Clozapine's Role in the Treatment of First-Episode Schizophrenia

Gary Remington, M.D., Ph.D.

Ofer Agid, M.D.

George Foussias, M.D., M.Sc.

Margaret Hahn, M.D., M.Sc.

Naren Rao, M.B.B.S., M.D.

Mark Sinyor, M.D.

Early and effective treatment in first-episode schizophrenia is associated with better outcomes. Evidence suggests that response is generally robust in a first antipsychotic trial, but a marked reduction in response rate is observed among patients for whom a second trial is warranted, and even further reductions are seen in subsequent trials. Clozapine, the treatment of choice in refractory schizophrenia, is routinely employed only as a third-line treatment, and it has been shown to markedly enhance the rate of response, even when compared with other atypical antipsychotics. This raises the question of whether clozapine would be more effectively positioned as a first-line treatment. Current evidence addressing this question does not support this position, although the limited data available and methodological issues preclude a firm conclusion. Practical issues related to clozapine use, in combination with the robust response reported for other agents when used as first-line treatment, certainly call into question the likelihood that clozapine would be chosen if it were an option at this stage. In contrast, the notable reduction in response rate to second-line treatments, coupled with clozapine's substantial response rate in refractory schizophrenia and evidence indicating better outcomes with early, effective treatment, makes a compelling argument for research examining clinical and functional outcomes with clozapine positioned as a second-line treatment.

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Clozapine is an early atypical antipsychotic, first synthesized in 1958. Although it was formulated as part of an effort to develop new antidepressants, preclinical work established its similarities to chlorpromazine, and it was ultimately evaluated for its potential antipsychotic properties (1). Even then, clozapine established itself as unique, as its low liability for extrapyramidal symptoms challenged a widely held notion at the time that clinical response was integrally linked to induction of extrapyramidal symptoms (2).

Clozapine's Link to Treatment Resistance

Shortly after its release in the early 1970s, clozapine was linked to a risk, albeit a low one, of agranulocytosis (1). As a result, its use was markedly curtailed and a requirement for mandatory blood monitoring was established in most countries. A seminal study in the late 1980s demonstrating clozapine's clinical superiority in refractory schizophrenia (3) established its position in North America as a treatment of "last resort," permitted only after the failure of other antipsychotics and only in conjunction with routine hematological monitoring.

Clozapine and Current Treatment Algorithms

Despite the introduction of a number of newer atypical antipsychotics over the past two decades, clozapine remains the treatment of choice in refractory schizophrenia, a position endorsed by various guidelines (4–7). As a rule, clozapine is recommended only after incomplete response to two adequate antipsychotic trials, which is reflected in some product monographs. For example, in Canada clozapine can be prescribed only as a third-line treatment (8), although in the United States it is permitted (although not recommended) as a second-line treatment (9).

The criteria that define treatment resistance have been modified to reflect changes in recommended antipsychotic dosing guidelines that now advocate somewhat lower dosages (10). Also, treatment criteria have been proposed for "ultraresistant schizophrenia," applicable to patients who demonstrate a suboptimal response to clozapine (11).

It is noteworthy that there remains a hesitancy in prescribing clozapine for individuals with refractory schizophrenia. For example, a review of the Veterans Affairs databases for 1999–2006 indicated that while the atypical antipsychotics were rapidly supplanting their conventional counterparts, clozapine use remained flat at 2%–3% (12). Other researchers have reported an average delay of 5 years in moving to clozapine in the face of treatment resistance (13).

Treatment Response in Early Schizophrenia

Schizophrenia is characterized by a differential response to antipsychotic treatment based on stage of illness, with

This article is featured in this month's AJP Audio and is an article that provides Clinical Guidance (p. 151)

A 22-year-old man with a history of untreated psychosis over 2 years enters a systematic treatment algorithm.

"Mr. A" was brought to the clinic by his parents. He was cooperative and denied any history of alcohol or drug use, which his parents corroborated. His parents noted that his early milestones and medical history were uneventful. Mr. A's academic performance was above average through high school, although he was not active socially.

