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Utility and Barriers to Clozapine Use:

A Joint Study of Clinicians' Attitudes From Singapore and Hong Kong

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ABSTRACT

Objective: This study aimed to survey clinicians' attitudes in Singapore and Hong Kong toward clozapine and elucidate the barriers to its prescription in patients with treatment-resistant schizophrenia.

Methods: All clinicians in psychiatry in both regions were invited through email to participate in an anonymous online survey. The survey collected information on the participants' characteristics, their experience with clozapine initiation, perceived usefulness of clozapine, barriers to clozapine initiation, and factors that might improve clozapine use. Data collection took place between December 2018 and March 2019 in Singapore and September 2019 and February 2020 in Hong Kong.

Results: A total of 261 clinicians (156 in Singapore, 105 in Hong Kong) responded to the survey. The majority of participants believed that clozapine was an effective and satisfactory treatment for schizophrenia. Clinicians were most concerned about the need for frequent blood monitoring (84.5% in Singapore; 87.5% in Hong Kong), clozapine's tolerability (51.9% in Singapore; 61.6% in Hong Kong), and medical complications (54.8% in Singapore; 49.1% in Hong Kong). Compared to Hong Kong, more clinicians in Singapore endorsed an underutilization of clozapine (67.9% in Singapore; 51.4% in Hong Kong) and a greater need for outpatient resources in terms of clinic and administrative support (74.4% in Singapore; 59.0% in Hong Kong) to improve clozapine prescription.

Conclusions: The underutilization of clozapine in treatment-resistant schizophrenia remains a concern in both regions. An integrated clozapine service that addresses the system barriers and clinicians' confidence in prescribing clozapine and managing its adverse effects would greatly improve the utilization of clozapine.

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Treatment resistance, which is defined as having nonresponse to at least 2 trials of antipsychotic medications of adequate dose and duration, occurs in approximately 15%–30% of patients with schizophrenia.^{1–5} Multiple clinical practice guidelines have established the role of clozapine as the gold standard for treating treatment-resistant schizophrenia.⁶ It is a cost-effective treatment for treatment-resistant schizophrenia⁷ that is associated with reduced hospital admissions and bed days and improvements in the overall symptoms of patients.^{8–10} However, the avoidance of clozapine remains rife in psychiatry across the world, with underutilization reported in countries such as the US, United Kingdom, Canada, New Zealand, and Australia.¹¹ Several papers have revealed delays in the initiation of clozapine of as long as 4–9 years.^{12,13} This delay in clozapine initiation in turn leads to an increased likelihood of developing resistance to clozapine, with a decrease in the odds of long-term response to clozapine by 6% for every 1-year delay in clozapine initiation.^{5,14}

Several reasons for the delay in clozapine prescription have been put forth. In surveys of clinicians' attitude toward clozapine in the United Kingdom, Israel, and India, the commonly cited barriers to clozapine prescribing include the burden of frequent blood test monitoring, nonadherence to clozapine, and the fear of serious side effects such as neutropenia and agranulocytosis.^{15–17} Other barriers tend to be specific to the local health care system and include factors such as the variations in resources within the psychiatric service and the presence of service fragmentation.¹⁸ Few studies have explored in detail the attitudes of clinicians toward clozapine use in East Asian and Southeast Asian societies.

The present study aimed to survey clinicians' attitudes toward clozapine and clarify the factors that limit the initiation of clozapine where it is indicated. Singapore and Hong Kong were chosen as the survey sites due to their similar characteristics as Asian city-states with high urban density, similar ethnicities of the population, and comparable models of mental health delivery—both regions run on a mixed medical economy in which a small proportion of psychiatrists practice in the private sector while the majority of mental health care is provided by the public sector.¹⁹ The understanding of these barriers would be the first step to developing strategies to improve clozapine prescription and outcomes of patients with treatment-resistant schizophrenia.

