic information was obtained using a semistructured questionnaire. Subjects were diagnosed by using the Structured Clinical Interview for *DSM-IV* Axis I Disorders, Clinician Version (SCID-CV).[33] Duration of untreated psychosis was operationalized as the time between onset of psychotic symptoms and the time when definitive diagnoses and treatment were established. All patients were assessed with the Positive and Negative Syndrome Scale (PANSS)[34] for schizophrenia and Global Assessment of Functioning (GAF) scale[35] at baseline and at 3, 6, 12, and 24 months. These ratings were performed by trained psychiatrists, and the interrater reliability was assessed to be 0.94.

A priori criteria were used to define symptomatic and functional remission. Symptomatic remission was defined based on the criteria proposed by the Schizophrenia Working Group,[36] ie, achieving and maintaining a PANSS rating of 3 or less for a duration of at least 6 months on the following items: delusions (P1), unusual thought contents (G9), hallucinatory behavior (P3), conceptual disorganization (P2), mannerisms (G5), blunted affect (N1), social withdrawal (N4), and lack of spontaneity (N6). Functional remission was defined as a GAF disability score of ≥ 61 with engagement in age-appropriate vocation. Patients who fulfilled the criteria for both symptomatic and functional remission were classified as being in recovery.[10]

Those who had been prescribed clozapine during the course of their follow-up with EPIP were identified by correlating the EPIP database with electronic integrated pharmacy systems. For patients who had been prescribed clozapine, additional clinical data were extracted from their medical records. These included names of antipsychotic drugs used prior to clozapine initiation, as well as their corresponding maximum dosage, duration of treatment, and reasons for discontinuation. Antipsychotic drugs were included so long as there was a prescription of a regular dose of an antipsychotic drug for at least 24 hours. An adequate antipsychotic treatment episode was defined as the prescription of a regular dose of antipsychotic drug at or above the minimum therapeutic dosage given the patient's age and dosing schedule for at least 6 weeks based on the National Institute for Health and Clinical Excellence (NICE) guidelines.[19] Treatment resistance was a priori defined as a lack of response to 2 adequate antipsychotic treatment episodes. The theoretical delay in clozapine initiation was defined as the time from the end of the second adequate antipsychotic treatment episode to the initiation of clozapine.[37] The specific reasons for discontinuation of antipsychotic drugs were categorized into lack of efficacy, intolerability of side-effects, nonadherence to treatment, and patient's or family's request. Whenever there was more than 1 reason for discontinuation, the single most significant reason, as documented, was given primacy.

Statistical analysis was performed using Statistical Package for the Social Sciences (SPSS) version 16.0 (SPSS Inc, Chicago, Illinois). In addition to descriptive statistics, multivariate analysis was performed to identify factors associated with clozapine use. Multiple logistic regression analysis was also performed to identify predictors of clozapine use. We included age, gender, ethnicity, marital status, employment status, education level, *DSM-IV* diagnosis, duration of untreated psychosis, and PANSS and GAF scores as predictors in the regression model. The χ^2 test was used to compare the rates of symptomatic remission, functional remission, and recovery between users and nonusers of clozapine. The differences were further analyzed using multiple logistic regression analysis to adjust for potential confounding factors including *DSM-IV* diagnosis, duration of untreated psychosis, and PANSS and GAF scores at baseline. Kaplan-Meier survival curves were utilized to estimate time to clozapine initiation. Cox proportional hazards regression model was used to identify variables associated with shorter time to clozapine initiation. Statistical significance was evaluated at the ≤ .05 level using 2-sided tests.

RESULTS

The EPIP had accepted 2,108 patients between April 2001 and June 2012. Clinical and demographic data were available for 2,064 patients after excluding 44 with missing data. Data from 1,603 patients (77.7%) who had completed at least 2 years of follow-up were available for baseline analyses after excluding 256 (12.4%) who were discharged early from the program because they had moved out of the country or wished to see another psychiatric service, 158 (7.6%) who

Table 1. Baseline Sociodemographic and Clinical Characteristics of Patients Who Had Completed at Least 2 Years of Follow-Up in the Early Psychosis Intervention Program (n = 1,603)

