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Delayed Initiation of Clozapine Continues to Be a Substantial Clinical Concern

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About 20% to 30% of people with schizophrenia fail to respond satisfactorily to trials with 2 or more antipsychotics given at adequate dosage for 4 to 6 weeks each and are considered as having treatment-resistant schizophrenia (TRS).[1] People with TRS have increased prevalence of smoking, substance abuse, criminal behaviour, functional impairment, psychiatric hospitalisation, impaired quality of life, and 3 to 11 times higher health care costs compared with those who are responsive to treatment.[2,3] Clozapine is the only medication with worldwide regulatory approval for managing TRS and has demonstrated superior efficacy over typical and atypical antipsychotics, with approximately 40% of patients responding adequately.[4,5] However, treatment with clozapine is not effective for a significant proportion of people with TRS, and there is emerging concern that delayed initiation of clozapine could be associated with suboptimal response.[6-8]

Nielsen et al.,[7] researching Denmark's nationwide databases, opined that each previous antipsychotic trial reduced the likelihood of response to clozapine by 8% to 11% and that one-third of the patients had 4 or more antipsychotics prior to commencing clozapine. Another study from Denmark suggested that while nearly 25% of people with TRS who were treated with clozapine showed moderate to substantial functional improvement, each year of delay was associated with a 15% decrease in the chance of functional improvement among females.[8] Promisingly, based on best available evidence, many recent revisions of clinical practice guidelines for schizophrenia, including that of the Canadian Psychiatric Association, have recommended that TRS should be identified early and that, once established, treatment with clozapine should not be delayed.[9,10] Theoretically, in many patients, TRS could be diagnosed as early as 3 months from onset of psychosis and clozapine introduced.

However, while the pathway from evidence generation to its synthesis and guideline development is robust and well developed, the route for the dissemination of these guidelines into clinical practice is much more arduous and poorly researched.[11] With regard to the pharmacoepidemiology of clozapine, both the rate of its use and the timing of its usage are clinically relevant. While there has been research interest in the past 2 decades on the area of underutilisation and low prescription rates of clozapine,[12] attempts to synthesise and analyse the data on the delayed initiation of clozapine have been much more limited. In this context, we reviewed the literature on the time taken for patients with schizophrenia to be commenced on clozapine in clinical practice and highlight the complex issues surrounding the delayed initiation. We searched the PubMed, PsycINFO, Embase, and Ovid MEDLINE databases up to December 2017 using the search terms *clozapine* in combination with *initiation* or *start* or *commence* or *first episode psychosis* or *early psychosis* or *early schizophrenia*. The search resulted in a total of 3371 studies. The 3 authors independently screened and reviewed the abstracts available in the English language and identified 10 relevant studies. The authors reviewed the full text of these studies and through cross-referencing identified an additional article. The findings are summarised in Table 1.[6,13-22]

Research focussed on this area has been somewhat limited and predominantly from Western countries. Furthermore, many methodological issues confounded these studies. None of them were prospective, data collation was

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Table 1. Summary of studies evaluating time to commence clozapine among people with schizophrenia.