METHODS

An anonymous online survey was conducted among clinicians in psychiatry in Singapore and Hong Kong to elucidate their attitudes toward clozapine initiation. The respondents included all

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Clinical Points

- Clozapine is the only effective and cost-effective antipsychotic for treatment-resistant schizophrenia, yet its initiation is often delayed.
- According to a clinician survey, the barriers to clozapine initiation in Singapore and Hong Kong included concerns about its adverse effects, frequent blood monitoring, and the administrative burdens of its initiation.
- An integrated clozapine service may aid in circumventing these perceived burdens in a busy public health care service.

residents in psychiatry, resident physicians, and psychiatrists in both regions. In Singapore, the eligible clinicians and their contact information were obtained from the Singapore Medical Council and the National Psychiatry Residency Program and crossed-checked against the email list of the psychiatric departments in all restructured hospitals and the available email addresses provided by the private clinics and hospitals. In Hong Kong, the survey invitations were sent through the Hong Kong College of Psychiatrists, the only professional organization for psychiatrists in Hong Kong. All trainees in psychiatry must register with this organization before starting their specialist training. Therefore, the college has the email addresses of all practicing psychiatric trainees and specialists in Hong Kong. At the time of the study, there were a total of 309 and 556 eligible participants, respectively, in Singapore and Hong Kong. Data collection took place between December 2018 and March 2019 in Singapore and September 2019 and February 2020 in Hong Kong.

Participants were invited via email to complete the survey on Questionpro, an online survey platform. The emails explained the purpose of the study and clearly mentioned the anonymous and voluntary nature of study participation. Two reminder emails were sent to each participant at separate intervals to encourage their participation in the study.

The survey employed was adapted from Gee et al¹⁵ in their study of attitudes toward clozapine prescription in practitioners in South London and Maudsley NHS Foundation Trust. Sociodemographic information was collected from all participants, and they were asked about their experience with the initiation of clozapine, their perceived usefulness of clozapine in clinical situations, the perceived barriers to clozapine initiation, and their thoughts about the additional administrative or clinical resources that would help to facilitate clozapine initiation in their workplace.

Ethics approval was granted by the relevant ethics review board, ie, the National Healthcare Group's Domain Specific Review Board in Singapore and the Institutional Review Board of the University of Hong Kong/Hospital Authority Hong Kong West Cluster in Hong Kong.

Statistical Analysis

The Statistical Package for Social Sciences (SPSS) version 23.0 was used for data analysis. Frequencies and

Table 1. Demographics of Participants

	Total (N = 261)		Singapore (N = 156)		Hong Kong (N = 105)	
	n	%	n	%	n	%
Gender						
Male	155	59.4	99	63.5	56	53.5
Female	106	40.6	57	36.5	49	46.7
Age group						
23–35 y	114	43.7	67	42.9	47	44.8
36–45 y	83	31.8	53	34.0	30	28.6
46–55 y	34	13.0	22	14.1	12	11.4
>55 y	30	11.5	14	9.0	16	15.2
Profession						
Resident or senior resident (ie, trainees in psychiatry)	81	31.0	53	34.0	28	26.7
Resident physician	4	1.5	4	2.6	NA	NA
Psychiatrist	176	67.4	99	63.5	77	73.3
Current work setting						
Inpatient	24	9.2	18	11.5	6	5.7
Outpatient	62	23.8	42	26.9	20	19.0
Mixed	175	67.0	96	61.5	79	75.2
Years of practice in psychiatry						
1–5	65	24.9	42	26.9	23	21.9
6–11	76	29.1	48	30.8	28	26.7
11–15	37	14.2	21	13.5	16	15.2
16–20	31	11.9	18	11.5	13	12.4
>20	52	19.9	27	17.3	25	23.9

Abbreviation: NA = not applicable.

percentages were calculated for categorical variables, while mode, median, and interquartile range were calculated for ordinal data. Comparisons were performed using corrected χ^2 test and Mann-Whitney *U* test, respectively. Associations were tested using Spearman rank correlation. All statistically significant differences were evaluated at the .05 level using 2-sided tests.

