



Clozapine: Is Now the Time for More Clinicians to Adopt This Orphan?

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ISSUE:

Although many patients with schizophrenia fail to respond adequately to trials of 2 or more antipsychotics, utilization of clozapine for these patients remains low, despite recommendations for its use by accepted treatment guidelines. Some experts estimate that 5–10 times more patients could benefit from clozapine than who are now receiving it. Learning how to manage the unique side effect profile of clozapine can potentially remove barriers to prescribing this agent and thus unlock its unique therapeutic efficacy for more patients.

Take-Home Points

- Most psychopharmacologists are aware of the superior efficacy of clozapine, but its utilization remains low.
- The main barrier to utilization is unfamiliarity with how to avoid or manage potentially difficult side effects.
- Gaining experience with this agent is an important aspect of the modern practice of psychopharmacology, as in many cases side effects can be managed adequately, enabling the potential therapeutic advantages of clozapine to be realized.

What Is So Great About Clozapine?

Most psychopharmacologists are aware of the special efficacy advantages of clozapine in the treatment of schizophrenia, namely, that it has generally greater efficacy than all other antipsychotics, especially when administered after adequate response to other antipsychotics has failed.^{1–5} In fact, there is an international consensus, reflected in treatment guidelines,⁶ that clozapine is recommended as the treatment of choice

for patients who have failed to respond to other antipsychotics. In addition, clozapine is well known to be the only antipsychotic documented to reduce suicide in schizophrenia.⁷ Clozapine is also the preferred antipsychotic for psychosis associated with either Lewy body dementia or Parkinson's disease (Table 1).^{5,8} All antipsychotics can reduce violence in psychotic patients,⁹ but clozapine seems to have by far the most robust actions in reducing aggression, hostility, and violence in schizophrenia.^{10–14}

In terms of tolerability, although clozapine is often thought of mostly as a drug with many side effects, clozapine in fact induces few if any extrapyramidal side effects, does not seem to cause tardive dyskinesia (and may even be helpful for some patients with tardive dyskinesia), and fails to elevate prolactin levels, which is quite different from the tolerability profiles of many other antipsychotics (Table 1).^{5,8} So with all these things going for it, why is clozapine used in only a small percentage of patients, and possibly in only about 1 in 10 of the patients for whom it might be indicated, especially in certain settings and in certain countries like the U.S.?^{3,4}

What's the Problem with Clozapine?

Due to side effects that can be greater than some other antipsychotics in many patients, and the need for



Table 1. Encouraging adoption of clozapine: potential advantages

- Superior efficacy for psychotic symptoms
- Superior efficacy for treatment-resistant psychosis
- Superior efficacy for aggression and violence
- Superior efficacy for reducing suicide
- Low/no EPS
- Low/no hyperprolactinemia
- Low/no tardive dyskinesia; can even improve tardive dyskinesia
- Use in Lewy body dementia
- Use in Parkinson's psychosis

Table 2. Barriers to adopting clozapine

- Wishing to avoid side effects
- Wishing to avoid blood monitoring
- Not knowing how to manage side effects if they arise
- Not knowing when termination of treatment is warranted or can be avoided
- Not knowing when to rechallenge after adverse effects

blood monitoring, which can be costly and a hassle, clozapine is not a first-line treatment for schizophrenia.^{4-6,8} In fact, many prescribers avoid using clozapine altogether. One study suggests that many psychiatrists have few if any patients on clozapine, or rarely start a new patient on this drug.³ "Side effects" is the usual explanation for why clozapine seems to be avoided by many psychopharmacologists,^{3,4} resulting in the possibility that up to 10-fold more patients may benefit or need this agent than are getting it in current practice in the U.S.⁴

The full explanation for the low use of clozapine, however, may be a bit more nuanced than simply problems with side effects. Namely, if a prescriber lacks experience managing patients with clozapine, and also is not comfortable with how to monitor for complications, prevent them, and deal with them should they arise, that prescriber may over-value potential side effects compared to potential benefits, and thus not use clozapine. A list of potential barriers to the use of clozapine is given in Table 2. A common myth among some psychiatrists is that clozapine is too

Table 3. Removing barriers to adopting clozapine: learn how to avoid or manage key side effects, including when to continue, discontinue, or rechallenge

- Ileus/constipation
- Blood monitoring/agranulocytosis/neutropenia/eosinophilia
- Weight gain/diabetes
- Myocarditis/QTc prolongation/tachycardia
- Neuroleptic malignant syndrome
- Hypersalivation

dangerous, and its risk–benefit ratio makes clozapine generally not worth prescribing.^{3,4} However, as a recent study has shown,¹⁵ despite potential complications from clozapine use, including weight gain and diabetes, it actually has a lower mortality rate than other antipsychotics, presumably due to its reduction of suicide, which is a frequent cause of death in this population.⁷

In fact, clozapine can be used safely (Table 3), because there is now a good deal of information available in the literature not only on its efficacy,¹⁻¹⁵ but also pragmatic tips on how to deal with side effects (eg, Refs.^{8,16-23}). For example, there are informed suggestions about what to monitor beyond just white blood cell counts,¹⁶ and criteria for when to terminate clozapine treatment when a side effect does arise, versus continuing treatment while the side effect is managed.¹⁷ Managing neutropenia is now informed by the new understandings about the prevalence of neutropenia in the general population, especially in various ethnic groups.^{18,19} Clinicians may come across patients who have benefitted from clozapine, but whose medication has been stopped either correctly, or even incorrectly by an overly worried prescriber. There are now criteria for when and how to rechallenge such patients with clozapine.²⁰ Finally, side effects such as hypersalivation²¹ and constipation^{22,23} can also be managed if they arise.

Conclusion

It may be time to take another look at clozapine and adopt this orphan into a modern practice of psychopharmacology.



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