Characteristic	Clozapine Prescribed: Yes (n = 69)[a]	Clozapine Prescribed: No (n = 1,534)[a]	Total (n = 1,603)[a]	*P* Value
Age, mean (SD), y	26.1 (6.2)	27.6 (6.7)	27.6 (6.6)	.070
Gender, n (%)				
Female	30 (43.5)	751 (49.0)	781 (48.7)	.373
Male	39 (56.5)	783 (51.0)	822 (51.3)	
Ethnicity, n (%)				
Chinese	52 (77.6)	1,173 (77.2)	1,225 (77.2)	.990
Malay	9 (13.4)	211 (13.9)	220 (13.9)	
Indian	5 (7.5)	105 (6.9)	110 (6.9)	
Others	1 (1.5)	30 (2.0)	31 (2.0)	
Marital status, n (%)				
Single	58 (86.6)	1,159 (79.4)	1,217 (79.8)	.647
Married	7 (10.4)	246 (16.9)	253 (16.6)	
Separated	1 (1.5)	15 (1.0)	16 (1.0)	
Divorced	1 (1.5)	38 (2.6)	39 (2.6)	
Widowed	0 (0.0)	1 (0.1)	1 (0.1)	
Employment status, n (%)				
Employed	11 (16.9)	458 (31.8)	469 (31.1)	.039*
Unemployed	36 (55.4)	639 (44.3)	675 (44.8)	
Economically inactive[b]	18 (27.7)	345 (23.9)	363 (24.1)	
Education level, n (%)				
Primary and below	5 (7.6)	194 (13.4)	199 (13.1)	.069
Secondary	31 (47.0)	492 (34.0)	523 (34.5)	
Tertiary	30 (45.5)	763 (52.7)	793 (52.3)	
DSM-IV diagnosis, n (%)				
Schizophrenia spectrum[c] and delusional disorder	60 (89.6)	1,086 (75.8)	1,146 (76.5)	.028*
Mood disorders with psychotic features	1 (1.5)	130 (9.1)	131 (8.7)	
Brief psychotic disorder and psychotic disorder not otherwise specified	6 (9.0)	216 (15.1)	222 (14.8)	
DUP, mean (SD), mo (median = 5)	18.0 (26.6)	14.3 (26.2)	14.5 (26.2)	.060
PANSS, mean (SD)				
Total score	71.3 (19.5)	66.7 (17.5)	66.9 (17.6)	.040*
Positive scale	21.1 (5.9)	19.7 (6.0)	19.8 (6.0)	.070
Negative scale	14.6 (7.9)	13.0 (7.1)	13.1 (7.2)	.054
General psychopathology scale	35.6 (10.3)	34.1 (9.8)	34.2 (9.8)	.220
GAF, mean (SD)				
Total score	37.7 (14.5)	40.7 (13.7)	40.6 (13.8)	.090
Symptomatology	38.6 (14.1)	41.1 (14.2)	41.0 (14.2)	.150
Disability	42.5 (12.4)	45.7 (13.3)	45.6 (13.3)	.050*

[a]Figures may not add up to the total n due to missing information.
[b]Economically inactive was defined as students and homemakers.
[c]Schizophrenia spectrum disorders include schizophrenia, schizophreniform disorder, and schizoaffective disorder.
*Significant at $P \leq .05$.
Abbreviations: DUP = duration of untreated psychosis, GAF = Global Assessment of Functioning, PANSS = Positive and Negative Syndrome Scale.

had defaulted, 28 (1.4%) who were deceased, and 19 (0.9%) whose diagnoses were later revised to nonpsychotic disorders.

The prevalence of clozapine use in patients who had completed at least 2 years of follow-up with EPIP was 4.3% (n = 69). Of the 28 patients who were deceased, 1 patient had been prescribed clozapine. We were unable to establish the cause of death for deceased patients, as their medical records were sealed. None of the patients who were discharged early, had defaulted, or had their diagnoses revised had been prescribed clozapine.

Table 1 shows the baseline clinical and demographic characteristics of patients who had completed at least 2 years of follow-up. The mean (SD) age was 27.6 (6.6) years. The majority were male (51.3%), Chinese (77.2%), single (79.8%), and unemployed (44.8%); had tertiary education (52.3%); and had schizophrenia spectrum (ie, schizophrenia, schizophreniform disorder, and schizoaffective disorder) and delusional disorders (76.5%). Their mean (SD) and median duration of untreated psychosis was 14.5 (26.2) and 5 months, respectively. Their mean (SD) PANSS and GAF total scores at baseline were 66.9 (17.6) and 40.6 (13.8), respectively.

As compared to patients who were not prescribed clozapine, those who were prescribed clozapine were significantly less likely to be employed ($P = .039$). They were also significantly more likely to have schizophrenia spectrum and delusional disorders ($P = .028$) and higher PANSS total ($P = .040$) and lower GAF disability ($P = .050$) scores at baseline (Table 1). Among those who were prescribed clozapine, increased age at onset was significantly associated with a lower likelihood of being prescribed clozapine (OR = 0.95; 95% CI, 0.90–0.99; $P = .045$), while those with secondary education had a higher likelihood of being prescribed clozapine as compared to those with primary education and below (OR = 3.06; 95% CI, 1.04–9.06; $P = .043$) (Table 2). For time to clozapine initiation, those with secondary education (HR = 2.97; 95% CI, 1.02–8.63; $P = .046$) (vs those with primary education and below) and those who were unemployed (HR = 2.34; 95% CI, 1.09–5.04; $P = .030$) and economically inactive (HR = 2.35; 95% CI, 1.01–5.49; $P = .048$) (vs those who were employed) were significantly associated with shorter time to clozapine initiation (Table 3).

