BJPsych | The British Journal of Psychiatry (2011) 198, 247–249. doi: 10.1192/bjp.bp.110.088690

Editorial

Clozapine: dangerous orphan or neglected friend?

Saeed Farooq and Mark Taylor

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.

Declaration of interest
S.F. has received fees as a speaker at a symposium organised by manufacturers of clozapine. No funding was received in relation to this editorial or research on this topic. M.T. has received hospitality or fees from various pharmaceutical firms, but not from the manufacturers of clozapine.

Saeed Farooq (pictured) is a consultant psychiatrist at the Wolverhampton City Primary Care Trust. He is a visiting professor at Staffordshire University in the UK and the Postgraduate Medical Institute Peshawar in Pakistan. Mark Taylor works for NHS Lothian in Edinburgh as consultant psychiatrist to the intensive home treatment team.

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[1] 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 ($g=-0.13$).[1] In a head-to-head comparison of SGAs[2] 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.[3,4] In phase 2 of the Clinical Antipsychotic Trial of Intervention Effectiveness (CATIE)[3] 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),[4] 136 participants exhibiting a poor response to $\geqslant 2$ 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[5] 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*[6] 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.[6] Clozapine may also play a role in diminishing substance misuse. For example, Brunette *et al*[7] 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

mortality compared with both those on other antipsychotics and those not taking regular medication.[8] This protective effect will in part be the result of the anti-suicidality effects mentioned above and despite its well-known metabolic side-effects; death from ischaemic heart disease was no different for clozapine than for any other medication studied. Recently, Kelly *et al*[9] also found in a retrospective cohort study that the risk of cardiovascular mortality did not differ significantly in participants started on clozapine ($n = 1084$) compared with those initiated on risperidone ($n = 602$) over 8–10 years of follow-up, despite the fact that clozapine is associated with more weight gain than risperidone.

Monitoring services have kept the risk of clozapine-induced blood dyscrasias within acceptable limits. The risk of clozapine-induced leucopenia or agranulocytosis decreases exponentially over time, and after 1 year of treatment the incidence of agranulocytosis is nearly equivalent to that observed in phenothiazines. Based on data from 30 studies, Merrill *et al*[10] concluded that clozapine is associated with a low (approximately 0.1%) risk of potentially fatal myocarditis or cardiomyopathy.

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) guidelines[14] 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. Wheeler[15] 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.

Clozapine – a last resort?

Sometimes in medicine the most serious and disabling conditions require treatments that are potentially toxic and difficult to manage. For example, methotrexate can cause many side-effects but has become first-line therapy in rheumatoid arthritis after the realisation that it can prevent irreversible damage during the early 'critical period' of illness. Clozapine cannot be offered as first-line therapy, particularly in view of the lack of evidence for efficacy in first-episode psychosis. However, Agid *et al*[17] were able to offer a trial of clozapine as early as 25 weeks, after participants failed to respond to two trials of SGAs following a standardised first-episode psychosis programme. Those participants who were treatment resistant, in this pragmatic study, and who received clozapine experienced an improvement in symptoms (mean Brief Psychiatric Rating Scale score decreased from 53.5 to 34.5). Those who were treatment resistant but had refused clozapine exhibited a two-point increase in mean Brief Psychiatric Rating Scale score (from 53 to 55) with continued SGAs. The authors[17] concluded that clozapine had an important role in individuals with a first episode who had failed to respond to SGAs in the first months of treatment.

Another less well-studied issue is the attitude towards clozapine of staff and patients. Taylor *et al*[18] surveyed individuals on clozapine and found that 87% felt that the advantages of clozapine outweighed any disadvantages. However, when Nielsen *et al*[19] systematically questioned 100 psychiatrists regarding attitudes to clozapine, they discovered that many were reluctant to prescribe clozapine as they felt their patients would not like it, and said they would rather combine two other antipsychotics for individuals who were treatment resistant. Nielsen *et al*[19] suggested that these negative beliefs may be linked to limited experience and knowledge, particularly as clozapine is now a generic drug and less actively marketed. A self-perpetuating cycle can then ensue, as trainees do not see the benefits of clozapine, and do not develop confidence in its use.

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.

Saeed Farooq, MCPS(Psych), FCPS(Psych), Wolverhampton City Primary Care Trust, Wolverhampton; **Mark Taylor**, FRCPsych, FRANZCP, NHS Lothian, Edinburgh, UK

Correspondence: Mark Taylor, NHS Lothian, Ballenden House, Edinburgh EH8 9HL, UK. Email: marktaylor2@nhs.net

First received 22 Oct 2010, final revision 25 Nov 2010, accepted 20 Dec 2010

https://doi.org/10.1192/bjp.bp.110.088690 Published online by Cambridge University Press

References

1 Leucht S, Corves C, Arbter D, Engel RR, Li C, Davis JM. Second-generation versus first-generation antipsychotic drugs for schizophrenia: a meta-analysis. *Lancet* 2009; **373**: 31–41.