Mr. A attended a local college, but during his second year, at age 20, he started hearing voices. He reported the voices to be persistent from the onset, with the predominant voice that of a female classmate "trying to hear my thoughts so she can get to know me better before starting our relationship." At times he heard other voices warning him that the police were monitoring his activities. His academic performance suffered, and toward the end of his second year, he dropped out and became more withdrawn socially, spending days at home.

Mr. A's score on the Brief Psychiatric Rating Scale (BPRS) was 70, and his severity subscore on the Clinical Global Impressions (CGI) scale was 6. The working diagnosis was schizophrenia, and pharmacological treatment was initiated according to the clinic's standardized treatment algorithm, which called for two trials with second-generation antipsychotics before trying clozapine, with each trial divided into three stages based on dosage (low, full, high) and lasting up to 4 weeks per stage. After 26 weeks of treatment (olanzapine, up to 30 mg/day, for a total duration of 14 weeks; risperidone, up to 7 mg/day, for a total duration of 12 weeks), only minor improvement was observed (BPRS score, 65; CGI severity subscore, 6). Mr. A reported that leaving his house remained difficult because he felt more "bothered" by the voices when he was out.

A clozapine trial was started at week 27, and within 1 week Mr. A reported "feeling much better"; the voices had decreased in frequency and intensity to a point where he could "concentrate and think" more clearly. Mr. A's parents reported "dramatic improvement" after 3 months (BPRS score, 40; CGI severity subscore, 3), and at 4 months Mr. A returned to school part-time. He quickly transitioned to full-time, and 1 year after the start of antipsychotic treatment (currently clozapine at 425 mg/day), he was assessed as being in full remission with very mild, transient hallucinations and unusual thought content (BPRS score, 22; CGI severity subscore, 3).

evidence that shorter duration of untreated psychosis is associated with greater antipsychotic response (14). Notwithstanding the different trial designs and thresholds that define clinical response, as well as nonpharmacological variables such as adherence problems, studies of patients with first-episode schizophrenia report response rates in the range of 40%–90% (15–26), although time to response increases and likelihood of response declines substantially in subsequent trials (27). In the largest study of its sort, our group followed 244 individuals with first-episode schizophrenia in a naturalistic design across two atypical antipsychotic trials before a switch to clozapine (15). The response rate was 75.4% the first trial, and it decreased to 16.7% in the second. Once again confirming clozapine's efficacy in refractory schizophrenia, the response rate increased to 75% in the third trial, when patients were switched to clozapine. A smaller (N=58) open study of first-episode schizophrenia patients who were switched to olanzapine after a failed risperidone trial (28) reported a response rate of 29.3%, which parallels the 25.7% response rate we observed for the same switch in our larger naturalistic trial (15). A second such study (N=51) reported a response rate of 35.3% in switching from olanzapine to risperidone (29).

Unfortunately, there is a paucity of research systematically evaluating response rates across multiple antipsychotic trials. This may reflect current limitations that we face in terms of biological markers and differential treatment strategies, in sharp contrast with other areas of medicine, such as infectious diseases. In the seminal trial establishing clozapine's superiority in treatment-resistant schizophrenia (N=319), patients were entered into a 6-week trial of haloperidol prior to random assignment to receive either clozapine or chlorpromazine; however, less than 2% met criteria for haloperidol response (3).

Taken together, the evidence suggests that repeated antipsychotic trials, except those of clozapine, are met with a progressive decrease in likelihood of response, leading some to call into question the benefit of switching antipsychotics in the populations with more chronic illness (30–33).

Clozapine as First-Line Treatment in Schizophrenia

Only four published trials have examined the use of clozapine as first-line treatment. An open 12-week trial (N=30) in China evaluating clozapine in first-episode schizophrenia found it to be both efficacious and safe, leading to the conclusion that clozapine should be used in this population (34). In a larger controlled study (N=160), also carried out in China, patients with first-episode schizophrenia were randomly assigned to receive clozapine or chlorpromazine and assessed over a 1-year follow-up period (35). While those receiving clozapine showed greater symptom improvement and attained remission sooner, as evaluated at 12 weeks, these differences were lost at endpoint, with remission rates of 81% and 79% for clozapine and chlorpromazine, respectively. Attrition was higher in the group treated with chlorpromazine

