The Impact of Clozapine Delay on Clinical Outcomes in Schizophrenia

Claire Law, MBBS, MRCPsych; Yuen Mei See, BSc (Psy); Jie Yin Yee, MSc; Boon Tat Ng, MClinPharm; Charmaine Tang Yu Zheng, MBBS, MRCPsych, MCI; and Jimmy Lee, MBBS, MMed, MCI

Abstract

Background: Clozapine is the drug of choice indicated for treatment-resistant schizophrenia (TRS), but delays in initiation and underutilization might have affected its effectiveness in practice. In this study, we sought to examine the clinical outcomes of patients on clozapine treatment and if a delay in initiation was associated with poorer outcomes.

Methods: This study was conducted at a tertiary mental health institution in patients aged 21 to 80 years from January 2016 to October 2019 who were on a stable dose of clozapine for 2 weeks. All patients were assessed using the Structured Clinical Interview for *DSM-IV-TR* (SCID-I) to ascertain diagnoses of schizophrenia and schizoaffective disorder. Each patient was assessed on the Positive and Negative Syndrome Scale (PANSS) and Social Occupational Functioning Assessment Scale (SOFAS). Past antipsychotic treatment trials were obtained from the medical records. Symptom remission status was defined using the PANSS symptom criteria proposed by Andreasen and colleagues in 2005. Functional remission was defined as a SOFAS score ≥60.

Results: A total of 159 individuals with schizophrenia or schizoaffective disorder were recruited. The mean age of patients was 40.01 years, and the majority of patients were male (64.2%) and Chinese (85.5%). Thirty-seven patients (23.3%) achieved symptom remission, and 101 (63.5%) achieved functional remission. The median number of antipsychotic trials before clozapine initiation was 6 (interquartile range, 5–8). Patients in either symptom or functional remission had shorter time periods and fewer numbers of antipsychotic trials before first clozapine initiation. However, the trend was statistically significant only for median number of antipsychotic trials in the functional remission (P=.027) and symptom remission (P=.011) groups.

Conclusion: Our study found a significant delay in the initiation of clozapine despite current guidelines indicating it for TRS. This delay might have contributed to the poorer clinical outcomes. Further research is needed to provide a clearer understanding of clozapine delay, evaluate its impact on outcomes, and find ways to improve access to clozapine.

J Clin Psychiatry 2023;84(5):22m14588

Author affiliations are listed at the end of this article.

Treatment-resistant schizophrenia (TRS) is a high-burden subgroup affecting approximately 30% or more patients with schizophrenia.[1] TRS is defined as two failed trials of non-clozapine antipsychotic medications of adequate dose and duration[2,3]; clozapine is the only antipsychotic with specific indication for use in TRS. Meta-analyses have shown clozapine to be superior to first- and second-generation antipsychotics in achieving better outcomes, including improvements in functioning, quality of life, and symptoms in TRS.[4] Several large-scale studies have also shown that clozapine use is associated with cognitive improvements,[5–7] reduction in mortality and suicidal behavior,[8–11] lower risks of rehospitalization and recurrences,[12] and reduction in medical expenses.[13]

Clozapine's notable side effects and strict monitoring protocols were identified by psychiatrists as barriers to its initiation.[14] Some of the side effects include constipation, hypersalivation, sedation, and metabolic disturbances.[15,16] Therefore, routine monitoring of common side effects and physical health is recommended. A recent joint study from Singapore and Hong Kong[17] identified that the main deterrence from patients' and clinicians' perspectives, respectively, was regular venipuncture and clozapine's associated adverse drug reactions—primarily agranulocytosis, neutropenia, and weight gain.

Therefore, despite its benefits and superiority, clozapine remains underutilized in clinical practice,[18] and a long delay in its initiation is common.[19] Consequently, a delay in clozapine initiation may contribute to poor treatment outcomes in TRS.[20] In this study, we sought to examine the clinical outcomes of patients on clozapine treatment in a tertiary mental health institution and if a delay in initiation was associated with poorer outcomes.

Editor's Note
We encourage authors to submit papers for consideration as a part of our Early Career Psychiatrists section. Please contact Joseph F. Goldberg, MD, at jgoldberg@psychiatrist.com.