Authors	Study period and location	Sample size (*n*)	Time to commence clozapine (TCC) (SD; range)	Number of antipsychotics trialled prior to clozapine	Comments
Taylor et al. 2003	January 1990–April 2001, multiple IP units in South East London	100	5[a,b] (NA; 0-11.1)	5.5[a]	• Significantly longer TCC was detected among those older than 30 years
Wheeler et al. 2008	1990–2004, CMHS, Auckland	917	9.7[a,c] (7.8; 0-43) 8[c,d]	3[d]	• Longer TCC was noticed among older patients and patients of European ethnicity and to have started clozapine when government funding was restricted (1993-1998)
Harrison et al. 2010	1990-2007, all adult mental health patients prescribed clozapine at a public secondary care mental health service, as at March 31, Auckland	402	2.8[a,e] since 1999 (1.9; NA) 5.7[a,e] before 1999 (3.3; NA)	3.5[a] 3[d]	• Mean TCC fell from 5.7 to 2.8 years since 1999 (when clozapine became widely available and nationally funded) • In 2004-2007, mean TCC was less than 1 • Trend toward reduced TCC in patients presenting more recently
Howes et al. 2012	January 2006–April 2010, IP and OP in South London and Maudsley NHS trust, United Kingdom	149	3.98[a,b] (4.14; 0-18.25)	3.9[a] 3[d]	• The study describes a significant relationship between TCC and longer duration of illness
Alessi–Severini et al. 2013	May 2010–September 2010, OP attending clinics at Schizophrenia Program, Winnipeg, Canada	74	Male: 8.9[c,d] (NA) Female: 7.7[c,d] (NA)	3.3[a]	• A trend toward earlier clozapine initiation was observed for those started on clozapine after 2005 with the mean TCC falling to 4.6 years
Najim et al. 2013	August 2004–October 2006, community hospital, semirural, South Essex, United Kingdom	42	5[a,b] (NA; 0.2-16.1)	4[a] 4[d]	• Significantly longer TCC was noted in patients who were: ○ Older than 30 years ○ Diagnosed with treatment resistance before 1991 ○ Treated before introduction of risperidone
Wheeler et al. 2014	1990-2007, IP and OP under the care of public secondary care mental health services in Auckland and Birmingham	Total: 664 Birmingham, 262 Auckland, 402	Birmingham 6.5[a,e] (3.8; NA) Auckland 5.3[a,e] (3.6; NA)	Birmingham: 4.3[a] Auckland 3.1[a]	• Mean TCC was less than 1 in 2004-2007 in both UK and New Zealand cohorts
Üçok et al.2015	Period of study not available, outpatient units, Istanbul	162	2.42[a,b] (NA; NA)	2.4[a]	• A shorter delay was found among the patients who were followed up since their first episode
Grover et al. 2015	January 2006–June 2014, both IP and OP at a tertiary care hospital, Chandigarh, India	200	1.93[a,b] (1.82; NA) 1[b,d]	3[a]	• Increased TCC among those with longer duration of illness and age >20 years
Tang et al. 2016	April 2001–June 2012, State Psychiatric Hospital, Singapore	69[f]	1.10[a,e] (0.76; NA) 0.374[a,b] (0.52; 0-2.25)	3.4[a] 3[d]	• Identified a shorter TCC among patients who were unemployed and economically inactive than those who were gainfully employed
Doyle et al. 2017	1995-2013,IP and OP who presented with a first episode psychosis between 1995 and 1999 at a CMHS in Dublin, Ireland	24	6.7[a,e] (3.5; 1-14)	4.85[a]	• Identified underutilisation of clozapine for management of treatment-resistant schizophrenia • The authors postulate several reasons for this and advocate for a better understanding of the barriers to prescribing clozapine

CMHS = Community Mental Health Service; IP = inpatients; OP = outpatients; NA = not available; TCC = time to commence clozapine in years.
[a]Mean.
[b]Measured from the establishment of treatment resistance.
[c]Measured from the onset of psychosis.
[d]Median.
[e]Measured from the first presentation to mental health service.
[f]Of 69 patients using clozapine, 44 patients had established treatment resistance; *n* = 44 used to calculate TCC from establishment of treatment resistance.

incomplete in many due to missing information, duplication of data in different studies cannot be ruled out, and some studies did not include a representative population of TRS in that region but were samples from selected clinical settings. Methods used to calculate delayed initiation of clozapine were different among the studies, generating difficulties in interpreting the results; some estimated the delay from the onset of psychosis[14,17] and others from the point of the first contact with health services[15,19,21,22] or from a theoretical point of treatment resistance (6 to 8 weeks after the second antipsychotic trial).[6,13,18,20,21] In addition, it should be noted that these studies captured only data of patients who were already on treatment with clozapine, and the considerable proportion of patients with TRS, ranging from 20% to 80%, who were yet to commence clozapine were not captured in these studies.[23]

Our review suggests a considerable delay for commencing clozapine among patients with schizophrenia. The mean time taken to start clozapine varied considerably among these studies, ranging from 0.4 years in Singapore[21] to 9.7 years in Auckland,[14] with a wide range from 0 to 43 years. The delay in commencing clozapine appears to be a worldwide phenomenon, spread across many countries. Canadian research that focusses on the delay in initiating clozapine is limited; Alessi-Severini et al.[17] observed a median delay of 7.7 years among females and 8.9 years among males calculated from the onset of psychosis in a small sample of 74 outpatients with TRS who were being treated with clozapine. While the 2 Asian studies found a minimal delay in commencing clozapine, these were carried out at tertiary care hospital settings in India and Singapore and might not apply to other settings in these countries.[20,21] The wide disparity in rates of clozapine prescription among Asian counties with meagre rates of prescription in Japan and Singapore (<2%) and higher rates of 30% to 40% from China and Taiwan raise the possibility that time taken to initiate clozapine could also vary significantly among these countries.[24] Encouragingly, some studies have observed a significant reduction in the delay for starting clozapine among those who were commenced on the medication in more recent years.[15,17,19-21] However, this finding is not uniform, with researchers from Denmark and the United Kingdom discovering no changes in the time to commence clozapine over time.[16,23] Other relevant patient-related factors that have been reported to be associated with the delayed commencement of clozapine include older age[13,14,18] and chronicity.[16]