RESULTS

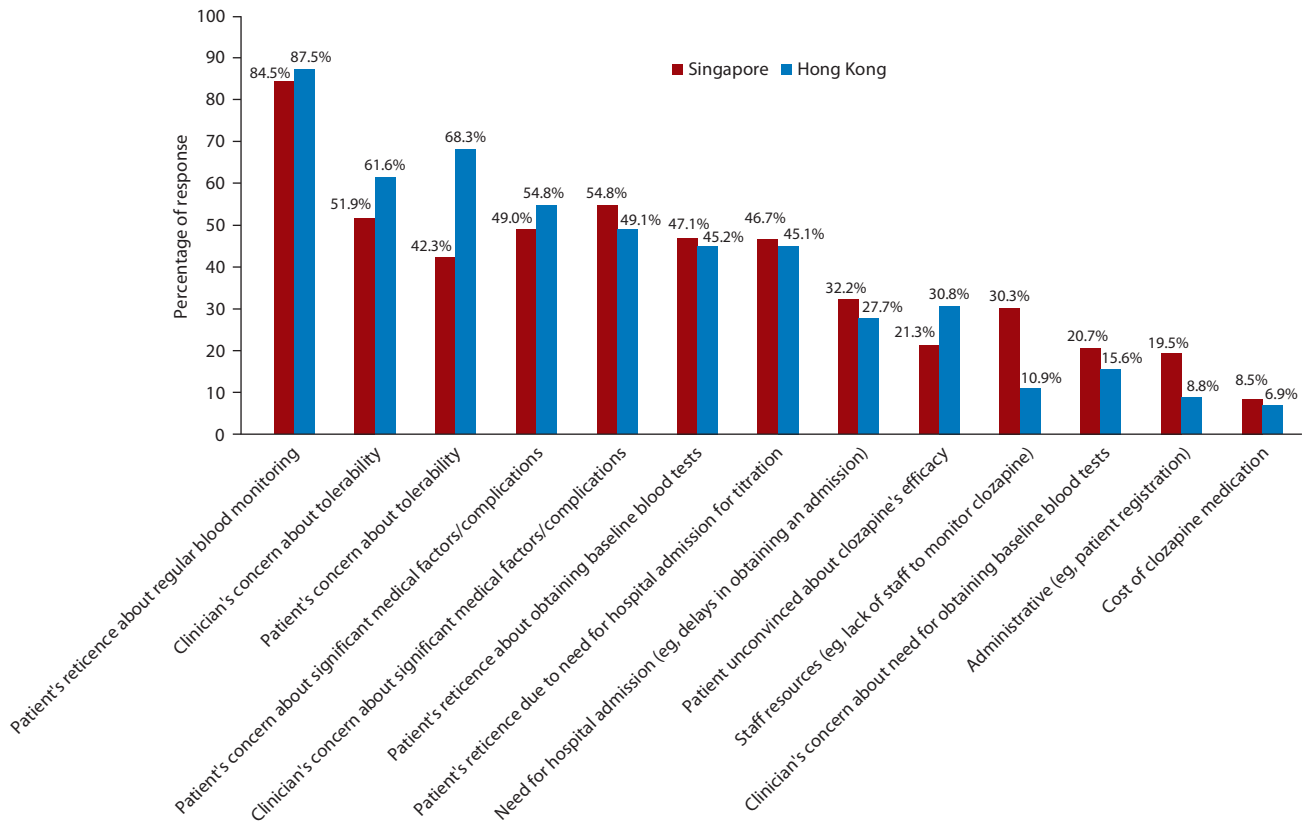
A total of 261 clinicians from both regions responded to the survey, resulting in response rates of 50% (156 out of 309 participants) in Singapore and 19% (105 out of 556 participants) in Hong Kong. Missing responses were noted in 0.3% and 1.3% of the total responses provided by the clinicians in Singapore and Hong Kong, respectively. As shown in Table 1, the respondents from both regions had comparable sociodemographic characteristics. The majority of respondents were male (59.4%) and working as psychiatrists (67.4%) in both inpatient and outpatient settings (67.0%), with 6 to 11 years of experience in psychiatry (29.1%).

Experience With the Initiation of Clozapine

The majority of respondents (76.9% in Singapore; 68.6% in Hong Kong) reported that less than 20% of patients under their care have treatment-resistant schizophrenia. Most respondents (57.1% in Singapore; 52.4% in Hong Kong) estimated that 0%–20% of their patients were eligible for clozapine but did not receive it.