Clinical Points

- Delay in clozapine initiation is prevalent in a tertiary psychiatric setting and is associated with poorer clinical outcomes.
- Barriers to clozapine use are likely complex and encompass multiple stakeholders.
- Efforts to address these barriers are needed to improve outcomes in treatment-resistant schizophrenia.

MATERIALS AND METHODS

Participants

This cross-sectional study was conducted at the Institute of Mental Health, the only psychiatric facility with dedicated clozapine services in Singapore. Individuals with schizophrenia or schizoaffective disorder, aged 21 to 80, on clozapine treatment for at least 12 weeks and maintained on stable doses for at least 2 weeks were enrolled in the current study, which was conducted from January 2016 to October 2019. Ethics approval for this study was provided by the National Healthcare Group's Domain Specific Review Board. Written informed consent was obtained from all study participants.

Assessments

Information on patients' sociodemographics, duration of illness, current medication regimen, past antipsychotic exposure, and smoking history and clinical information were collected through interviews and reviews of medical records. Anthropometric measurements such as weight, height, waist circumference, and blood pressure were also collected during the visit.

All patients were assessed using the Structured Clinical Interview for *DSM-IV-TR* (SCID-I) to ascertain diagnoses.[21] Clinical symptoms were assessed on the Positive and Negative Syndrome Scale (PANSS)[22] by trained raters with established interrater reliability at > 0.8. The PANSS 5-factor structure model, which included positive symptoms, negative symptoms, cognitive/disorganization, depression/anxiety, and hostility, was adopted.[23]

The 36-item interviewer-administered version of the World Health Organization Disability Assessment Schedule 2.0 (WHODAS 2.0) [24] was used to evaluate the individual's functioning and disability across 6 domains (cognition, mobility, self-care, getting along with others, life activities, and participation) over a period of 30 days. Each item is rated on a 5-point Likert scale from 1 (no difficulty) to 5 (extreme/cannot do). Items in each domain were summed and weighted. All 6 weighted scores were then converted into a summary score ranging from 1 to 100, with a higher score indicating greater disability. The Social and Occupational Functioning Assessment scale (SOFAS) was used to assess the functional outcomes of patients.[25]

Symptom remission status was determined using the remission criteria proposed by Andreasen and colleagues in 2005.[26] Functional remission was defined as having a SOFAS score equal to or more than 60.[2]

Sample Collection and Measurement of Clozapine Levels

A sample of venous whole blood was collected from all patients into K_2 EDTA blood tubes 12 hours after last clozapine dose. The whole blood was centrifuged at 3,000 rpm for 10 minutes for collection of plasma, which was stored at −80°C. Levels of clozapine and norclozapine in plasma were quantitated using the high-performance liquid chromatography–ultraviolet (HPLC-UV) method with loxapine as internal standard.

Statistical Analysis

All statistical analyses were performed using IBM SPSS Statistics 23 (IBM Co.). Mean and standard deviations or median (if normality was not satisfied) was calculated for continuous variables, whereas frequencies and percentages were calculated for categorical variables. For comparison between two groups, the Mann-Whitney *U* test was used if normality assumption was violated, while the *t* test was used if normality assumption was met. The χ^2 test was used to analyze the categorical data. Statistical significance was determined at $P < .05$.

RESULTS

A detailed description of the patients' demographics and clinical characteristics is presented in Table 1. A total of 159 individuals with schizophrenia or schizoaffective disorder were recruited. The mean age of patients was 40.01 years, and the majority were male (64.2%), Chinese (85.5%), never married (84.3%), and non-smokers (86.2%).

The median duration of current clozapine treatment (from the commencement of the latest clozapine trial to the time of data collection) was 30.18 months (interquartile range [IQR], 9.89–94.39). The median number of antipsychotic trials before clozapine initiation was 6 (IQR, 5–8). Current clozapine doses ranged from 37.50 mg/d to 750 mg/d (median = 300 mg/d). One hundred patients (62.9%) were on clozapine monotherapy. Plasma clozapine levels of the patients ranged from 48.25 ng/mL to 2,642.60 ng/mL, with a median value of 776.26 ng/mL. Most of the patients (84.9%) had plasma clozapine levels greater than 350 ng/mL.