At the end of 2 years, 53.6% (n = 37) of patients who were prescribed clozapine had achieved symptomatic remission. Criteria for functional remission was met by 39.1% (n = 27), and 18.8% (n = 13) of patients met criteria for both symptomatic and functional remission and were considered to have achieved recovery. Correspondingly, among those not prescribed clozapine, 54.3% (n = 833) had achieved symptomatic remission, 52.1% (n = 799) had achieved functional remission, and 30.1% (n = 462) were considered to have achieved recovery. The rates of functional remission ($P = .019$) and recovery ($P = .046$) were significantly different between users and nonusers of clozapine. However, after adjusting for sociodemographic variables, diagnosis, duration of untreated psychosis, and PANSS and GAF scores at baseline using multiple logistic regression analyses, we found no statistically significant differences between clozapine users and nonusers in terms of functional remission ($P = .067$) and recovery ($P = .263$) rates.

Table 2. Predictors of Clozapine Use (n = 69)

Characteristic	OR[a]	95% CI	*P* Value
Age	0.95	0.90–0.99	.045*
Gender			
Female	Reference		
Male	1.23	0.71–2.11	.461
Ethnicity			
Chinese	Reference		
Malay	1.02	0.48–2.16	.956
Indian	1.16	0.44–3.07	.769
Others	0.90	0.11–7.23	.923
Marital status			
Single	Reference		
Married	0.97	0.37–2.52	.943
Separated/divorced/widowed	1.22	0.24–6.37	.811
Employment status			
Employed	Reference		
Unemployed	1.98	0.95–4.12	.067
Economically inactive[b]	1.97	0.37–2.52	.129
Education level			
Primary and below	Reference		
Secondary	3.06	1.04–9.06	.043*
Tertiary	1.96	0.66–5.86	.227
DSM-IV diagnosis			
Schizophrenia spectrum[c] and delusional disorder	Reference		
Mood disorders with psychotic features	0.13	0.02–1.00	.050
Brief psychotic disorder and psychotic disorder not otherwise specified	0.68	0.28–1.66	.397
Duration of untreated psychosis	1.01	0.99–1.02	.182
PANSS			
Positive scale	1.04	0.98–1.10	.161
Negative scale	1.01	0.97–1.05	.686
General psychopathology scale	0.99	0.96–1.02	.533
GAF			
Symptomatology	0.99	0.96–1.02	.454
Disability	1.00	0.97–1.03	.990

[a]Obtained using multiple logistic regression.
[b]Economically inactive was defined as students and homemakers.
[c]Schizophrenia spectrum disorders include schizophrenia, schizophreniform disorder, and schizoaffective disorder.
*Significant at $P \leq .05$.
Abbreviations: GAF = Global Assessment of Functioning, OR = odds ratio, PANSS = Positive and Negative Syndrome Scale.

Table 3. Factors Associated With Shorter Time to Clozapine Initiation (n = 69)

Characteristic	HR[a]	95% CI	*P* Value
Age	0.95	0.90–1.00	.060
Gender			
Female	Reference		
Male	1.23	0.72–2.10	.440
Ethnicity			
Chinese	Reference		
Malay	1.02	0.50–2.12	.941
Indian	0.92	0.32–2.58	.867
Others	0.91	0.12–6.87	.928
Marital status			
Single	Reference		
Married	1.07	0.42–2.76	.882
Separated/divorced/widowed	1.33	0.30–5.88	.704
Employment status			
Employed	Reference		
Unemployed	2.34	1.09–5.04	.030*
Economically inactive[b]	2.35	1.01–5.49	.048*
Education level			
Primary and below	Reference		
Secondary	2.97	1.02–8.63	.046*
Tertiary	1.93	0.66–5.68	.232
DSM-IV diagnosis			
Schizophrenia spectrum[c] and delusional disorder	Reference		
Brief psychotic disorder and psychotic disorder not otherwise specified	0.71	0.30–1.70	.488
Duration of untreated psychosis	1.01	0.99–1.01	.147
PANSS			
Positive scale	1.04	0.98–1.09	.197
Negative scale	1.01	0.97–1.05	.654
General psychopathology scale	0.99	0.96–1.02	.572
GAF			
Symptomatology	0.98	0.95–1.02	.378
Disability	0.99	0.97–1.03	.908

[a]Obtained using Cox proportional hazards regression.
[b]Economically inactive was defined as students and homemakers.
[c]Schizophrenia spectrum disorders include schizophrenia, schizophreniform disorder, and schizoaffective disorder.
*Significant at $P \leq .05$.
Abbreviations: GAF = Global Assessment of Functioning, HR = hazard ratio, PANSS = Positive and Negative Syndrome Scale.