The delay in commencing clozapine can have detrimental effects on patient outcomes, particularly as the first years after diagnosis are vitally important as many patients would be studying or employed and are likely to have better family support and thus are in a position to profit from the resolution of symptoms and achieve functional recovery. Often, adequate and sustained symptom control is a necessary prerequisite for good functional recovery.[25] In addition to its demonstrated efficacy in markedly reducing hospitalisation, the reported usefulness of clozapine for lowering suicidal, self-harm, aggressive, and violent behaviour as well as substance abuse are potential additional benefits with early commencement of this medication.[2,3,26,27] A recently published Canadian research study that used predefined algorithmic treatment in first-episode schizophrenia observed that 17.4% of patients did not respond to 2 consecutive trials of antipsychotics of adequate duration and dosage.[28] Among the nonresponders, 75% of the patients who agreed to a trial of clozapine responded well, but none of the patients who continued with the original antipsychotic improved. This study demonstrates the constructive role of early identification of TRS and the role of clozapine in its management. Evidence generated from meta-analytic reviews of the adverse functional implication of long duration of untreated psychosis further substantiates the need for effective management of psychosis from illness onset.[29]

Based on the prevalence of TRS and its response rate to clozapine, it can be estimated that approximately 20% of patients with schizophrenia should be receiving clozapine.[30] Research analysing the prescription of antipsychotics for schizophrenia in the Canadian province of Quebec found that clozapine prescriptions ranged from 3.9% to 10.8%, with a mean of 6.9%,[31] which is much lower than the figures reported from countries such as Finland, Iceland, and New Zealand and the proposed ideal rate of prescription of clozapine of about 20%. The prevalence of clozapine use in the first few years of schizophrenic illness has been poorly researched in Canada but is believed to be quite low.[32] An international study using clozapine databases from different countries found that the peak prevalence of clozapine usage was significantly higher in the age group of 40 to 59 years when compared with younger age groups, indicating that perhaps across the globe, treatment with clozapine begins much later in the course of illness.[30]

Possible Reasons for Delayed Initiation and Potential Solutions

Although a theoretical possibility, it is unlikely that the delayed commencement of clozapine is an artefact secondary to a significant proportion of patients with schizophrenia developing treatment resistance later in the course of their illness. There is convincing evidence from recent research that close to 70% to 80% of patients with TRS have this condition from the onset of psychotic illness.[33,34] Tentative evidence supports conceptualising TRS as a separate subtype with its own distinct neurobiological features, such as more prominent glutamatergic abnormalities, minimal dopaminergic abnormalities, significant decreases in grey matter volume, and other neuroimaging abnormalities compared with treatment-responsive schizophrenia patients.[35] Given the demonstarted benefits of early initiation of clozapine in TRS and the lack of suitable evidence-based alternative treatments, the delay observed in initiating clozapine in ordinary clinical practice is puzzling. The responsible factors are likely to be multiple and complex, and systematic research

comprehensively exploring the reasons behind the disparity between evidence generation and its translation into clinical practice are required. While there have been attempts to evaluate the attitude of psychiatrists, clinicians, patients, and families to clozapine,[36-38] research in this area has been somewhat limited, and the generalisability of findings to different settings, cultures, and countries is doubtful.