The median disability for the entire sample as measured by WHODAS 2.0 was 16.93. Mean (SD) scores for PANSS and SOFAS were 59.10 (13.38) and 59.30 (13.35), respectively.

Thirty-seven patients (23.3%) achieved symptom remission. Compared to patients in symptom remission,

Table 1.

Sociodemographic and Clinical Characteristics of Patients (n = 159)[a]

Characteristic	Value
Age, y	40.01 (11.01)
Sex (male), n (%)	102 (64.2)
Marital status, n (%)	
Single	134 (84.3)
Married	15 (9.4)
Separated/divorced	10 (6.3)
Ethnicity, n (%)	
Chinese	136 (85.5)
Malay	9 (5.7)
Indian	9 (5.7)
Other	5 (3.1)
Currently smoking, n (%)	22 (13.8)
Employed, n (%)	64 (40.3)
BMI, kg/m^2	24.75 (4.71)
Age at onset of illness, y	23.74 (6.41)
Duration of illness, y	16.48 (10.54)
Time from diagnosis to first CLZ trial, mean, y	10.69 (9.69)
No. of antipsychotic trials before first CLZ use	6.35 (2.30)
Duration of current CLZ treatment, mo	55.10 (60.15)
Clozapine monotherapy, n (%)	100 (62.9)
Daily CLZ dose, mg	310.77 (149.52)
Plasma CLZ, ng/mL	859.96 (519.99)
Plasma NCLZ, ng/mL	299.30 (379.45)
PANSS score	
Positive	11.93 (5.36)
Negative	14.25 (5.18)
Cognitive/Disorganization	12.80 (4.02)
Depression/Anxiety	9.63 (3.72)
Hostility	4.93 (1.72)
Total	59.10 (13.38)
SOFAS score	59.30 (13.35)
WHODAS 2.0 score	18.85 (14.46)

[a]Values are shown as mean (SD) unless otherwise noted.
Abbreviations: BMI = body mass index, CLZ = clozapine, NCLZ = norclozapine, PANSS = Positive and Negative Syndrome Scale, WHODAS 2.0 = World Health Organization Disability Assessment Schedule 2.0, SOFAS = Social and Occupational Functioning Assessment Scale.

unremitted patients had significantly higher daily clozapine dose (median = 300 mg vs 225 mg, $P < .001$), higher plasma clozapine level (median = 851.19 ng/mL vs 592.89 ng/mL, $P = .002$), higher plasma norclozapine level (median = 280.24 ng/mL vs 150.10 ng/mL, $P < .001$), lower BMI (median = 23.58 kg/m^2 vs 27.85 kg/m^2, $P = .007$), and more antipsychotic trials before first clozapine initiation (median = 7 vs 5, $P = .011$). Patients not in remission had significantly lower rates of employment (30.8% vs 70.3%, $P < .001$). Age, age at onset of illness, duration of illness, duration of current clozapine treatment, clozapine monotherapy, and total years of education were not significantly different (all $P > .05$) between patients in symptom remission and non-remission.

One hundred one patients (63.5%) achieved functional remission. Patients who achieved functional remission had significantly lower daily clozapine dose (median = 300 mg vs 337.50 mg, $P = .007$), higher employment rates (47.52% vs 27.59%, $P = .014$), and fewer antipsychotic trials before first clozapine initiation (median = 6 vs 7, $P = .027$) compared to patients not in remission. Patients in either symptom or functional remission had shorter time periods and fewer antipsychotic trials before first clozapine initiation. However, the trend was statistically significant for median number of antipsychotic trials in the functional remission and symptom remission groups (see Tables 2 and 3).

DISCUSSION

This study examined the clinical outcomes of TRS patients who were on clozapine treatment and whether a delay in clozapine initiation was associated with poorer outcomes. Our results showed that 64% of the patients achieved functional remission, but a smaller proportion achieved symptom remission. We also found a significant delay in clozapine initiation: the mean time taken to start clozapine was about 10 years, with a median of 6 antipsychotic trials before clozapine. Patients in either functional or symptomatic non-remission groups had longer time periods and higher number of antipsychotic trials before the first commencement of clozapine.

