Editorial

Clozapine: dangerous orphan or neglected friend?
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Summary
Evidence concerning the superior efficacy and effectiveness of clozapine has not fully informed routine clinical practice. This is possibly because of the perception that clozapine is a dangerous therapeutic agent. Clozapine use may actually promote longevity, and earlier use of clozapine in adequate dosages represents a neglected therapeutic opportunity in this age of stagnated antipsychotic innovation.

Real innovation in developing antipsychotic medication has stagnated. Treatment-resistant psychosis is a common clinical problem, leading to significant individual disability and costs to society. Clozapine remains the only medication licensed for treatment-resistant schizophrenia, a form of chemotherapy for schizophrenia – the most effective but possibly also seen as the most toxic in its class. We believe it is timely to examine not only the advantages of clozapine but also concerns lying behind its delayed use and underutilisation.

Superior efficacy and effectiveness of clozapine?

The superior efficacy and effectiveness of clozapine have been established in a number of studies. Meta-analytic review demonstrated that clozapine was significantly better at ameliorating symptoms than first-generation antipsychotics (FGAs), and some (but not all) second-generation antipsychotics (SGAs). The symptom-reduction effect size (Hedges' $g$) for clozapine was $-0.52$ compared with amisulpride ($g=-0.31$); olanzapine ($g=-0.28$); and risperidone ($g=-0.13$). In a head-to-head comparison of SGAs including only double-blind studies, clozapine proved superior to zotepine and to risperidone (in doses $>400$ mg/day) but was not superior to olanzapine and quetiapine, although this non-superiority may have been the result of study designs that required an upper dose limit for clozapine of $400$ mg/day.

The superior effectiveness of clozapine is supported by two large independently funded studies. In phase 2 of the Clinical Antipsychotic Trial of Intervention Efficacy (CATIE) participants were re-randomised to receive open-label clozapine or double-blinded risperidone, olanzapine or quetiapine, mainly because of a lack of therapeutic effect in phase 1. The time to all-cause medication discontinuation, the primary outcome measure, was significantly better for clozapine compared with all the other drugs studied apart from olanzapine. The number needed to treat for the all-cause discontinuation of clozapine was four compared with risperidone, and three compared with quetiapine. Clozapine was significantly superior to olanzapine, quetiapine and risperidone in terms of time to discontinuation due to inadequate therapeutic effect. In the Cost Utility of the Latest Antipsychotic Drugs in Schizophrenia Study (CUTLASS), 136 participants exhibiting a poor response to $>2$ antipsychotic agents were randomised to receive either clozapine or a non-clozapine SGA, and their quality of life was compared over 1 year. Clozapine was found to be significantly superior to non-clozapine SGAs with regard to symptoms, and exhibited a trend towards superiority regarding quality of life ($P = 0.08$). Finally, a large observational study from Finland also showed that following first hospital admission for schizophrenia, individuals treated with clozapine had the lowest risk of treatment discontinuation and of rehospitalisation of all the ‘initiated’ oral antipsychotics studied.

Clozapine also seems to be a broad-spectrum antipsychotic, with robust evidence of effectiveness in suicidality, aggression and substance misuse. In the USA, clozapine is approved by the Food and Drug Administration for the management of suicidality in people with schizophrenia or schizoaffective disorder. In addition, clozapine has been shown to have anti-aggressive properties. For example, Krakowski et al undertook a randomised controlled trial of people with schizophrenia who were not treatment resistant but had had confirmed episodes of assault and persistent aggression during 1 year of hospitalisation. Clozapine was superior to both olanzapine and haloperidol in reducing the number and severity of assaults, and in reducing overall aggression. Clozapine may also play a role in diminishing substance misuse. For example, Brunette et al found after 10 years of follow-up that clozapine was associated with reduced relapse of substance misuse when compared with other antipsychotics.

Is clozapine dangerous?

Clozapine use is limited by a number of troublesome adverse effects such as hypersalivation, drowsiness and constipation. Life-threatening side-effects such as myocarditis, cardiomyopathy, agranulocytosis, a lowered seizure threshold and metabolic syndrome may be associated with increased mortality. However, Tiihonen et al compared mortality in 66 881 Finns regularly using antipsychotic medication with the death rate in the general Finnish population (52 million) over 11 years, and found that people regularly taking clozapine had the lowest risk of premature
Clozapine use in clinical practice

Prevalence estimates of treatment-resistant schizophrenia vary depending upon the definition used, but between one-fifth and one-third of individuals with schizophrenia have a suboptimal response to adequate trials of antipsychotic medication. Studies based on prescription patterns in routine practice almost universally show that a much lower proportion of individuals with schizophrenia are prescribed clozapine, even after taking into account potential barriers such as inadequate service provision. For example, prescription rates reported for clozapine are between 1 and 1.8% in large data-sets from the Veterans Health Administration in the USA.11 In Italy, a prescription rate of 1.5% has been reported,12 and in England data from 41 mental health trusts showed that only 30% of those eligible were actually receiving clozapine.13 Low rates of clozapine use would suggest that only those individuals who are suicidal or those whose condition is most refractory are enrolled, which in turn would reflect on the outcomes in these populations. The common alternative to clozapine is antipsychotic polypharmacy, which may only serve to worsen treatment resistance and add to the side-effects burden.

An even more important issue seems to be a delay in starting individuals on clozapine. National Institute for Health and Clinical Excellence (2009) guidelines14 state that clinicians should 'offer clozapine to people with schizophrenia whose illness has not responded adequately to treatment despite the sequential use of adequate doses of at least two different antipsychotic drugs' (p.177). It is not often realised that this ubiquitously quoted recommendation is not evidence based. It is a safety measure, perhaps derived from entry criteria in earlier randomised controlled trials of clozapine. However, even if one follows these guidelines, it should be possible to offer clozapine to individuals with treatment-resistant schizophrenia within a few months of first ever starting antipsychotics. Wheeler15 estimated that the mean duration between year of first contact with a clinician and starting clozapine in 2796 individuals was 9.7 years; and Taylor et al.16 calculated that the mean delay in using clozapine was 5 years in individuals admitted to London hospitals.

The underutilisation and delayed initiation of clozapine may be exacerbated by suboptimal dosing. Plasma level studies generally show that higher clozapine levels correlate with an excellent clinical response, whereas lower clozapine plasma levels were associated with a poor response, suggesting that many individuals require doses greater than 400 mg/day. This may be further complicated by the high prevalence of cigarette smoking in this population, which can affect serum levels.

Conclusions

Clozapine has demonstrably better efficacy and effectiveness than other antipsychotics, and is useful when concerns exist over suicidality, aggression and comorbid substance misuse. A number of factors, including a worrying side-effect profile and consequent limited license, clinicians’ negative beliefs and possible issues with service provision, conspire to lead to the delayed use and under-utilisation of clozapine. Additionally, clozapine is a commercial orphan, neither marketed nor promoted. Despite these factors, clozapine remains an important therapy option that can sometimes transform an individual’s life. Clozapine should not be considered a treatment of ‘last resort’ but drug of first choice as soon as non-responsiveness to established first-line treatments is evident.
References


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