Medical records for 68 patients were available for extraction of additional clinical data. Table 4 illustrates the prescription patterns of antipsychotic drugs prior to clozapine initiation. The majority of these antipsychotic drugs (53.4%) were discontinued due to a lack of efficacy; 36.0% were due to intolerability of side effects, 5.3% were due to treatment adherence issues, and 5.3% were due to patients' and families' preferences. A total of 20 patients (29.4%) had received antipsychotic drug treatment above maximum doses—12 patients (17.6%) were prescribed olanzapine 25 mg/d, 7 (10.3%) were prescribed olanzapine 30 mg/d, and 1 (1.5%) was prescribed quetiapine 900 mg/d. The mean total number of different antipsychotic drugs prescribed prior to clozapine initiation was 3.4 (SD = 1.2) (median = 3, interquartile range [IQR] = 1.8; range, 2–7). The mean total number of different typical and atypical antipsychotic drugs prescribed prior to clozapine initiation was 1.2 (SD = 1.2) (median = 1, IQR = 2.0; range, 0–4) and 2.2 (SD = 0.9) (median = 2, IQR = 1.0; range, 1–5), respectively. Prior to clozapine initiation, 75.0% of patients were prescribed ≥ 3 different antipsychotics (Figure 1).

Among those who were prescribed clozapine, the mean (SD) time to clozapine initiation from first contact with EPIP was 57.4 (39.3) weeks. Before initiation of clozapine, 44 patients (64.7%) had at least 2 adequate antipsychotic treatment episodes and therefore fulfilled the criteria for treatment resistance. The mean theoretical delay in clozapine initiation for the 44 patients who had at least 2 adequate antipsychotic treatment episodes was 19.3 weeks (SD = 27.1; range, 0–117).

DISCUSSION

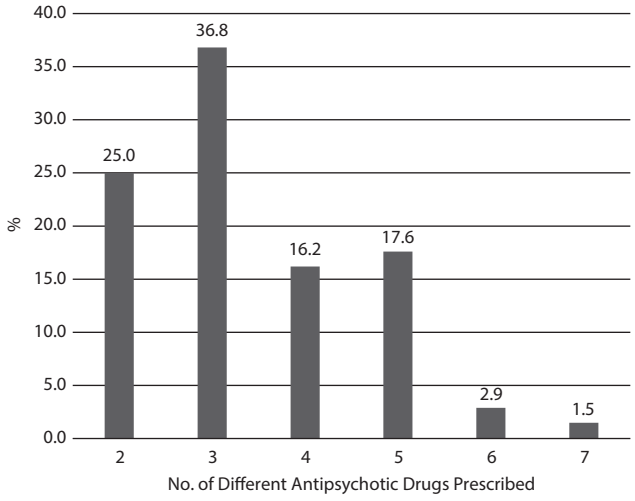
Schizophrenia is estimated to be treatment resistant in approximately 30% of patients.[38–40] It is likely that the prevalence of treatment resistance in the study population was much higher than the observed prevalence of clozapine initiation (ie, 4.3%). Further detailed analyses revealed several shortcomings in the prescription practices. First, clozapine initiation was delayed by an average of 5 months, with the longest delay being 2.5 years. Second, prior to commencing clozapine, about one-third of patients had

Table 4. Prescription Patterns of Antipsychotic Drugs Used Prior to Clozapine Initiation

Antipsychotic	Prescription Frequency, n (%)	Maximum Dose, Median (IQR), mg	Maximum Dose, Range, mg	Duration of Treatment, Mean (SD), wk	Duration of Treatment, Range, wk	Reasons for Discontinuing, n (%)[a]
Oral typical antipsychotic						
Haloperidol	27 (11.8)	5.0 (5.0)	1.5–25.0	9.0 (15.0)	1–60	A: 7 (25.9); B: 19 (70.4); C: 1 (3.7)
Trifluoperazine	14 (6.1)	10.0 (4.0)	2.0–20.0	16.4 (36.5)	1–136	A: 3 (21.4); B: 10 (71.4); D: 1 (7.1)
Sulpiride	9 (3.9)	600.0 (600.0)	100.0–1000.0	45.0 (63.7)	1–167	A: 5 (55.6); B: 3 (33.3); C: 1 (11.1)
Chlorpromazine	4 (1.7)	100.0 (193.8)	25.0–250.0	20.3 (17.0)	5–44	A: 2 (50.0); B: 1 (25.0); D: 1 (25.0)
Oral atypical antipsychotic						
Risperidone	60 (26.2)	4.0 (2.0)	0.5–6.0	20.4 (30.3)	1–164	A: 30 (50.0); B: 22 (36.7); C: 4 (6.7); D: 4 (6.7)
Olanzapine	50 (21.8)	20.0 (5.0)	10.0–30.0	28.4 (36.5)	2–155	A: 37 (74.0); B: 8 (16.0); C: 1 (2.0); D: 4 (8.0)
Quetiapine	15 (6.6)	500.0 (350.0)	100.0–900.0	34.3 (40.0)	1–147	A: 13 (86.7); C: 2 (13.3)
Aripiprazole	13 (5.7)	15.0 (11.3)	10.0–30.0	16.2 (13.3)	1–36	A: 8 (61.5); B: 3 (23.1); C: 1 (7.7); D: 1 (7.7)
Amisulpride	3 (1.3)	350.0 (100.0)	300.0–400.0	10.5 (3.5)	8–13	A: 2 (66.7); B: 1 (33.3)
Paliperidone	2 (0.9)	6.0 (6.0)	3.0–9.0	17.0 (20.0)	3–31	A: 1 (50.0); B: 1 (50.0)
Depot antipsychotic[b]						
Flupenthixol	13 (5.7)	125.0 (0.0)	83.3–187.5	16.3 (23.9)	1–73	A: 6 (46.2); B: 7 (53.8)
Risperidone	6 (2.65)	125.0 (56.25)	75.0–150.0	23.3 (17.7)	6–56	A: 4 (66.7); D: 2 (33.3)
Fluphenazine	5 (2.2)	250.0 (104.15)	125.0–250.0	7.6 (7.0)	2–17	A: 1 (20.0); B: 4 (80.0)
Pipotiazine	5 (2.2)	93.8 (93.8)	31.3–156.3	9.0 (10.2)	3–27	A: 2 (40.0); B: 3 (60.0)
Zuclopenthixol	3 (1.3)	166.7 (187.5)	62.5–250.0	32.7 (30.5)	2–63	A: 2 (66.7); C: 1 (33.3)