Clozapine is a highly regulated medication that requires mandatory monitoring over a prolonged period, and its use is frequently associated with many side effects, such as sedation, hypersalivation, constipation, weight gain, and other metabolic problems.[39] Also, rarely there could be potentially lethal complications associated with clozapine treatment, such as agranulocytosis, thromboembolism, myocarditis, cardiomyopathy, pericarditis, apnoea, ileus, polyserositis, convulsions, neuroleptic malignant syndrome, rhabdomyolysis, diabetic ketoacidosis, colitis, and interstitial nephritis.[40] Apprehension about these adverse effects and compliance with treatment, overestimation of the likelihood of life-threatening complications, practical difficulties in implementing the mandated rigorous monitoring regimes, and the requirement to start clozapine as an inpatient at many services have been suggested by both clinicians and patients as important reasons for the delayed initiation and underutilisation of clozapine treatment.[36,37] The positive effect of clozapine on all-cause mortality detected in many population-based cohort studies[41,42] seems to have achieved little traction for alleviating clinicians' concerns about its cardiovascular and metabolic adverse effects. The limited number of studies that have explored the attitudes of patients and families suggest that the vast majority have a favourable opinion about clozapine.[38] The marked variation in clozapine prescription rates between clinicians within the same health services and between health services with demographically similar patient groups suggests that patient-related factors are unlikely to be the main reason for the delayed commencement and underutilisation of clozapine.[23,36,37] Interestingly, surveys of clinicians in different countries have found that despite professed knowledge of guidelines recommending clozapine for TRS, a significant proportion of them reported that they would rather combine 2 nonclozapine antipsychotics or increase dosages of antipsychotics past recommended maximum dosages before trialling clozapine.[36,37] Clozapine is a generic medication, and it is possible that the abundant availability and marketing of atypical antipsychotics with a more benign side effect profile has led to overuse of higher dosages of these medications and antipsychotic polypharmacy for which there is no clear emprical evidence[43] with consequent delay in prescription of clozapine. Furthermore, while the beneficial effect of clozapine in TRS is often delayed, adverse effects could manifest early in the treatment and can discourage both patients and clinicians. Practical difficulties in differentiating TRS from confounding factors for relapse/nonremission of psychosis, such as nonadherence to treatment and substance abuse, could be additional impediments in the decision-making process to start clozapine early.

While it is encouraging that many clinical practice guidelines have robustly endorsed early identification of TRS and initiation of clozapine, it is unfortunately not clear whether these guidelines have had a significant impact on health care provider performance and patient outcomes.[11,44] Many psychiatric practitioners, while acknowledging that clinical decisions and practices should be based on the best available evidence, still are not enthusiastic about its implementation in their clinical practice.[44] While many resources and much expertise have been focussed on knowledge synthesis and guideline development, less attention has been given to study the reasons for the gap in the dissemination of these guidelines into clinical practice. Sernayak et al.[45] found that despite having good knowledge of guidelines, in only 5% of cases did psychiatrists switch the antipsychotic for treatment-nonresponsive patients, and concerns about the patient's adherence to treatment after the switch and uncertainty about clinically meaningful and sustainable effects of treatment were stated as equally important rationales for not implementing the guideline. Developing or adapting guidelines locally, taking into account local context and feasibility, might enhance clinicians' adherence to guidelines.[46] Recently, some researchers have proposed a change of the terminology from *treatment resistance*, with its connotation of chronicity, to *clozapine eligibility*[32] as more appropriate to describe the group of patients with schizophrenia who did not respond to 2 adequate trials of antipsychotics. However, it is unclear how widely this term has diffused into clinical practice and academic circles and influenced clozapine prescription.

While regular local education, audit, and feedback on patient outcomes seem to have a positive effect on the prescription of clozapine in the short term, their long-term efficacy has not been demonstrated.[47] Similarly, the effectiveness of peer and leadership support by "clozapine experts," advocacy groups, and patient- and family-led initiatives to enhance the acceptance of clozapine by other clinicians and patients is being explored but needs further evaluation. Service-related issues affecting the timely prescription of clozapine also require further scrutiny. A clozapine-friendly culture of services including establishment of streamlined clozapine clinics with multidisciplinary staffing, implementation of point-of-care haematological monitoring services, provision of transport of patients to the clozapine clinic, ability to start clozapine as outpatients, easing clozapine-related administrative burden, enhancing ease of access to specialist services to manage adverse effects, and local availability of clozapine experts could go a long way in alleviating patients' and clinicians' concerns and in enhancing appropriate and timely prescription of clozapine.[48]

Conclusions

There is sufficient evidence from the existing literature to construe that clozapine, which is undoubtedly the most effective treatment for TRS, is underutilised and its prescription delayed in clinical practice, generating significant adverse consequences. The factors leading to the delayed initiation of clozapine are of complex origin and encompass clinicians, patients, families, and mental health service administrators. These issues require multifaceted interventions and cannot be solved by solely developing evidence-based guidelines. A paradigm shift in the focus of the research from guideline development to implementing evidence-based guidelines into clinical practice is warranted. Based on available evidence, we would like to suggest that in the management of people with TRS with clozapine, treatment delayed should be considered as treatment denied. Mental health services and regulatory bodies should assume a more proactive role in facilitating, monitoring, and rewarding timely evidence-based prescription for TRS. The recommendation to rearticulate TRS as clozapine-eligible psychosis needs further consideration. Although hesitancy in prescribing clozapine is understandable in some instances, the right of patients with TRS to access treatments with the best evidence safely and in a timely manner should guide clinical practice.

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