The most common location where clinicians initiate clozapine was the inpatient setting only (51.3% in Singapore; 65.7% in Hong Kong), followed by both inpatient and

Figure 1. Factors That Lead to Delays in the Initiation of Clozapine “Fairly” or “Very” Frequently



outpatient settings (32.7% in Singapore; 28.6% in Hong Kong) and, lastly, outpatient only (16.0% in Singapore; 5.7% in Hong Kong).

Opinions of Clozapine and Its Underutilization

When asked to rate the effectiveness of clozapine in treating schizophrenia compared to other antipsychotics on a 1–10 Likert scale (1 indicating “much less effective,” 5 being “about the same,” and 10 being “much more effective”), most respondents in Singapore and Hong Kong thought that clozapine was more effective—the mode of the score was 8 (median = 8; interquartile range, 7–8) for both regions. The correlation analysis showed a positive correlation between years of practice in psychiatry and the clinician's perception of clozapine's effectiveness compared to other antipsychotics in the Hong Kong sample ($r=0.27$, $P=.01$), while no significant relationship was found in the Singapore sample ($r=0.12$, $P=.15$).

Most respondents in both regions reported that patients treated with clozapine were more satisfied compared to those on other antipsychotics (78.8% in Singapore; 88.6% in Hong Kong), with a higher proportion of Hong Kong clinicians endorsing this satisfaction compared to their Singaporean counterparts ($\chi^2_{1, 261} = 4.16$, $P=.04$).

A higher proportion of respondents in Singapore thought that clozapine was underutilized in comparison to their Hong Kong counterparts. 67.9% of respondents in Singapore and

51.4% in Hong Kong agreed or strongly agreed that clozapine was underutilized; 25.0% of respondents in Singapore and 36.2% in Hong Kong had a neutral view, while the rest disagreed with this statement ($\chi^2_{2, 261} = 7.40$, $P=.03$).