(22.5% compared with 15%), indicating greater patient retention with clozapine. A follow-up study with 9-year data offers further confirmation of the 1-year findings (36). Remission rates (78%) and relapse rates (14%) were essentially identical in the two treatment groups, while significantly greater attrition occurred in the chlorpromazine group. Median time to discontinuation was 39 months for clozapine, compared with 23 months for chlorpromazine, with significantly more patients on clozapine at endpoint (26%) compared with chlorpromazine (10%). Finally, a U.S. study followed 38 patients with first-episode schizophrenia who were treated with clozapine; there was no control group, but results were compared with those of a previous study of first-episode schizophrenia treated with fluphenazine (37). The cumulative response rate in clozapine-treated patients was 66.4% at 13 weeks, with none responding thereafter, a response rate in keeping with that reported for fluphenazine (38). The median time to response was 11 weeks with clozapine, compared with 9 weeks for fluphenazine.

Interpreting the Evidence

Efficacy

It is critical that the available data be interpreted correctly. In one open trial, clozapine was found to be safe and efficacious (34). In another, a cumulative response rate of 66.4% was calculated for clozapine (37), comparable to a previously reported rate for fluphenazine (38). In the one controlled trial in which first-episode patients were randomized to treatment with clozapine or chlorpromazine, with results reported at 1 year and at 9 years, the data on clinical outcome are specific only to clozapine compared with chlorpromazine at the 1-year mark. Over that period, clozapine-treated patients demonstrated greater symptom improvement and earlier remission than those treated with chlorpromazine, although the differences were lost by 1 year (35). Thereafter, the results speak to what occurs in individuals *started* on either of these medications, since at 9 years only 26.3% (21/80) participants remained on clozapine, compared with 10% (8/80) on chlorpromazine; the remaining patients in each group were on a variety of medications (36). Although the small sample sizes at endpoint limit any conclusions that can be drawn from these findings, the available data tell us that longer-term outcome in a group of patients is not influenced by the type of antipsychotic used as first-line treatment. However, the data do not shed light on how those who remained on clozapine compare with those who remained on chlorpromazine over the duration of follow-up—an important distinction.

While there is a high response rate to the first antipsychotic, the rate markedly drops off among patients who require a second trial and appears to decrease even further with subsequent trials, except with clozapine.

Safety and Tolerability

No antipsychotic generates more concern regarding safety issues than clozapine, particularly the risk of agranulocytosis, and it is reassuring that no deaths or seizures were reported in any of the aforementioned studies (34–37). In one of the open trials (37), clozapine was discontinued in 16.7% (6/36) of participants because of low white counts, although none of these cases progressed to agranulocytosis. One patient in the 9-year follow-up investigation who remained on clozapine over the study's duration developed agranulocytosis, although this instance actually reflected a lower proportion (4.8%) than was observed among those who received chlorpromazine over the duration, where two individuals (25%) developed agranulocytosis (36). In this same subsample, there were no differences between groups in weight gain, fasting glucose level, and ECG measures, including heart rate and QT interval. The lack of difference in weight is interesting. We are reminded that the sample was exclusively Chinese, but the study also spanned an interval of 9 years, and other investigations have also reported a lack of difference between atypical and conventional antipsychotics in chronic samples (39). Conventional antipsychotics themselves carry a notable liability for weight gain (40, 41), and the impact of other nonpharmacological variables may serve to mask differences between agents (42–44), especially as the illness progresses.

Also in this subsample, reports of tardive dyskinesia totaled one (4.8%) for clozapine and two (25%) for chlorpromazine (36). With the atypical agents now the treatment of choice in first-episode schizophrenia, the more relevant question is how other atypical agents compare, and here data are lacking. There is evidence of a differential risk between atypical agents (45), although the frequency of antipsychotic switching and clozapine's position in treatment algorithms make it difficult to produce accurate figures for each agent.

Of the 160 individuals assessed at the 9-year follow-up (N=80/group), only one from each arm was withdrawn specifically because of side effects (36).