In this study, symptom remission rates appear low despite adequate clozapine doses and levels. Of note, 84.9% of the patients in this study achieved plasma clozapine concentration levels of at least 350 ng/mL. Those not in symptom remission had higher doses of clozapine, with corresponding higher plasma clozapine and norclozapine levels. This finding suggests limited benefit with higher doses of clozapine when it comes to symptom remission. This was further supported by findings on patients with functional remission, who were on lower daily doses of clozapine as well. Taken together, our study findings call into question the utility of further increasing clozapine doses in addressing clozapine resistance in schizophrenia. The study did not collect information on indications for continued clozapine use in individuals with clozapine resistance and its effectiveness. It is possible the patients might have responded best (albeit partially) to clozapine, or that clozapine use was indicated for hostility, aggression, and suicide,[27,28] hence the continued prescription despite a lack of remission.

Our results suggest that a delay in clozapine treatment is associated with poorer clinical outcomes. Both symptom and functional non-remitters had a longer time to clozapine initiation and more antipsychotic trials compared to remitters. This finding is in keeping with those of previous studies[29] performed for which likelihood of response to clozapine reduced by 8%–11% with each antipsychotic trial. Another study, by Yoshimura and colleagues,[30] reported similar findings: patients who received clozapine within 2.8 years of TRS onset had a treatment response rate of 81.6%,

Table 2.

Comparison Between Symptom Remission and Non-Remission[a]

Variables	Symptom Remission (n = 37)	Symptom Non-Remission (n = 117)	Statistic Value	*P* Value
Age, y	37.78 (9.81)	40.35 (11.25)	*U* = 1879.00	.227
Years of education	12.27 (2.33)	11.88 (3.03)	*U* = 1786.50	.472
Employment, n (%)	26 (70.27)	36 (30.77)	$\chi^2_1 = 18.24$	< .001
Age at onset of illness, y	23.73 (6.66)	23.74 (6.35)	*U* = 2091.00	.875
BMI, kg/m^2	26.60 (5.17)	24.20 (4.40)	*U* = 1523.00	.007
Duration of illness, y	14.10 (9.76)	16.97 (10.52)	*U* = 1779.00	.135
Duration of current CLZ treatment, mo	63.72 (66.84)	52.29 (58.23)	*U* = 1938.00	.416
Clozapine monotherapy, n (%)	26 (70.27)	71 (60.68)	$\chi^2_1 = 1.108$	.292
Daily CLZ dose, mg	225.34 (107.55)	338.25 (152.34)	*U* = 1216.5	< .001
Plasma CLZ, ng/mL	632.77 (368.53)	937.38 (539.90)	*U* = 1410.00	.002
Plasma NCLZ, ng/mL	201.83 (130.17)	294.79 (137.46)	*U* = 1252.00	< .001
Time from diagnosis to first CLZ trial, y	8.51 (8.44)	11.08 (9.72)	*U* = 1703.5	.092
No. of antipsychotic trials before first CLZ use	5.47 (1.84)	6.59 (2.40)	*U* = 1466.00	.011

[a]Values are shown as mean (SD) unless otherwise noted.
Abbreviations: BMI = body mass index, CLZ = clozapine, NCLZ = norclozapine.

Table 3.

Comparison Between Functional Remission and Non-Remission[a]