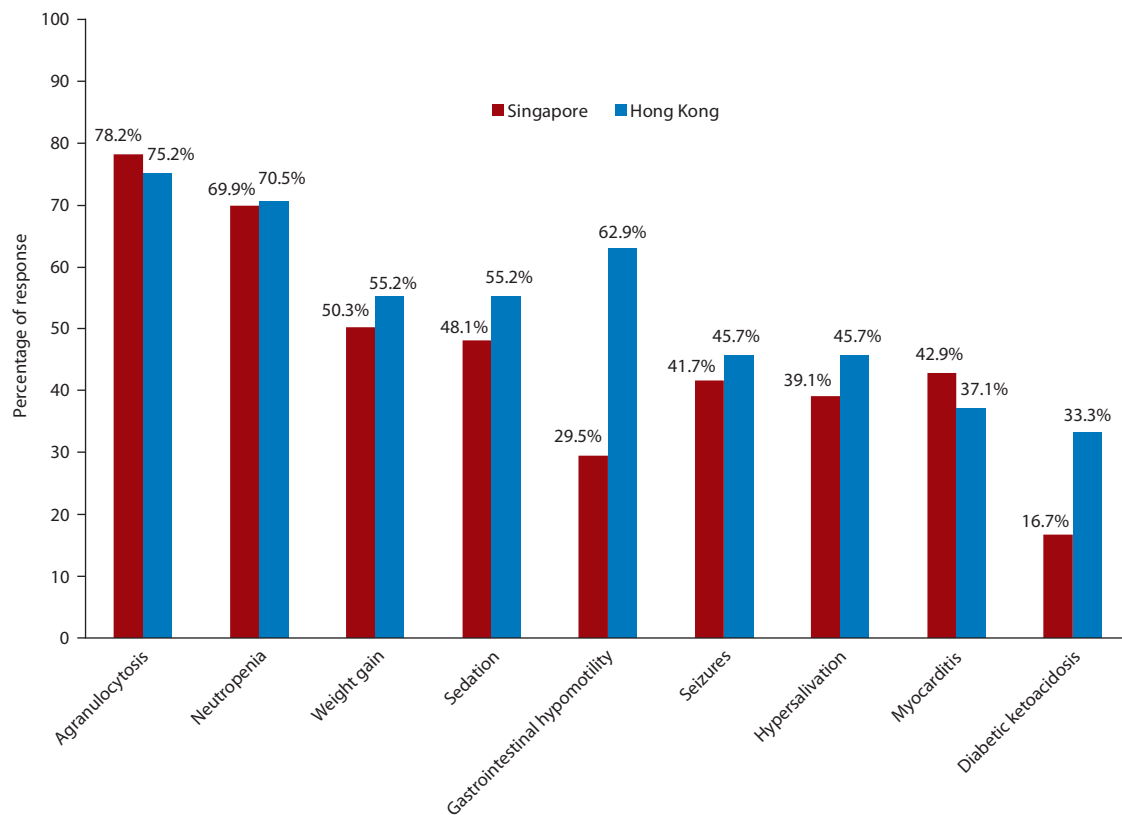
Factors Leading to Clozapine Delay

As shown in Figure 1, the dominant patient factor that delayed the initiation of clozapine was the patient's concern about regular blood monitoring (84.5% in Singapore; 87.5% in Hong Kong). From the clinicians' perspective, tolerability of clozapine (51.9% in Singapore; 61.6% in Hong Kong) and its medical complications (54.8% in Singapore; 49.1% in Hong Kong) were the top two concerns.

When the results were compared between Singapore and Hong Kong, clinicians in Hong Kong were more likely to endorse “patient's concerns about tolerability” of clozapine as a barrier to its initiation (68.3%) than their Singapore counterparts (42.3%) ($\chi^2_{1, 256} = 15.33$, $P<.001$). Clinicians in Singapore were more likely to endorse administrative barriers (19.5% in Singapore; 8.8% in Hong Kong, $\chi^2_{1, 254} = 5.59$, $P=.02$) and lack of staff as reasons for clozapine's underutilization (30.3% in Singapore; 10.9% in Hong Kong; $\chi^2_{1, 255} = 13.37$, $P<.001$).

The 3 side effects that concerned clinicians the most were (1) agranulocytosis (78.2% in Singapore; 75.2% in Hong Kong), (2) neutropenia (69.9% in Singapore; 70.5% in Hong Kong), and (3) weight gain (50.3% in Singapore;

Figure 2. Side Effects That Clinicians Think Are "Important" or "Very Important"



55.2% in Hong Kong). Other side effects of concern are shown in Figure 2. When the results were compared between clinicians in Singapore and Hong Kong, those in Hong Kong were more likely to worry about side effects of gastrointestinal hypomotility ($\chi^2_{1, 261} = 28.53, P < .001$) and diabetic ketoacidosis ($\chi^2_{1, 261} = 9.73, P = .002$) than their Singapore counterparts.

Factors to Improve Clozapine Utilization

While respondents from both regions agreed that additional clinical or administrative resources would facilitate the initiation of clozapine in their workplace, a higher proportion of respondents in Singapore (74.4%) believed that more resources were needed to improve clozapine prescription compared to their Hong Kong counterparts (59.0%) ($\chi^2_{1, 261} = 6.78, P = .01$).

As shown in Figure 3, more than half of the respondents in both regions felt that having adequate outpatient clinic resources to assess patients and initiate them on clozapine treatment (70.3% in Singapore; 60.2% in Hong Kong) and adequate resources in monitoring clozapine treatment (eg, blood tests; 64.5% in Singapore; 50.5% in Hong Kong) would be helpful in improving the rates of clozapine prescription, with a higher proportion of clinicians in Singapore endorsing the need for adequate resources in monitoring clozapine treatment than their Hong Kong counterparts ($\chi^2_{1, 258} = 5.03, P = .03$).

