Optimizing Treatment With Clozapine

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Clozapine is the only antipsychotic agent that is effective in treatment-resistant schizophrenia. Despite its superior efficacy to chlorpromazine and the fact that it has fewer extrapyramidal side effects than conventional antipsychotics do, clozapine is relatively underused. This may be due in part to a lack of appreciation of clozapine's favorable risk-benefit ratio in many patients. In addition, clozapine is only indicated for use in patients who fail to respond adequately to standard antipsychotic treatment. Treatment with clozapine considerably improves psychiatric well-being and reduces readmission to the hospital and reduces family burden in many severely ill patients. However, clozapine is associated with severe side effects, including weight gain, tachycardia, sedation, seizures, and agranulocytosis. These risks must be weighed against the risks associated with schizophrenia (e.g., suicide). The death rate attributed to clozapine-induced agranulocytosis has been low, a fact that is largely attributable to safety measures such as the Clozaril National Registry. Determining the optimal dosage for each patient will maximize the benefits of treatment while reducing side effects. In some patients, monitoring plasma levels of drug may aid in optimizing treatment. The optimal plasma level of clozapine is 200 to 350 ng/mL. This usually corresponds to a daily dose of 200 to 400 mg, although dosage must be individualized. If patients improve significantly during treatment with clozapine, they should continue to be treated with clozapine and should be withdrawn from this treatment only when medically warranted. Psychotic relapse rates may be as high as 80% among patients switched from clozapine to other novel antipsychotic agents.
(J Clin Psychiatry 1998;59[suppl 3]:44–48)

Estimates are that about 30% of patients who have schizophrenia derive little if any benefit from treatment with antipsychotic agents.[1] This figure may underrepresent the actual problem of inadequate response to antipsychotics, though, because a large number of patients may respond only partially. If these partial responders are included, the proportion of the treatment-resistant population may increase to over 50%.[2]

Resistance to treatment[3,4] currently is defined clinically by a set of criteria, primarily the Brief Psychiatric Rating Scale (BPRS) and Clinical Global Impressions (CGI) scale scores. Notably, the length of adequate drug trials has been modified recently to reduce the required number of drug failures: thus, a patient with schizophrenia now is considered to be resistant to treatment after 2 previous drug failures instead of 3, as first proposed.[3–5]

Several important antipsychotic agents have emerged since clozapine was introduced in the United States, including risperidone, olanzapine, and quetiapine. Most of these drugs are more effective and have fewer side effects than conventional neuroleptic agents do in treatment-responsive patients,[6–8] but none of them have been proven yet to be as effective as clozapine in treatment-resistant schizophrenia[4]—a population of patients who are, typically, chronically and severely ill. In this patient population, clozapine has been reported to be effective in controlling persistent aggression,[9,10] decreasing the incidence of suicide attempts,[11,12] decreasing the incidence of moderate tardive dyskinesia,[13,14] and treating comorbid substance abuse.[15,16]

Despite its well-established clinical efficacy,[17] clozapine is relatively underutilized.[4] This may be attributed partially to a pattern of use that has been restricted to patients with schizophrenia who are the most difficult to treat and to a tendency among some clinicians to focus on the risks rather than the benefits of using clozapine. The major risk associated with clozapine use is agranulocytosis, the incidence of which now is estimated to be 0.38%.[18] However, epidemiologic data suggest that the risk of agranulocytosis is very low relative to the risk factors associated with schizophrenia itself, especially suicide.[11]

The purpose of this article is to review the benefits and risks of treatment with clozapine, including the risks of switching patients from clozapine to other antipsychotic agents, with the idea of encouraging clinicians to reconsider the use of clozapine in their patients with treatment-resistant schizophrenia, taking into account the data that

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have accumulated since the introduction of clozapine to the marketplace.

BENEFITS OF THERAPY WITH CLOZAPINE

Clozapine is still the only drug that has proven efficacy in treatment-resistant schizophrenia,[4,19] showing superiority to chlorpromazine in reducing both positive and negative symptoms.[3] In 1988, the results of a pivotal multicenter study of patients with treatment-resistant schizophrenia showed that 30% of 126 clozapine-treated patients responded, compared with only 4% of 141 chlorpromazine-treated patients.[3] Breier et al.[20] reported that 42% of patients who responded poorly or partially to typical neuroleptic agents responded to clozapine. Lieberman et al.[2] reported that the response rate to clozapine was 50% among previously treatment-refractory patients and 76% among treatment-intolerant patients.

Clozapine is also beneficial for patients who are intolerant of the motor-related side effects (e.g., extrapyramidal syndrome [EPS], tardive dyskinesia) associated with treatment with neuroleptic agents.[5] In fact, the presence of motor side effects with prior treatment is believed to predict a favorable response to clozapine.[2] Tamminga et al.[13] provided evidence that clozapine elicited greater benefits than haloperidol on indices of motor symptoms in dyskinetic patients after 12 months ($p < .001$) and dramatically reduced symptoms of tardive dyskinesia after long-term treatment.