[a]A = lack of efficacy, B = side effects, C = nonadherence, D = patient's/family's request.
[b]Depot dosages were converted to chlorpromazine equivalents based on international consensus and guidelines.
Abbreviation: IQR = interquartile range.

Figure 1. Frequency of Different Antipsychotic Drugs Prescribed Prior to Clozapine Initiation (n = 68)



received antipsychotic drug treatment above maximum dosages. Third, 75% of patients were prescribed ≥ 3 different antipsychotics prior to clozapine initiation.

Globally, studies of clozapine utilization have shown that adherence to guidelines has been poor, with clozapine being consistently underutilized in the United States,[41] United Kingdom,[37,42] Canada,[43–45] New Zealand,[46] and Australia.[47,48] In the United Kingdom, substantial delays to clozapine initiation (average of 4 to 5 years) remain, and antipsychotic polypharmacy (36.2%) and dosing above maximum limits (34.2%) continue to be a problem.[37,42,49] In Canada, 68% of patients had tried 3 or more antipsychotics before switching to clozapine; and the median length of therapy prior to clozapine initiation was 8.9 years in males and 7.7 years in females.[44] Compared to these data, this study seemed to reveal a much shorter delay in clozapine initiation, which could be attributed to better care provided by a multidisciplinary early intervention service. However, the fact that previous studies examined chronic schizophrenia populations and not first-episode psychosis populations is something that needs to be considered, as results may not be directly comparable. More significantly, it is important to note that patients were followed up by EPIP for only 2 to 3 years. Hence, there could have been lengthier delays that were not picked up.

The methodology employed to calculate theoretical delays in clozapine initiation was probably the most accurate approach possible for a retrospective review. However, it was a conservative approach that did not take into account inappropriate extensions of antipsychotic trials despite lack of treatment response. Indeed, a closer look at the data gave indications that clozapine was not introduced at the earliest opportunity. Beyond the low prevalence of clozapine initiation, high rates of prescription above recommended maximum dosages (an approach that clearly has risks outweighing benefits) were also identified. Furthermore, 75% of patients were prescribed at least 3 different antipsychotics prior to clozapine initiation even though the main reason for discontinuation of an antipsychotic drug was lack of efficacy. The study data also revealed that antipsychotic drugs prescribed prior to clozapine initiation were of adequate dosages and generally for long durations (ranging from a mean of 7.6 to 45.0 weeks). Adding to this, the average time to clozapine initiation from first contact with EPIP was approximately 13 months. It was likely that either patients were not readily accepting recommended clozapine treatment or psychiatrists were inappropriately extending ineffective antipsychotic trials instead of switching patients to clozapine.

Given the undisputed benefits of clozapine for treatment-resistant schizophrenia, we wanted to identify predictors of

clozapine use in patients with first-episode psychosis so that vulnerable patients could be identified early and draw maximum benefits from clozapine. Compared to patients who never received clozapine, clozapine users were more likely to be unemployed and have higher PANSS total and lower GAF disability scores at baseline, indicating that they were more unwell (both in terms of symptoms and function) compared to their counterparts. Despite a small sample size (n = 69), younger age at onset was identified as a key predictor of clozapine use. This was consistent with results from a large-scale Danish study[50] that looked at predictors of clozapine use in treatment-resistant schizophrenia. When predictors for shorter time to clozapine initiation were examined, results indicated that patients who were unemployed and economically inactive (ie, students and homemakers) were more likely to be started on clozapine earlier than those who were gainfully employed. Compared to patients with primary education level, those who had obtained secondary but not tertiary education were found to predict both clozapine use and shorter time to clozapine initiation—an interesting finding worth exploring in future prospective studies involving larger sample sizes. Overall, results from this study suggest that having a younger age at onset, having lower baseline functioning (as indicated by a lack of employment and having a lower GAF disability score), and being more symptomatic at baseline (as indicated by having a higher PANSS total score) are factors associated with clozapine use in patients with first-episode psychosis.