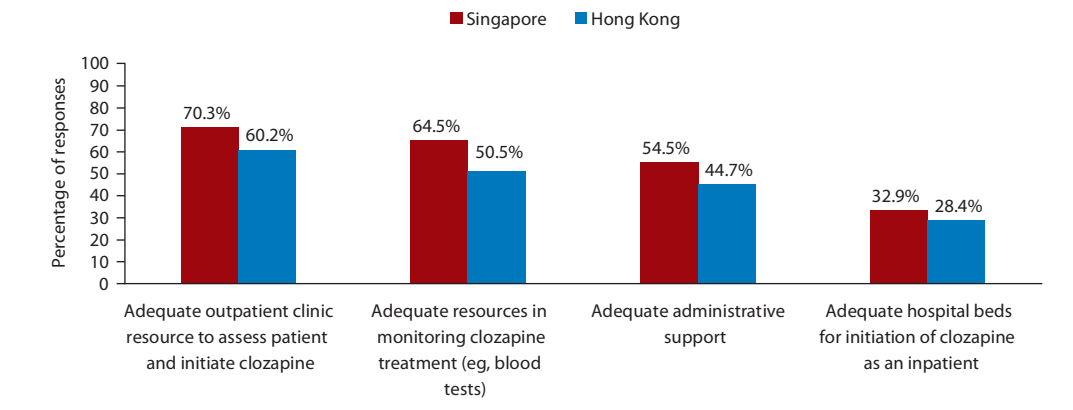
DISCUSSION

In our study, clinicians from Hong Kong and Singapore were asked for their opinions on clozapine use in schizophrenia and the barriers to its prescription. The majority of participants believed that clozapine was an effective and satisfactory treatment for schizophrenia compared to other antipsychotics. This was similar to the views of practitioners surveyed in recent studies in United Kingdom,¹⁵ Israel,¹⁶ and India¹⁷ and in contrast to an earlier 2010 Denmark study in which 66% of clinicians felt that patients were less satisfied with treatment with clozapine compared to other atypical antipsychotics.²⁰ More than half of the clinicians in Singapore and Hong Kong reported an underutilization of clozapine, with more clinicians in Singapore endorsing the underutilization of clozapine within their practice and a greater need for more resources to improve their prescribing of clozapine compared to those in Hong Kong. The clinicians from both regions shared very similar responses in terms of their top concerns for factors that hindered clozapine prescription, the side effects of clozapine that concerned them the most, and the types of support required to improve the use of clozapine in their practice.

The dominant barriers to clozapine prescription were identified by clinicians in this study to be (1) the need for frequent blood monitoring and (2) the adverse effects and

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Figure 3. Factors Thought to Be Helpful for the Prescription of Clozapine



tolerability of clozapine, both of which are directly related to clozapine's unique pharmacologic profile. The results were consistent with the leading concerns highlighted in surveys of practitioners in the United Kingdom, India, and Israel; practitioners in the latter two countries further described concerns about the patient's nonadherence to clozapine as a barrier to its prescription.^{15-17,21} Health system factors were also identified as key areas to focus on. These include the need for more resources in terms of outpatient clinic support (where clozapine initiation least occurs) and the provision of adequate resources for monitoring the frequent blood testing needed for clozapine treatment.

Many clinicians may avoid prescribing clozapine because the side effects of clozapine can be greater than those of other antipsychotics.²² This discomfort with managing the side effects of clozapine may stem from the clinicians' lack of experience with using clozapine.²³ To address clinicians' concerns about managing clozapine's adverse effects and instill within them the confidence to use clozapine, teaching of clozapine prescription should ideally go beyond the mere understanding of theoretical knowledge and involve active modeling from experienced clozapine prescribers and clinical experience in the prescription and follow-up of patients on clozapine.²⁴

Several solutions have also been recommended to reduce the burden of the frequent blood monitoring. One such solution would be the simplification of blood monitoring through the use of point-of-care testing devices instead of venipuncture.^{21,25} Some European countries have also proposed an easing of the frequency of blood monitoring to a quarterly basis in mentally competent and adequately informed patients after the first 6 months of clozapine treatment.^{6,26} Given that the risk of clozapine-induced agranulocytosis is minimal after the first 18 weeks of treatment,^{27,28} and as blood monitoring is no longer cost-effective after 6 months, this proposal may have its merits.²⁹ Nonetheless, further studies will be needed to determine the safety of this recommendation. The recent reduction of blood monitoring frequency for clozapine patients to once every 3 months during the COVID-19 pandemic (recommended by the Consensus Statement on the Use

of Clozapine During the COVID-19 Pandemic³⁰) may provide some real-world data to help determine the safety of reduced monitoring.