Variable	Functional Remission (n = 101)	Functional Non-Remission (n = 58)	Statistic Value	*P* Value
Age, y	39.94 (10.75)	40.26 (11.54)	*U* = 2901.00	.920
Years of education	12.07 (2.67)	11.81 (3.23)	*U* = 2383.50	.740
Employment, n (%)	48 (47.52)	16 (27.59)	$\chi^2_1 = 6.09$	.014
Age at onset of illness, y	24.03 (6.41)	23.22 (6.44)	*U* = 2483.50	.275
BMI, kg/m^2	24.88 (4.68)	24.52 (4.79)	*U* = 2748.00	.517
Duration of illness, y	16.09 (10.88)	17.18 (9.96)	*U* = 2575.00	.453
Duration of current CLZ treatment, mo	59.60 (63.07)	46.84 (53.97)	*U* = 2464.00	.245
Clozapine monotherapy, n (%)	66 (65.35)	24 (41.38)	$\chi^2_1 = 0.71$	.398
Daily CLZ doses, mg	282.80 (130.47)	359.48 (168.25)	*U* = 2174.00	.007
Plasma CLZ, ng/mL	833.41 (488.26)	905.73 (572.12)	*U* = 2783.00	.673
Plasma NCLZ, ng/mL	257.54 (138.10)	370.57 (594.20)	*U* = 2376.00	.72
Time from diagnosis to first CLZ trial, y	10.11 (9.55)	11.72 (9.95)	*U* = 2395.00	.217
No. of antipsychotic trials before first CLZ use	6.01 (2.18)	6.96 (2.41)	*U* = 2100.00	.027

[a]Values are shown as mean (SD) unless otherwise noted.
Abbreviations: BMI = body mass index, CLZ = clozapine, NCLZ = norclozapine.

but the rate of response to clozapine declined to 30.8% in patients initiating clozapine after 2.8 years. Taken together, these findings indicate that a delay in clozapine initiation leads to adverse clinical outcomes in TRS.

Our study found deviations from current antipsychotic treatment guidelines, which resulted in a delay in clozapine initiation that was comparable to those reported in previous studies of between 5 and 10 years.[31,32] The 2008 study by Wheeler[32] found that 3.5 antipsychotic trials were administered before clozapine was first used; the 2003 study by Taylor and colleagues[31] found that the average was 9 antipsychotic trials. Notably, our result reflects the practice of clinicians in Hong Kong and Singapore, which was reported earlier.[33] Surveyed clinicians had reported familiarity with treatment guidelines and endorsed the underutilization of clozapine.[17] However, they cited barriers to clozapine initiation, which include clinician, patient, and system factors. It has been reported that clinicians would employ non-clozapine antipsychotic polypharmacy or high-dose antipsychotic treatment before commencing clozapine.[33–35] As a result, patients are often subjected to lengthy periods of ineffective antipsychotic treatment before the initiation of clozapine.[31,32] Apart from clinician factors, patient-related factors and health system factors also play major roles in clozapine delay. Refusal of hematologic monitoring, concerns about side effects and tolerability, resource limitations, and costs are often cited by clinicians as barriers to prescribing clozapine to eligible patients.[17,36]

Interestingly, our results show a sizeable discrepancy in the proportions of patients in symptomatic remission (23%) and functional remission (64%) on clozapine

treatment. This discrepancy could have been contributed by the SOFAS assessment, which assesses only functioning and does not consider symptom severity, unlike some other functioning scales, eg, the Global Assessment of Functioning (GAF). Additionally, it is possible that due to the chronicity of the illness, the patients might have developed coping strategies to adapt.[37] It is also likely that they had been through rehabilitation programs or placed in environments that were modified or designed to maximize their functioning, eg, supported employment, in spite of persistent symptoms. This last point might explain the relatively high employment rate of 30.77% in the symptom non-remission group.

Strengths and Limitations

The study sample is representative of the clinical practice in a naturalistic outpatient setting, but there are limitations to note. Some of the medical and treatment history was obtained from medical records, which might be missing or incomplete, including reasons for antipsychotic switches. The onset of TRS could not be reliably captured; hence, a delay in clozapine initiation was defined as from time of diagnosis to clozapine initiation. Reasons for delay in clozapine initiation were unavailable. Due to the cross-sectional study design, the study might not have included poor responders to clozapine who discontinued. In addition, the rating scales administered during the interview represent a snapshot of an individual's clinical state and may not be representative of his or her longitudinal illness course. To better evaluate the impact of clozapine delay on outcomes, future studies might consider a prospective study design.