Finally, rates of remission and recovery at 2 years were examined. Despite being more unwell at baseline, patients who were treated with clozapine managed to attain rates of remission and recovery similar to those who never received clozapine, indicating that clozapine may indeed have an important role in improving outcomes in first-episode psychosis.

This study had a few limitations. A retrospective study design was employed, and additional clinical data not available on the EPIP database were obtained from medical records. Consequently, it is possible that some details could have been missed, if not documented properly. Also, we were not able to determine the exact reason for initiation of clozapine. It is conceivable that some patients were started on clozapine for reasons of treatment intolerance rather than treatment resistance. However, atypical antipsychotics have been available as alternatives to clozapine for treatment intolerance. Since all patients in the study had received at least 1 atypical antipsychotic drug prior to starting clozapine, it is very unlikely that antipsychotic intolerance was the predominant or sole reason for many, if any, of the patients commencing clozapine. Lastly, the sample size of clozapine users (n = 69) was small and could have accounted for the lack of significant predictors of clozapine use.

Notwithstanding these limitations, there were several strengths in the study. To the best of our knowledge, this is the first Asian study assessing the use of clozapine in a first-episode psychosis population. The comprehensiveness of our analyses allowed us to draw accurate and substantiated conclusions. Also, a retrospective, naturalistic study approach eliminated recall bias and allowed for a true depiction of prescription practices since clinicians were not aware at the point of prescription that such a study would be done. A major strength of the study was the robustness of the data. We were able to utilize a registry that captured information prospectively. The variables collected were clearly defined and objectified by the use of standard psychiatric rating instruments. Data integrity was subjected to stringent and regular quality checks by the relevant governing body. The integrity of the EPIP database was further demonstrated by the fact that only 2.1% of patients had missing data albeit the data examined spanned over 11 years.

In conclusion, we have confirmed in this study that the prescribing of clozapine is low, delayed, and preceded by attempts at prescription of antipsychotic drugs above recommended maximum limits. We also found that having a younger age at onset, having lower baseline functioning (as indicated by a lack of employment and having a lower GAF disability score), and being more symptomatic at baseline (as indicated by having a higher PANSS total score) are factors associated with clozapine use. We take reference from the findings of our study to lay a platform for future research examining the earlier use of clozapine in first-episode psychosis as well as barriers to clozapine initiation.

Submitted: April 18, 2015; accepted November 25, 2015.

Online first: October 11, 2016.

Drug names: aripiprazole (Abilify and others), clozapine (Clozaril, FazaClo, and others), haloperidol (Haldol and others), olanzapine (Zyprexa and others), paliperidone (Invega and others), quetiapine (Seroquel and others), risperidone (Risperdal and others).

Potential conflicts of interest: None.

Funding/support: None.

Previous presentation: Parts of this study were presented as "Prescription patterns prior to clozapine initiation in first episode psychosis." Poster presented at the 4th Schizophrenia International Research Society Conference; April 5–9, 2014; Florence, Italy ▪ "Sociodemographic and clinical factors associated with clozapine use in first episode psychosis." Poster presented at the 9th International Conference on Early Psychosis; November 17–19, 2014; Tokyo, Japan.

Additional information: The Early Psychosis Intervention Programme (EPIP) database is an on-going registry capturing sociodemographic and clinical data of patients presenting to EPIP with first-episode psychosis. This registry has been registered with the Singapore National Healthcare Group (NHG) free standing database. Data are captured prospectively, and data integrity is maintained by stringent and regular quality checks. The database is owned by the Department of Early Psychosis Intervention (EPIP) in the Institute of Mental Health (IMH), Singapore. The database resides in a stand-alone, password protected PC in the EPIP office. Requests for access to this database can be made in writing to Ms Lye Yin Poon, Manager, EPIP, IMH, at lye_yin_poon@imh.com.sg.

