Current status of clozapine in the United States

Deanna L. KELLY*, Heidi J. WEHRING, Gopal VYAS

Clozapine is the only antipsychotic in the United States that has been approved by the Food and Drug Administration (FDA) for treatment-resistant schizophrenia. It provides effective treatment even when patients do not respond to other second-generation antipsychotics.[1] It also remains the most effective antipsychotic available. No existing first or second-generation antipsychotic has been consistently found to be as effective as clozapine monotherapy in treatment-resistant patients.[2-4] Among patients who entered Phase 2 of the Clinical Antipsychotic Trial of Intervention Effectiveness (CATIE) because of lack of efficacy in Phase 1 of the study, those treated with clozapine (open label) averaged significantly greater time to treatment discontinuation (10.5 months) compared to patients treated with other antipsychotic medications (2.7-3.3 months). At three months, total symptom scores also improved to a significantly greater degree in the clozapine group compared to those treated with risperidone or quetiapine.[5] Similarly, in the open-label, randomized CUTLASS (Cost Utility of the Latest Antipsychotic Drugs in Schizophrenia Study) trial, clozapine treatment was associated with significantly greater improvement in total scores of the Positive and Negative Symptom Scale (PANSS) and better patient subjective ratings compared to risperidone, olanzapine, quetiapine, and amisulpiride.[6] Another large, nonrandomized effectiveness study, the Schizophrenia Outpatient Health Outcomes (SOHO) study, also found clozapine to be superior on clinician and patient ratings at six months compared to other antipsychotics.[7] Based on clinical trials, meta-analyses, and large naturalistic studies clozapine is recommended as the most effective agent in schizophrenia, but the recommendations indicate that it should only be used when other agents fail.[8]

Clozapine has also been shown to have significant benefits for a number of other indications. In addition to the FDA indication for treatment-resistant schizophrenia, clozapine also carries an indication for the treatment of recurrent suicidal behavior in schizophrenia and schizoaffective disorder. This is the only other FDA approved indication for clozapine. The effectiveness of clozapine for reducing the risk of recurrent suicidal behavior was demonstrated in the International Suicide Prevention Trial (InterSePT),[9] a 2-year, multi-center, randomized study comparing clozapine and olanzapine in 980 people with schizophrenia or schizoaffective disorder. All subjects were considered at high risk for suicide because of previous suicide attempts or current suicidal ideation and were seen weekly for 6 months and then biweekly for 18 months. During the 2-year period, fewer clozapine treated subjects attempted suicide (34% v. 55%) and fewer required hospitalization or rescue interventions to prevent suicide.[10]

A few randomized double-blind trials have also evaluated the effectiveness of clozapine to reduce symptoms of hostility and aggression. A 12-week study compared clozapine, olanzapine and haloperidol in the treatment of physical assaults and other aggressive behaviors in physically assaultive people with schizophrenia or schizoaffective disorder. They found that clozapine was superior to both olanzapine and haloperidol in reducing the number and severity of physical assaults and reducing overall aggression.[11] In a secondary analyses of a double-blind trial in patients with treatment-resistant schizophrenia, Volavka and colleagues reported that clozapine was more effective for reducing aggressive behavior[12] and for improving measures of hostility[13] than olanzapine, risperidone, or haloperidol. In addition, several earlier studies found that clozapine was superior to haloperidol for reducing hostility symptoms as measured by the Brief Psychiatric Rating Scale (BPRS).[3,14] Given its benefits in individuals with schizophrenia for aggressiveness, clozapine has also been used for intermittent explosive disorder and for aggressive adolescents; however, no controlled trials have assessed its safety or efficacy in these populations.[15]