Cost

To the best of our knowledge, no studies to date have specifically examined direct and indirect costs for clozapine compared with other antipsychotics in first-episode schizophrenia. Given the existing evidence demonstrating

similar rates of remission and no differences on various measures of clinical and functional outcome relative to chlorpromazine (35, 36), it seems unlikely that substantial savings are to be gained. Findings demonstrate otherwise, however, when clozapine is compared with other antipsychotics in treatment-resistant schizophrenia (46–48). Finally, cost must be discussed on a country-by-country basis because of differences in patent laws and availability of generics. In China, for example, the low cost of clozapine, and the advantage it offers over more costly and newer atypical antipsychotics as a result, has been identified as a factor that has encouraged its widespread use (49).

Conclusions and Recommendations

Research has approached the issue of clozapine as first-line treatment in schizophrenia from two perspectives. The first addresses whether longer-term outcome is influenced differentially by use of clozapine as first-line treatment compared with other antipsychotics. The evidence gathered to date, albeit limited, suggests that this is not the case. More patients stay on clozapine, and in the early stages of treatment they may also show a more robust response compared with patients treated with other antipsychotics. However, the evidence indicates that in the longer term, most patients will not continue on clozapine, and over time the group will not look any different from those started on another antipsychotic (36).

The second perspective addresses whether outcome differs over the longer term between patients who receive clozapine and those who receive other antipsychotics as first-line treatment but continue on the same treatment. To date, only two studies have addressed this question. One was an open trial that retrospectively compared improvement with clozapine and improvement with fluphenazine in an earlier study, concluding that clozapine was not clinically superior (37). The other, a randomized controlled trial, compared clozapine and chlorpromazine over 1 year and found comparable results at endpoint (35). These findings may not be so surprising. Response rates are relatively robust in first-episode schizophrenia, as high as almost 90% (21), which establishes a ceiling effect that minimizes the chances of distinguishing between different agents.

In summary, it is difficult to make a case for clozapine as a first-line treatment. As noted, there is a high response rate in the first-episode population regardless of the choice of antipsychotic. Existing evidence does not support increased concerns about safety, but the practical demands of routine hematological monitoring make clozapine an unlikely choice without evidence of clear superiority. That said, there is insufficient evidence to determine whether outcomes differ over the longer term between individuals started and maintained on clozapine and those treated with other antipsychotics. There are simply not enough data, and potentially important outcome measures (e.g., suicidality) have not yet been assessed on a larger scale. Thus, it is premature to discount the benefits of clozapine as a first-line treatment, and further studies are warranted. Whether positive findings would translate to changes in clinical practice is open to debate.

In contrast, the case can readily be made that clozapine should at least be considered as second-line treatment, and we strongly advocate research that can shed light on this issue. Various key findings fuel this argument: 1) While there is a high response rate to the first antipsychotic, the rate markedly drops off among patients who require a second trial and appears to decrease even further with subsequent trials, except with clozapine. 2) Clozapine reinstates a higher response rate, even as a third-line treatment, raising the question of whether this effect might be enhanced with clozapine used as a second-line treatment. 3) A longer duration of untreated psychosis diminishes the likelihood of remission. 4) Treatment with clozapine leads to earlier and longer remission intervals.

Whether shifting clozapine from third-line to second-line treatment would favorably affect outcome is not clear based on available evidence. What makes this question so important and clinically relevant, though, is the current state of the art. Despite the introduction of numerous new medications in the past two decades, many individuals with schizophrenia continue to do poorly, and for these patients clozapine represents the most effective alternative available. It may well turn out that there are no added benefits to the use of clozapine as a second-line treatment, but to avoid the question because of safety concerns neither can be substantiated nor is in the best interest of efforts to enhance outcomes in schizophrenia.

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Clinical Guidance: Clozapine in First-Episode Schizophrenia

First-episode schizophrenia has a high rate of response to standard treatments. The limited evidence on clozapine as a first-line treatment so far does not show greater efficacy at 1 year. Remington et al. consider the possibility of clozapine as a second-line treatment if one is needed, based on the evidence that other atypical antipsychotics have low response rates as second-line treatment, whereas clozapine as a third choice is often successful. The added burden of regular blood testing with clozapine as a second-line treatment is offset by the opportunity for earlier response, which may decrease longer term disability.