As for the health system barriers, a broader reexamination of our current services for clozapine delivery may shed light on the gaps that exist within our health care system. In Singapore and Hong Kong, mental health care for those with severe mental illnesses such as schizophrenia is primarily delivered by publicly funded tertiary psychiatric services.^{31,32} Initiating clozapine in the public general psychiatry services can be challenging because of the high patient volumes and limited contact time clinicians have with patients in these services.³³ These factors make it difficult for clinicians to offer the weekly outpatient reviews needed for dose titration, monitoring of adverse effects, and blood investigations during the early stage of clozapine initiation. General psychiatric services may also lack a centralized infrastructure for coordinating the numerous services needed by patients on clozapine, such as family and patient education, laboratory facilities, medical consultation, adherence monitoring, and overall service coordination.³⁴

In contrast, the early intervention services for psychosis in both regions have fared better in reducing their delays in clozapine initiation. The Hong Kong Early Intervention Service³⁵ has a shorter delay to clozapine initiation in comparison with the standard service.⁵ The Early Psychosis Intervention Program in Singapore also has a relatively short delay in clozapine prescribing of 19.3 weeks¹¹ compared to the delays of up to 5.5 years in services in other countries.³⁶ Both early intervention services have adopted a strong case management model and a multidisciplinary approach to care that allows for a smooth coordination of the diverse needs of their patients. Their success at clozapine initiation hints at the potential for a specialized and integrated clozapine service to overcome the barriers that exists in the general psychiatric services.

Increasingly, dedicated clozapine services with an interprofessional model of care are advocated to optimize the prescribing of clozapine.⁶ These services tap into expertise of psychiatric pharmacists, trained psychiatric

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nurses, and allied health professionals to manage the multiple needs of patients on clozapine and aid in the provision of psychoeducation, monitoring of medication adherence, management of adverse effects, and review of stable patients.^{21,37,38} These multidisciplinary approaches have been beneficial in increasing patient health literacy related to clozapine, improving clozapine continuation rates and patient/caregiver satisfaction, reducing resource utilization, and increasing service cost savings.^{21,38} Such models of care may serve as references for the development of similar services within our regions. One potential drawback of a specialized clozapine service is the deskilling of clinicians outside of the service in the use of clozapine, due to the lack of exposure to clozapine and a reliance on the knowledge of the specialized team.¹⁶ The development of a clozapine service should include active educational and training opportunities for trainees and psychiatrists in order to ensure that all clinicians are familiar with the use of clozapine.

Strength and Limitations

This is the first survey that assessed clinicians in psychiatry in Singapore and Hong Kong for their attitudes toward clozapine initiation in schizophrenia. The response rates of 50% in Singapore and 19% in Hong Kong could be better, but these were comparable to the average response rates in previous survey studies from the same regions.^{39,40} There was a good completion of the survey questions by the respondents, with missing responses in 0.3% and 1.3% of the total responses in Singapore and Hong Kong, respectively. The comparable sociodemographic

characteristics of respondents in both regions also allowed for a more meaningful comparison of the survey responses. Nonetheless, the survey results should be interpreted in light of the study's limitations, including the possibility of a selection bias. Clinicians who are experienced with use of clozapine, as well as those who are concerned about its underutilization, were more likely to respond to the survey. In contrast, those who are indifferent to clozapine or harbor a negative attitude toward it may have been less inclined to participate in the study. Because of the self-report nature of this study, the respondents were susceptible to recall and reporting bias.

CONCLUSION

In conclusion, clinicians in both Singapore and Hong Kong agree that clozapine is underutilized, due to concerns about its tolerability and adverse effects, the frequent need for blood monitoring, and the perceived administrative burdens of initiating this medication. Given that clozapine is the only antipsychotic with good evidence for effectiveness⁶ and cost-effectiveness⁷ in treating patients with treatment-resistant schizophrenia, efforts should be made to improve its access and initiation. A good understanding of the barriers to clozapine prescribing within both regions would aid in improving the use of clozapine, starting with the redesign of the model of the clozapine service to address the system barriers to clozapine prescription and reduce the burden of frequent blood monitoring, as well as the provision of training and supervision to improve clinicians' confidence in prescribing clozapine and managing its adverse effects.²⁴

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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.

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