REFERENCES

1. Addington J, Addington D. Symptom remission in first episode patients. *Schizophr Res*. 2008;106(2–3):281–285.
2. Huber CG, Naber D, Lambert M. Incomplete remission and treatment resistance in first-episode psychosis: definition, prevalence and predictors. *Expert Opin Pharmacother*. 2008;9(12):2027–2038.
3. Lambert M, Conus P, Schimmelmann BG, et al. Comparison of olanzapine and risperidone in 367 first-episode patients with non-affective or affective psychosis: results of an open retrospective medical record study. *Pharmacopsychiatry*. 2005;38(5):206–213.
4. Lambert M, Naber D, Schacht A, et al. Rates and predictors of remission and recovery during 3 years in 392 never-treated patients with schizophrenia. *Acta Psychiatr Scand*. 2008;118(3):220–229.
5. Malla A, Norman R, Bechard-Evans L, et al. Factors influencing relapse

during a 2-year follow-up of first-episode psychosis in a specialized early intervention service. *Psychol Med*. 2008;38(11):1585–1593.
6. Manchanda R, Norman RM, Malla AK, et al. Persistent psychoses in first episode patients. *Schizophr Res*. 2005;80(1):113–116.
7. Menezes NM, Malla AM, Norman RM, et al. A multi-site Canadian perspective: examining the functional outcome from first-episode psychosis. *Acta Psychiatr Scand*. 2009;120(2):138–146.
8. Simonsen E, Friis S, Opjordsmoen S, et al. Early identification of non-remission in first-episode psychosis in a two-year outcome study. *Acta Psychiatr Scand*. 2010;122(5):375–383.
9. AlAqeel B, Margolese HC. Remission in schizophrenia: critical and systematic review. *Harv Rev Psychiatry*. 2012;20(6):281–297.
10. Verma S, Subramaniam M, Abdin E, et al. Symptomatic and functional remission in patients with first-episode psychosis. *Acta Psychiatr Scand*. 2012;126(4):282–289.
11. Agid O, Remington G, Kapur S, et al. Early use of clozapine for poorly responding first-episode psychosis. *J Clin Psychopharmacol*. 2007;27(4):369–373.
12. Overall JEG. The Brief Psychiatric Rating Scale. *Psychol Rep*. 1962;10:799–812.
13. Guy W. *ECDEU Assessment Manual for Psychopharmacology*. Revised Edition. US Dept Health, Education, and Welfare publication (ADM) 76-338. Rockville, MD: National Institute of Mental Health; 1976:218–222.
14. Addington D, Bouchard RH, Goldberg J, et al; Canadian Psychiatric Association. Clinical practice guidelines: treatment of schizophrenia. *Can J Psychiatry*. 2005;50(suppl 1):7S–57S.
15. Barnes TRE; Schizophrenia Consensus Group of British Association for Psychopharmacology. Evidence-based guidelines for the pharmacological treatment of schizophrenia: recommendations from the British Association for Psychopharmacology. *J Psychopharmacol*. 2011;25(5):567–620.
16. Buchanan RW, Kreyenbuhl J, Kelly DL, et al; Schizophrenia Patient Outcomes Research Team (PORT). The 2009 schizophrenia PORT psychopharmacological treatment recommendations and summary statements. *Schizophr Bull*. 2010;36(1):71–93.
17. Lehman AF, Lieberman JA, Dixon LB, et al; American Psychiatric Association; Steering Committee on Practice Guidelines. Practice guideline for the treatment of patients with schizophrenia, second edition. *Am J Psychiatry*. 2004;161(2 suppl):1–56.
18. Moore TA, Buchanan RW, Buckley PF, et al. The Texas Medication Algorithm Project antipsychotic algorithm for schizophrenia: 2006 update. *J Clin Psychiatry*. 2007;68(11):1751–1762. *10.4088/JCP.v68n1115*
19. National Institute for Health and Clinical Excellence (NICE). Psychosis and schizophrenia in adults: treatment and management. NICE Website. https://www.nice.org.uk/guidance/cg178. Updated February 2014.
20. Osser DN, Roudsari MJ, Manschreck T. The psychopharmacology algorithm project at the Harvard South Shore Program: an update on schizophrenia. *Harv Rev Psychiatry*. 2013;21(1):18–40.
21. Asenjo Lobos C, Komossa K, Rummel-Kluge C, et al. Clozapine versus other atypical antipsychotics for schizophrenia. *Cochrane Database Syst Rev*. 2010;10(11):CD006633.
22. McGurk SR. The effects of clozapine on cognitive functioning in schizophrenia. *J Clin Psychiatry*. 1999;60(suppl 12):24–29.
23. Manschreck TC, Redmond DA, Candela SF, et al. Effects of clozapine on psychiatric symptoms, cognition, and functional outcome in schizophrenia. *J Neuropsychiatry Clin Neurosci*. 1999;11(4):481–489.
24. Hagger C, Buckley P, Kenny JT, et al. Improvement in cognitive functions and psychiatric symptoms in treatment-refractory schizophrenic patients receiving clozapine. *Biol Psychiatry*. 1993;34(10):702–712.
