

# Clozapine: a distinct, poorly understood and under-used molecule

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Consensus of opinion is rare in psychiatry. Even in the field of clinical trials, where experimentation is tightly controlled and regulatory bodies scrutinize the proof, controversies are frequent and difficult to resolve.<sup>1</sup> One issue for which there is a widespread consensus is the unique place that clozapine occupies in the treatment of severe mental illnesses, particularly refractory schizophrenia. This molecule is distinct because of its effectiveness, numerous and sometimes mysterious pharmacological characteristics, serious side effects and under use.

Historically, clozapine was distinguished by one of its dangerous and sometimes lethal side effects, agranulocytosis, which almost caused its complete banishment from the psychiatric pharmacopoeia.<sup>2</sup> It was only rescued when its superior therapeutic effects compared with chlorpromazine in patients with refractory schizophrenia were demonstrated.<sup>3</sup> Since its controlled comeback, clozapine has consistently demonstrated advantages in a variety of clinical situations. Its enhanced therapeutic profile in patients with schizophrenia who respond poorly to other antipsychotic medications, both typical<sup>3-5</sup> and atypical,<sup>6-8</sup> have been reported in many studies and encompass many dimensions of the schizophrenia syndrome.<sup>9,10</sup> Positive symptoms are most consistently improved by clozapine, but there are also reports indicating that anxiety, mood and negative symptoms<sup>11</sup> as well as hostile behaviours<sup>12</sup> are better controlled with clozapine than with other neuroleptics, although the data are less consistent. Moreover, it has been reported that patients are more likely to remain compliant with clozapine than with other atypical antipsychotics.<sup>13-15</sup> Clozapine is also the only antipsychotic medication that has shown an anticraving effect for drugs of abuse,<sup>16</sup> a significant effect in reducing suicide rates in patients with schizophrenia<sup>17</sup> and an efficacy on refractory mood disorders.<sup>18</sup> Every clinician who has prescribed clozapine can recount a few experiences of seeing patients emerge from their chaotic psychotic experience. This is one of the most rewarding experiences that a psychiatrist can have in his or her professional life, and it is among the most important strikes we have made against one of the most devastating diseases affecting mankind.

Expiration of the patent on clozapine in 2007 has lessened the burden of economic constraints against the use of clozapine. However, side effects remain a major issue affecting the choice to use the drug. With respect to both the presence and absence of side effects, clozapine again distinguishes itself. Historically, clozapine was the first neuroleptic identified without motor side effects. In this regard, it is the prototypical molecule of a new generation of antipsychotic agents that have limited or no adverse effects on movement while curbing psychotic symptoms. These atypical neuroleptics almost completely replaced the older generation of antipsychotics. Although this major shift in practice was initially hailed as one of the most important and positive changes in the treatment of schizophrenia,<sup>19</sup> recent studies seriously questioned this change in practice, both on the grounds of efficacy and safety.<sup>20</sup> Indeed, while most of the new generation antipsychotics do not distinguish themselves from the older ones with regards to efficacy and effectiveness,<sup>21</sup> there are unquestionable and major problems associated with the use of this new class of molecules: increased food intake,<sup>22</sup> weight gain and dysregulation of glucose and lipid metabolism,<sup>20</sup> all of which are risk factors for cardiovascular morbidity and mortality. Here, sadly, clozapine again came out ahead,<sup>23</sup> further demonstrating the uniqueness of this molecule with respect to both beneficial and adverse effects. Patients taking clozapine can sometimes gain more than 25 kg, posing a real dilemma to clinicians about how to optimize remission while keeping the patient's physical well-being and safety under control. These effects came under very strong scrutiny in the last decade because of their possible contribution to the major mortality gap (20–25 yr) between patients with schizophrenia and the general population.<sup>24</sup>

Although this tension between controlling psychotic symptoms and side effects will always remain an issue for each individual patient, a recent epidemiologic study,<sup>25</sup> the largest of its kind, surprisingly suggested that clozapine is paradoxically associated with decreased overall mortality at the population level. This study, which analyzed mortality between

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1996 and 2006 in all Finnish patients diagnosed with schizophrenia, showed that patients taking any antipsychotic had significantly lower mortality compared with patients not taking an antipsychotic drug. It further showed that clozapine fared better than 6 other drugs (and polypharmacy), being associated with a substantially lower risk of death, including suicide, compared with a range of other antipsychotics, even those with more neutral metabolic side effects. Although this study has been criticized on many of its methodological aspects,<sup>26</sup> it suggests another important public health advantage of clozapine use.