In general in the United States the use of clozapine is restricted to those people with schizophrenia who have failed first-line treatments. The reason for this restriction is its risk of severe side effects. However, the efficacy of clozapine in first episode, antipsychotic-
naïve patients has been evaluated in one double blind comparative trial.\[16\] One hundred-sixty drug-naïve patients in China were randomized for 52 weeks to either clozapine or chlorpromazine. In the first three months clozapine was superior to chlorpromazine on many symptom ratings and the median time to response was eight weeks compared to twelve weeks in the chlorpromazine group. While clozapine was also associated with fewer adverse effects (particularly extrapyramidal side effects) throughout the study, the two treatment groups tended to converge with respect to symptom improvements at the one-year mark.\[16\] Both groups gained significant amounts of weight (9.9 kg in the clozapine group; 8.5 kg in the chlorpromazine group), but there was no significant differences in weight gain between groups. In 2011 Guo and colleagues\[21\] reported that at the end of a 12-month open label prospective observational trial of early stage schizophrenia in China, clozapine had the numerically lowest rate (36.7%) of antipsychotic discontinuation (compared to chlorpromazine, sulpiride, risperidone, olanzapine, quetiapine and aripiprazole) but the differences in discontinuation rates for the different medications (range=36.7-46.9%) were not statistically significant.

Clozapine (mean dose: 176 mg/day) was also found to be superior to haloperidol in a six-week double blind comparison in childhood onset schizophrenia.\[18\] Another study in children found that clozapine was more effective in reducing symptoms than olanzapine in a double-blind 8-week trial;\[19\] however, clozapine was associated with more adverse effects. These studies in childhood onset schizophrenia included children who had been nonresponsive to previous antipsychotic treatment and, thus, may differ from first episode treatment-naïve patients who develop schizophrenia in early adulthood. In addition to these possible target groups for clozapine it may also be useful for patients with polydipsia/hyponatremia, refractory bipolar disorder, and a history of neuroleptic malignant syndrome (NMS).

Despite the overwhelming evidence of the superior efficacy and effectiveness of clozapine compared to other antipsychotics in treatment-resistant schizophrenia, clozapine is prescribed infrequently in the United States, at a disproportionately lower rate than the estimated prevalence of treatment-resistant schizophrenia.\[20-24\] Although clozapine is available in generic formulations and is widely used in other countries (e.g., 36-38% in Australia;\[21\] 28% in China and 20-30% in Taiwan),\[25\] the use of clozapine in the United States remains infrequent.\[21,26\] In fact, in the United States the market share of clozapine has been steadily declining, accounting for 11% of all prescriptions for antipsychotics in 1999, 9% in 2000, about 4% in 2006 and 3% in 2008.\[26\] In addition, Kreyenbuhl and colleagues\[27\] reported that antipsychotic polypharmacy is a more frequent treatment strategy than clozapine monotherapy in the Veteran Administration system of the United States, suggesting that clinicians are more likely to use antipsychotic polypharmacy than clozapine despite the lack of empirical evidence to support the former practice. Moreover, racial disparities in the use of clozapine have been consistently observed, with African-Americans less likely to receive this medication than Caucasians.\[28-30\]

To date, there have been few empirical investigations of the reasons for the infrequent use of clozapine in the United States,\[31\] although possible explanations include its strict hematological monitoring requirements and the potential for serious side effects including agranulocytosis, myocarditis, other inflammatory reactions, seizures, sedation, weight gain, diabetes mellitus and other metabolic abnormalities.\[22,30\] Other possible explanations include lack of knowledge about the benefits of clozapine or negative attitudes towards the medication among physicians, patients and families.\[32\] More aggressive marketing of other second-generation antipsychotic medications by pharmaceutical companies may also contribute to the infrequent use of clozapine.\[33\]

While serious side effects undoubtedly limit the use of clozapine, the fact still remains that many more people with schizophrenia in the United States could benefit from this medication.\[34\] In New Zealand between 2000 and 2004 clozapine use among patients with schizophrenia increased from 21% to 32.8% and there were associated increases in the proportion of patients who had regular occupational activity and decreases in hospitalization rates and in the rates of compulsory treatment.\[35\] Rates of clozapine use have also been increasing in other countries over the past decade, including Korea, Singapore, Taiwan, Malaysia and India. In China, where rates of clozapine use are very high (40% in 2001 and 2004), there has been a decline in its use in recent years (to 27%); this may be related to a recent expansion of health insurance to cover additional second-generation antipsychotic medications (previously only clozapine and risperidone, were covered) and to stricter implementation of the prescribing guidelines for clozapine in many psychiatric hospitals. But the rates of clozapine use in China remain much higher than in Western countries.

In the United States unless there is a significant change in prescribing practices the next generation of clinicians may have little training in treating patients with clozapine, which would lead to a continued decline in its use. Many argue for fewer restrictions in the use of clozapine.\[36-37\] This is one of the most under used evidence-based treatments available in psychiatry.