25. Tiihonen J, Wahlbeck K, Lönnqvist J, et al. Effectiveness of antipsychotic treatments in a nationwide cohort of patients in community care after first hospitalisation due to schizophrenia and schizoaffective disorder: observational follow-up study. *BMJ*. 2006;333(7561):224–227.
26. Tiihonen J, Lönnqvist J, Wahlbeck K, et al. 11-year follow-up of mortality in patients with schizophrenia: a population-based cohort study (FIN11 study). *Lancet*. 2009;374(9690):620–627.
27. Meltzer HY. Suicide in schizophrenia, clozapine, and adoption of evidence-based medicine. *J Clin Psychiatry*. 2005;66(4):530–533. *10.4088/JCP.v66n0417*
28. Meltzer HY, Alphs L, Green AI, et al; International Suicide Prevention Trial Study Group. Clozapine treatment for suicidality in schizophrenia: International Suicide Prevention Trial (InterSePT). *Arch Gen Psychiatry*. 2003;60(1):82–91.
29. Hennen J, Baldessarini RJ. Suicidal risk during treatment with clozapine: a meta-analysis. *Schizophr Res*. 2005;73(2–3):139–145.
30. Royal College of Psychiatrists. *Report of the Second Round of the National Audit of Schizophrenia (NAS) 2014*. London, UK: Healthcare Quality Improvement Partnership; 2014.
31. Chong SA, Lee C, Bird L, et al. A risk reduction approach for schizophrenia: the Early Psychosis Intervention Programme. *Ann Acad Med Singapore*. 2004;33(5):630–635.
32. American Psychiatric Association. *Diagnostic and Statistical Manual for Mental Disorders*, Fourth Edition, Text Revision. Washington, DC: American Psychiatric Association; 2000.
33. First MB, Spitzer RL, Gibbon M, et al. *Structured Clinical Interview for DSM-IV Axis I Disorders, Clinician Version (SCID-CV)*. Washington, DC: American Psychiatric Press, Inc.; 1996.
34. Kay SR, Fiszbein A, Opler LA. The Positive and Negative Syndrome Scale (PANSS) for schizophrenia. *Schizophr Bull*. 1987;13(2):261–276.
35. Frances A, Pincus HA, First MB. *The Global Assessment of Functioning Scale (GAF) in Diagnostic and Statistical Manual of Mental Disorder-IV*. Washington, DC: American Psychiatric Association; 1994.
36. Andreasen NC, Carpenter WT Jr, Kane JM, et al. Remission in schizophrenia: proposed criteria and rationale for consensus. *Am J Psychiatry*. 2005;162(3):441–449.
37. Howes OD, Vergunst F, Gee S, et al. Adherence to treatment guidelines in clinical practice: study of antipsychotic treatment prior to clozapine initiation. *Br J Psychiatry*. 2012;201(6):481–485.
38. Mortimer AM, Singh P, Shepherd CJ, et al. Clozapine for treatment-resistant schizophrenia: National Institute of Clinical Excellence (NICE) guidance in the real world. *Clin Schizophr Relat Psychoses*. 2010;4(1):49–55.
39. Lieberman JA, Kane JM, Johns CA. Clozapine: guidelines for clinical management. *J Clin Psychiatry*. 1989;50(9):329–338.
40. Taylor D, Paton C, Kapur S. *The Maudsley Prescribing Guidelines*. 10th ed. London, UK: Informa Healthcare; 2009.
41. Moore TA, Covell NH, Essock SM, et al. Real-world antipsychotic treatment practices. *Psychiatr Clin North Am*. 2007;30(3):401–416.
42. Taylor DM, Young C, Paton C. Prior antipsychotic prescribing in patients currently receiving clozapine: a case note review. *J Clin Psychiatry*. 2003;64(1):30–34. *10.4088/JCP.v64n0107*
43. Alessi-Severini S, Biscontri RG, Collins DM, et al. Utilization and costs of antipsychotic agents: a Canadian population-based study, 1996–2006. *Psychiatr Serv*. 2008;59(5):547–553.
44. Alessi-Severini S, Le Dorze JA, Nguyen D, et al. Clozapine prescribing in a Canadian outpatient population. *PLoS One*. 2013;8(12):e83539.
45. Latimer E, Wynant W, Clark R, et al. Underprescribing of clozapine and unexplained variation in use across hospitals and regions in the Canadian province of Québec. *Clin Schizophr Relat Psychoses*. 2013;7(1):33–41.
46. Wheeler AJ. Treatment pathway and patterns of clozapine prescribing for schizophrenia in New Zealand. *Ann Pharmacother*. 2008;42(6):852–860.
47. Conley RR, Kelly DL, Lambert TJ, et al. Comparison of clozapine use in Maryland and in Victoria, Australia. *Psychiatr Serv*. 2005;56(3):320–323.
48. Malalagama G, Bastiampillai T, Dhillon R. Clozapine use in Australia. *Australas Psychiatry*. 2011;19(2):175.
49. Najim H, Heath D, Singh P. Antipsychotic prescribing before clozapine in a community psychiatric hospital: a case note review. *Psychiatr Danub*. 2013;25(suppl 2):S165–S170.
50. Nielsen J, Nielsen RE, Correll CU. Predictors of clozapine response in patients with treatment-refractory schizophrenia: results from a Danish Register Study. *J Clin Psychopharmacol*. 2012;32(5):678–683.