Given all of these facts, if one had a relative with schizophrenia, it would be only natural to make every effort to ensure that he or she is given the opportunity to try clozapine if other antipsychotics were ineffective. Not only may it help him or her to better control the symptoms of illness, but it may also prevent early death. In fact, consensus treatment guidelines for schizophrenia from a wide range of prominent expert panels<sup>27-31</sup> recommend the use of clozapine after the failure of 2 adequate trials with antipsychotic medications, including an atypical one, to produce adequate response or in patients with persistent suicidal gestures or ideation. Unfortunately, the clinical reality does not show that we, as clinicians or care systems, are doing our best to give our patients this chance. The under use of clozapine has been documented in many jurisdictions<sup>23,32-36</sup> (although the rates of clozapine use are remarkably high in China<sup>37</sup>). For example, a recent New Zealand study reported a 13.6% increase in clozapine use when audit and feedback were used as an intervention to promote adherence to best practice guidelines for the treatment of schizophrenia.<sup>36</sup> As another example, in a recent American multisite trial examining the clinical effectiveness of antipsychotic medication for chronic schizophrenia, only 11% of patients used clozapine during phase 3 of the trial, although 51% had previously discontinued other medication because of inadequate therapeutic effectiveness.<sup>23</sup> Possibly because of the mixed picture of increased efficacy with sometimes severe side effects, clinicians hesitate to prescribe clozapine to the patients who need it. Controlled use (regular surveillance of white blood cells) may be difficult to implement and may also contribute to the under use of clozapine. Difficulties in selecting the patients who are eligible for clozapine may add to this problem.

We believe that the suboptimal use of clozapine is currently one of the more serious problems in the treatment and science of schizophrenia that needs to be addressed. Indeed, identifying new molecules to treat schizophrenia is a very important task. However, optimizing the use and knowledge of molecules that have proven to be effective at the individual and population levels is equally, if not more, important. The questions that need to be addressed in this regard span the spectrum of research, from the organization of care to more effective ways to control medication adherence and tolerance. As a start, a number of indices of quality of care could be derived and used to evaluate practice in mental health institutions as well as in individual practices. Proportions of patients with the diagnosis of schizophrenia who are given trials of or are receiving clozapine could be monitored by regulatory agen-

cies and psychiatric institutions; this should be around 25% given the rate of treatment resistance in schizophrenia. Effects of variations in the rate of clozapine use on the well-being of patients should be assessed. Regular reviews of files to identify patients who need to be given the option of trying clozapine could be implemented and monitored. Research surveying physicians to identify barriers to prescribing clozapine would be useful. Identifying the various mechanisms used to deliver and/or monitor clozapine in various psychiatric settings and how these mechanisms correlate with prescription profiles could provide information about which systems provide optimal support. Eventually, we should assess the effectiveness of the interventions aimed at improving the capacity of clinicians to identify patients who may need clozapine, encouraging them to prescribe it and providing ancillary facilities to deal with monitoring of side effects.

It may also be important for mental health research agencies to give priority to further the basic understanding of clozapine's mechanisms of action, both those underlying its therapeutic efficacy and side effects. The precise mechanisms responsible for clozapine's superior clinical efficacy are still unclear. Clozapine is a relatively weak dopamine D<sub>2</sub> antagonist with binding activity at a variety of other receptors including multiple dopaminergic, serotonergic (5-HT), muscarinic, adrenergic and histaminergic receptor subtypes.<sup>38</sup> Working on the idea that clozapine's effectiveness might arise from activity at one of these sites, compounds selective for a single subtype of dopaminergic, serotonergic, muscarinic or adrenergic receptor have been developed but have shown little efficacy as antipsychotic agents. Further mechanisms proposed to explain the therapeutic effectiveness of clozapine and other atypical antipsychotics include their high ratio of 5-HT<sub>2A</sub>/D<sub>2</sub> receptor antagonism, their loose binding to the D<sub>2</sub> receptor resulting in an intermittent D<sub>2</sub> blockade or the regional selectivity of their D<sub>2</sub> binding favouring extrastriatal brain regions.<sup>39-42</sup> More recently, it is being speculated that it is the fact that clozapine acts at so many different receptors (i.e., its "enriched" or "dirty" pharmacology) that allows for clozapine's effectiveness against multiple aspects of schizophrenia symptomatology.<sup>42,43</sup> Metabolic side effects of the atypical antipsychotic medications appear to be correlated with their affinity for H<sub>1</sub> histaminergic receptors and ability to inhibit glucose transport. However, the mechanisms mediating the metabolic effects of atypical antipsychotic drugs are incompletely understood and likely involve interactions with multiple neurotransmitters, receptors and other molecular targets.<sup>44</sup>

Given that clozapine is both the most effective atypical antipsychotic and has the most profound metabolic side effects, Girgis and colleagues<sup>44</sup> recently postulated that the therapeutic effectiveness of atypical antipsychotics may in fact be related to an interaction with the insulin signalling pathway in the brain. Thus, resolving the mechanisms responsible for clozapine's clinical profile remains an area of active research. Studying this unique molecule still holds the potential to provide us with better insight about how to develop safer and more effective medications for the treatment of one of our most severe psychiatric disorders.

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