Conflict of interest

The authors report no conflict of interest related
References

1. Conley RR, Kelly DL. Management of treatment resistance in schizophrenia. *Biol Psychiatry* 2001;50(11):898-911.
2. Brier A, Buchanan RW, Kirkpatrick B, Davis OR, Irish D, Summerrfelt A, et al. Effects of clozapine on positive and negative symptoms in outpatient schizophrenia. *Am J Psychiatry* 1994;151(1):20-26.
3. Kane JM, Marder SR, Schooler NR, Wirshing WC, Umbricht J. Grant support from Janssen Pharmaceutica.
4. Azorin JM, Spiegel R, Remington G, Vanelle JM, Pere JJ, Guguere C. Atypical and conventional antipsychotic drugs in treatment-naive first episode schizophrenia: a 52 week randomized trial of clozapine vs. chlorpromazine. *Neuropsychopharmacology* 2003;28(5):995-1003.
5. Volavka J, Czobor P, Sheitman B, Lindenmayer JP, Citrome L, Meltzer HY, Rosenheck RA, et al. Effectiveness of clozapine versus new atypical drugs, and new atypical drugs versus placebo in schizophrenia. *Am J Psychiatry* 2003;160(1):320-323.
6. Buchanan RW, Kreyenbuhl J, Kelly DL, Noel JM, Boggs DL, Fischer BA, et al. The 2009 schizophrenia PORT psychopharmacological treatment recommendations and summary statements. *Schizophr Bull* 2010;36(1):71-93.
7. Volavka J, Czobor P, Shethman B, Lindenmayer JP, Citrome L, McEvoy JP, et al. Clozapine, olanzapine, risperidone, and haloperidol in moderately refractory schizophrenia: a 6-month randomized and double-blind comparison. *Arch Gen Psychiatry* 2001;58(10):965-972.
8. Azorin JM, Spiegel R, Remington G, Vanelle JM, Pere JJ, Guguere C, et al. A double-blind comparative study of clozapine and risperidone in the management of severe chronic schizophrenia. *Am J Psychiatry* 2001;158(8):1305-1313.
9. Buchanan RW, Kreyenbuhl J, Kelly DL, Noel JM, Boggs DL, Fischer BA, et al. The 2009 schizophrenia PORT psychopharmacological treatment recommendations and summary statements. *Schizophr Bull* 2010;36(1):71-93.
10. McEvoy JP, Lieberman JA, Stroup TS, Davis SM, Meltzer HY, 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(4):600-610.
11. Lewis SW, Davies L, Jones PB, Barnes TR, Murray RM, Kerwin R, et al. Randomized controlled trials of conventional antipsychotic versus new atypical drugs, and new atypical drugs versus clozapine, in people with schizophrenia responding poorly to, or intolerant of, current drug treatment. *Health Technol Assess* 2006;10(17):1-165.
12. Haro JM, Edgell ET, Novick D, Alonso J, Kennedy L, Jones PB, et al. Effectiveness of antipsychotic treatment for schizophrenia: 6-month results of the Pan-European Schizophrenia Outpatient Health Outcomes (SOHO) study. *Acta Psychiatr Scand* 2005;111(3):220-231.
13. Meltzer HY, Alphs L, Green AI, Altamura C, Anamdi R, Bertoldi A, et al. Clozapine treatment for suicidality in schizophrenia. *International Suicide Prevention Trial (InterSePT).* *Arch Gen Psychiatry* 2003;60(1):82-91.
14. Buchanan RW, Brier A, Kirkpatrick B, Ball P, Carpenter WT Jr. Positive and negative symptom response to clozapine in schizophrenic patients with and without the deficit syndrome. *Am J Psychiatry* 1998;155(6):751-760.
15. Kent R, Chalansani R, Chengappa KN, Dieringer MF. The off-label use of clozapine in adolescents with bipolar disorder, intermittent explosive disorder, or post traumatic stress disorder. *J Child Adolesc Psychopharmacol* 2004;14(1):57-63.
16. Lieberman JA, Phillips M, Gu H, Stroup S, Zhang P, Kong L, et al. Atypical and conventional antipsychotic drugs in treatment-naive first episode schizophrenia: a 52 week randomized trial of clozapine vs. chlorpromazine. *Neuropsychopharmacology* 2003;28(5):995-1003.