CONCLUSION

Our study found significant delays in clozapine initiation and provides indication that such delays may be associated with poorer clinical outcomes in TRS. Additionally, the present study found low rates of symptom remission among TRS patients on clozapine treatment. The factors leading to the delayed clozapine initiation are often complex and encompass clinicians, patients, families, and mental health service administrators.[17] Further work is needed to address barriers that lead to clozapine delay and improve outcomes in TRS.

Article Information

Published Online: August 23, 2023. https://doi.org/10.4088/JCP.22m14588

Submitted: July 24, 2022; accepted April 24, 2023.

To Cite: See YM, Yee JY, Ng BT, et al. The impact of clozapine delay on clinical outcomes in schizophrenia. *J Clin Psychiatry.* 2023;84(5):22m14588.

Author Affiliations: Department of Forensic Psychiatry, Institute of Mental Health, Singapore (Law); Research Division, Institute of Mental Health, Singapore (See, Yee, Lee); Department of Pharmacy, Institute of Mental Health, Singapore (Ng); Department of Psychosis, Institute of Mental Health, Singapore (Zheng, Lee); Lee Kong Chian School of Medicine, Nanyang Technological University, Singapore (Lee).

Corresponding Author: Jimmy Lee, MBBS, MMed, MCI, 10 Buangkok View, Buangkok Green Medical Park, Singapore 534194 (jimmy_lee@imh.com.sg).

Relevant Financial Relationships: Dr Lee has received honoraria from Sumitomo Pharmaceuticals, Lundbeck Singapore, Otsuka Pharmaceutical, and Janssen Pharmaceutical. All other authors declare that they have no conflict of interest.

Funding/Support: The research was funded by the National Healthcare Group, Clinician Scientist Career Scheme (Grant no: NHG-CSCS/15007).

Role of the Funders/Sponsors: The funders had no role in the study design, data collection, data analysis, decision to publish, or preparation of the manuscript.

Previous Presentation: Presented at the Singapore Health & Biomedical Congress (SHBC); October 2021; Singapore.

References

1. Polese D, Fornaro M, Palermo M, et al. Treatment-resistant to antipsychotics: a resistance to everything? psychotherapy in treatment-resistant schizophrenia and nonaffective psychosis: a 25-year systematic review and exploratory meta-analysis. *Front Psychiatry.* 2019;10:210.
2. Howes OD, McCutcheon R, Agid O, et al. Treatment-resistant schizophrenia: Treatment response and resistance in psychosis (TRRIP) working group consensus guidelines on diagnosis and terminology. *Am J Psychiatry.* 2017;174(3):216–229.
3. Lee J, Takeuchi H, Fervaha G, et al. Subtyping schizophrenia by treatment response: antipsychotic development and the central role of positive symptoms. *Focus Am Psychiatr Publ.* 2016;14(3):396–402.
4. Siskind D, McCartney L, Goldschlager R, et al. Clozapine *v.* first- and second-generation antipsychotics in treatment-refractory schizophrenia: systematic review and meta-analysis. *Br J Psychiatry.* 2016;209(5):385–392.
5. Asenjo Lobos C, Komossa K, Rummel-Kluge C, et al. Clozapine versus other atypical antipsychotics for schizophrenia. *Cochrane Database Syst Rev.* 2010;(11):CD006633.
6. 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.
7. McGurk SR. The effects of clozapine on cognitive functioning in schizophrenia. *J Clin Psychiatry.* 1999;60(suppl 12):24–29.
8. Hennen J, Baldessarini RJ. Suicidal risk during treatment with clozapine: a meta-analysis. *Schizophr Res.* 2005;73(2–3):139–145.
9. 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). (published correction appears in Arch Gen Psychiatry.2003 Jul;60(7) *Arch Gen Psychiatry.* 2003;60(1):82–91.
10. Meltzer HY. Suicide in schizophrenia, clozapine, and adoption of evidence-based medicine. *J Clin Psychiatry.* 2005;66(4):530–533.
11. 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.
12. 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.
13. Essock SM, Frisman LK, Covell NH, et al. Cost-effectiveness of clozapine compared with conventional antipsychotic medication for patients in state hospitals. *Arch Gen Psychiatry.* 2000;57(10):987–994.
14. Thien K, O'Donoghue B. Delays and barriers to the commencement of clozapine in eligible people with a psychotic disorder: a literature review. *Early Interv Psychiatry.* 2019;13(1):18–23.
15. Warnez S, Alessi-Severini S. Clozapine: a review of clinical practice guidelines and prescribing trends. *BMC Psychiatry.* 2014;14(1):102.
16. Nielsen J, Damkier P, Lublin H, et al. Optimizing clozapine treatment. *Acta Psychiatr Scand.* 2011;123(6):411–422.
17. Zheng S, Lee J, Chan SKW. Utility and barriers to clozapine use: a joint study of clinicians' attitudes from Singapore and Hong Kong. *J Clin Psychiatry.* 2022;83(4):21m14231.
18. Bachmann CJ, Aagaard L, Bernardo M, et al. International trends in clozapine use: a study in 17 countries. *Acta Psychiatr Scand.* 2017;136(1):37–51.
19. Doyle R, Behan C, O'Keeffe D, et al. Clozapine use in a cohort of first-episode psychosis. *J Clin Psychopharmacol.* 2017;37(5):512–517.
20. Varghese M T, Jyothi KS, Shaji KS, et al. Delaying clozapine: how long is too long? *Gen Psychiatr.* 2020;33(2):e100172.
21. First MB, Gibbon M. The Structured Clinical Interview for *DSM-IV* Axis I Disorders (SCID-I) and the Structured Clinical Interview for *DSM-IV* Axis II Disorders (SCID-II). In: Hilsenroth MJ, Segal DL, Hersen M, eds. *Comprehensive Handbook of Psychological Assessment*. Vol 2. John Wiley & Sons, Inc; 2004:134–143.