2 Leucht S, Komossa K, Rummel-Kluge C, Corves C, Hunger H, Schmid F, et al. A meta-analysis of head-to-head comparisons of second-generation antipsychotics in the treatment of schizophrenia. *Am J Psychiatry* 2009; **166**: 152–63.

3 McEvoy JP, Lieberman JA, Stroup TS, Davis SM, Meltzer H Y, Rosenheck RA, et al. Effectiveness of clozapine versus olanzapine, quetiapine, and risperidone in patients with chronic schizophrenia who did not respond to prior atypical antipsychotic treatment. *Am J Psychiatry* 2006; **163**: 600–10.

4 Lewis SW, Barnes TRE, Davies L, Murray RM, Dunn G, Hayhurst KP, et al. Randomized controlled trial of effect of prescription of clozapine versus other second-generation antipsychotic drugs in resistant schizophrenia. *Schizophr Bull* 2006; **32**: 715–23.

5 Tiihonen J, Wahlbeck K, Lonnqvist J, Klaukaa T, Ioannidis JPA, Volavka J, et al. Effectiveness of antipsychotic treatments in a nationwide cohort of 2230 patients in community care after first hospitalisation due to schizophrenia and schizoaffective disorder: observational follow up study. *BMJ* 2006; **333**: 224.

6 Krakowski MI, Czobor P, Citrome L, Bark N, Cooper TB. Atypical antipsychotic agents in the treatment of violent patients with schizophrenia and schizoaffective disorder. *Arch Gen Psychiatry* 2006; **63**: 622–9.

7 Brunette MF, Drake RE, Xie H, McHugo GJ, Green AI. Clozapine use and relapses of substance use disorder among patients with co-occurring schizophrenia and substance use disorders. *Schizophr Bull* 2006; **32**: 637.

8 Tiihonen J, Lönnqvist J, Wahlbeck K, Klaukka T, Niskanen L, Tanskanen A, et al. 11-year follow-up of mortality in patients with schizophrenia: a population-based cohort study (FIN11 study). *Lancet* 2009; **374**: 620–7.

9 Kelly DL, McMahon RP, Liu F, Love RC, Wehring HJ, Shim JC, et al. Cardiovascular disease mortality in patients with chronic schizophrenia treated with clozapine: a retrospective cohort study. *J Clin Psychiatry* 2010; **71**: 304–11.

10 Merrill DB, Dec GW, Goff DC. Adverse cardiac effects associated with clozapine. *J Clin Psychopharmacol* 2005; **25**: 32–41.

11 Weissman EM. Antipsychotic prescribing practices in the Veterans Healthcare Administration – New York metropolitan region. *Schizophr Bull* 2002; **28**: 31–42.

12 Tognoni G. Pharmacoepidemiology of psychotropic drugs in patients with severe mental disorders in Italy. Italian Collaborative Study Group on the Outcome of Severe Mental Disorders. *Eur J Clin Pharmacol* 1999; **55**: 685–90.

13 Downs J, Zinkler M. Clozapine: national review of postcode prescribing. *Psychiatr Bull* 2007; **31**: 384–7.

14 National Collaborating Centre for Mental Health. *Schizophrenia: Core Interventions in the Treatment of Schizophrenia in Adults in Primary and Secondary Care (Updated Edition) (NICE Clinical Guideline CG82)*. National Institute for Health and Clinical Excellence, 2009.

15 Wheeler AJ. Treatment pathway and patterns of clozapine prescribing for schizophrenia in New Zealand. *Ann Pharmacother* 2008; **42**: 852–60.

16 Taylor DM, Young C, Paton C. Prior antipsychotic prescribing in patients currently receiving clozapine: a case note review. *J Clin Psychiatry* 2003; **64**: 30–4.

17 Agid O, Remington G, Kapur S, Arenovich T, Zipursky R. Early use of clozapine for poorly responding first-episode psychosis. *J Clin Psychopharm* 2007; **27**: 369–73.

18 Taylor D, Shapland L, Laverick G, Bond J, Munro J. Clozapine – a survey of patient perceptions. *Psychiatr Bull* 2000; **24**: 450–2.

19 Nielsen J, Dahm M, Lublin H, Taylor D. Psychiatrists' attitude towards and knowledge of clozapine treatment. *J Psychopharmacology* 2010; **24**: 965–71.

https://doi.org/10.1192/bjp.bp.110.088690 Published online by Cambridge University Press