17. Guo X, Fang M, Zhai J, Wang B, Wang C, Hu B, et al. Effectiveness of maintenance treatments with atypical and typical antipsychotics in stable schizophrenia with early stage: 1-year naturalistic study. *Psychopharmacology* 2011;216(4):475-484.
18. Kumar S, Frazier JA, Jacobsen LK, McKenna K, Gordon CT, Lenane MC, et al. Childhood-onset schizophrenia. A double blind clozapine-haloperidol comparison. *Am J Psychiatry* 1996;53(12):1090-1097.
19. Shaw P, Sporn A, Gogtay N, Overman GP, Greenstein D, Gochman P, et al. Childhood-onset schizophrenia: a double-blind randomized clozapine-olanzapine comparison. *Arch Gen Psychiatry* 2006;63(7):721-730.
20. Fayak M, Flowers C, Signorelli D, Simpson G. Psychopharmacology: underuse of evidence-based treatments in psychiatry. *Psychiatr Serv* 2003;54(11):1453-1456.
21. Conley RR, Kelly DL, Lambert TJ, Love RC. A comparison of clozapine use in Maryland and in Victoria, Australia. *Psychiatr Serv* 2005;56(3):320-323.
22. Lieberman JA. Maximizing clozapine therapy: managing side effects. *J Clin Psychiatry* 1998;59(Suppl 3):38-43.
23. Taylor DM, Yound C, Paton C. Prior antipsychotic prescribing in patients currently receiving clozapine: a case note review. *J Clin Psychiatry* 2003;64(1):30-34.
24. Weissman EM. Antipsychotic prescribing practices in the Veterans Healthcare Administration-New York metropolitan region. *Schizophr Bull* 2002;28(1):31-42.
25. Xiang YT, Wang CY, Si TM, Lee EH, He YL, Ungvari GS, et al. Clozapine use in schizophrenia: findings of the research on Asia psychotropic prescription (REAP) studies from 2001 to 2009. *Aust N Z J Psychiatry* 2011;45(11):968-975.
26. IMS Health, NDTI. January 1999, 2000, 2002, 2006, 2008.
27. Kreyenbuhl J, Valenstein M, McCarthy JF, Ganoczy D, Blow FC. Long-term combination antipsychotic treatment in VA patients with schizophrenia. *Schizophr Res* 2006;84(1):90-99.
28. Mallinger JB, Fisher SG, Brown T, Lamberti JS. Racial disparities in the use of second-generation antipsychotics for the treatment of schizophrenia. *Psychiatr Serv* 2006;57(1):133-136.
29. Copeland LA, Zeber JE, Valenstein M, Blow FC. Racial disparity in the use of atypical antipsychotic medications among veterans. *Am J Psychiatry* 2003;160(10):1817-1822.
30. Kelly DL, Dixon L, Kreyenbuhl J, Lehman AF, Love RC, Medoff D, et al. Clozapine utilization and outcomes by race in a public mental health system: 1994-2000. *J Clin Psychiatry* 2006;67(9):1404-1411.
31. O’Brien A. Starting clozapine in the community: a U.K. perspective. *CNS Drugs* 2004;18(13):845-852.
32. Nielsen J, Dahm M, Lublin H, Taylor D. Psychiatrists’ attitude towards and knowledge of clozapine treatment. *J Psychopharmacol* 2010;24(7):965-971.
33. Kelly DL, Kreyenbuhl J, Buchanan RW, Malhotra MK. Why not clozapine? *Clinical Schizophrenia & Related Psychoses*, 2007;1(1):92-95.

34. Naber D. Optimizing clozapine treatment. *J Clin Psychiatry* 1999;60 (Suppl 12):35-38.

35. Wheeler A, Humberstone V, Robinson G. Outcomes for schizophrenia patients with clozapine treatment: how good does it get? *J Psychopharmacol* 2009;23(8):957-965.

36. Agid O, Foussias G, Singh S, Remington G. Where to position clozapine: re-examining the evidence. *Can J Psychiatry* 2010;55(10):677-684.

37. Kerwin R. When should clozapine be initiated in schizophrenia? Some arguments for and against earlier use of clozapine. *CNS Drugs* 2007;21(4):267-278.