22. Kay SR, Fiszbein A, Opler LA. The positive and negative syndrome scale (PANSS) for schizophrenia. *Schizophr Bull*. 1987;13(2):261–276.
23. Lim K, Peh OH, Yang Z, et al. Large-scale evaluation of the Positive and Negative Syndrome Scale (PANSS) symptom architecture in schizophrenia. *Asian J Psychiatr*. 2021;62:102732.
24. Üstün TB, Kostanjsek N, Chatterji S, et al, eds. *Measuring Health and Disability: Manual for WHO DIsability Assessment Schedule WHODAS 2.0*. World Health Organization; 2010.
25. Goldman HH, Skodol AE, Lave TR. Revising *Axis V* for *DSM-IV*: a review of measures of social functioning. *Am J Psychiatry*. 1992;149(9):1148–1156.
26. 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.
27. Glazer WM, Dickson RA. Clozapine reduces violence and persistent aggression in schizophrenia. *J Clin Psychiatry*. 1998;59(suppl 3):8–14.
28. Frogley C, Taylor D, Dickens G, et al. A systematic review of the evidence of clozapine's anti-aggressive effects. *Int J Neuropsychopharmacol*. 2012;15(9):1351–1371.
29. 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.
30. Yoshimura B, Yada Y, So R, et al. The critical treatment window of clozapine in treatment-resistant schizophrenia: secondary analysis of an observational study. *Psychiatry Res*. 2017;250:65–70.
31. 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.
32. Wheeler AJ. Treatment pathway and patterns of clozapine prescribing for schizophrenia in New Zealand. *Ann Pharmacother*. 2008;42(6):852–860.
33. Zheng S, Chan SKW, Lee J. Managing treatment resistance in schizophrenia: a joint study in Hong Kong and Singapore. *Front Psychiatry*. 2022;13:1005373.
34. 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.
35. Nielsen J, Dahm M, Lublin H, et al. Psychiatrists' attitude towards and knowledge of clozapine treatment. *J Psychopharmacol*. 2010;24(7):965–971.
36. Tungaraza TE, Farooq S. Clozapine prescribing in the UK: views and experience of consultant psychiatrists. *Ther Adv Psychopharmacol*. 2015;5(2):88–96.
37. Farhall J, Greenwood KM, Jackson HJ. Coping with hallucinated voices in schizophrenia: a review of self-initiated strategies and therapeutic interventions. *Clin Psychol Rev*. 2007;27(4):476–493.