Besides improvement of both positive and negative symptoms, clozapine may improve organization of thoughts and certain aspects of cognitive function and enable patients to resume functioning in a low normal range.[21] In line with such overall improvement in psychopathologic characteristics, treatment with clozapine is associated with improved compliance with the medication regimen and less need for hospitalization.[21,22]

Some clinicians who have had extensive experience with the use of clozapine believe that the regular periodic visits required to monitor the patient's blood may have therapeutic value themselves. The relatively frequent contact between patient and clinician that results from the need for blood monitoring actually fosters the establishment of a therapeutic alliance, countering social isolation and creating more opportunities to evaluate the patient's psychopathologic improvement subjectively and to monitor his or her compliance with the treatment regimen.

The Clozaril National Registry (CNR) also has played an important role in ensuring the safety of patients who are treated with clozapine.[18] The usefulness of the accumulated data on file at the CNR is unparalleled for research purposes in any pharmaceutical setting. These data are an invaluable source of information for epidemiologic analyses that can be used to improve further the therapeutic management of schizophrenia and related illnesses. Furthermore, the personnel at the CNR have many years of global experience in handling data and evaluating safety, which should be reassuring to physicians who strive to uphold their patients' therapeutic well-being and safety.

THERAPEUTIC CHALLENGES OF CLOZAPINE THERAPY

The mechanism of action of clozapine, and thus the reason for its therapeutic efficacy, is unknown, although it has unique pharmacologic properties, including a high level of activity at D_1 and D_4 dopaminergic, α-adrenergic, serotonergic, histaminergic, nicotinic, and muscarinic receptor sites.[23–25] As a result of this broad range of activity, polypharmacy often has been attempted when an alternative to clozapine has been sought. When multiple medications are administered, though, it is difficult to titrate the level of each drug and, more importantly, it is difficult to attribute any side effects to a particular agent. In fact, no polypharmaceutical regimens have shown the same efficacy as clozapine. On the other hand, monotherapy helps to maximize the benefits and minimize the side effects by allowing an accurate determination of the optimal dosage and the time to response.[26,27]

Patients With Suboptimal Response

Some treatment-refractory patients fail to improve appreciably with clozapine. We have found that 20% to 40% of treatment-resistant patients respond suboptimally to a trial with clozapine. Some of these individuals may exhibit more structural anomalies in their brains than normal individuals,[28,29] suggesting that preexisting structural neuropathology may limit their responsiveness to pharmacotherapy in general. Accurately identifying these patients and discontinuing clozapine is important to reduce the risk from the use of this drug.

Effects of Withdrawing Treatment

A consensus panel of the National Institute of Mental Health has recommended that, if a patient is responding well to treatment with clozapine, withdrawal from the medication should be avoided unless it is medically warranted.[30] This recommendation was made on the basis of findings that abrupt withdrawal of clozapine may lead to a rebound phenomenon, which some investigators have attributed to the cholinergic component of clozapine.[31–34] Cholinergic rebound after the withdrawal of medication typically is associated with somatic symptoms such as malaise, agitation, insomnia, restlessness, anorexia and nausea,[35] and, sometimes, EPS.[30] These symptoms may manifest fairly rapidly. The propensity for the rapid onset of these withdrawal symptoms has been linked to the relatively short elimination half-life of clozapine, by which it dissociates from its receptors (e.g., $5\text{-}HT_2$, D_2, D_3, and D_4)

more rapidly than other antipsychotics do, possibly leading to a rapid dissipation of its pharmacologic effects.

Aside from these somatic symptoms, withdrawal of clozapine also may result in a recurrence of psychotic symptoms.[30,33,36] Of course, this risk of rebound psychosis requires close monitoring of patients, particularly when dealing with patients who have a history of inwardly or outwardly directed violence. Patients who have been treated with clozapine are usually chronically ill and are typically resistant to treatment, and some are suicidal or persistently aggressive,[9,10,12] thus in particular need of monitoring if the medication must be withdrawn.

Switching From Clozapine

Clozapine is still the only agent that has demonstrated superior efficacy in patients with treatment-resistant schizophrenia to date.[4,19] However, physicians are eager to try novel agents as they are introduced, in the hope of finding one that will reduce the symptoms of schizophrenia adequately and will be convenient to prescribe and use, without the perceived risks of clozapine. Risperidone, olanzapine, quetiapine, sertindole, and ziprasidone are among the newer-generation antipsychotic agents that are currently available or will be marketed soon.[6,8]

Previous studies have shown little benefit from trying more than 2 antipsychotic agents before declaring that a patient is resistant to treatment and prescribing clozapine—there is only a 9% chance that these patients will respond to treatment with other antipsychotic agents.[37] Considering that prolonged mental illness may be damaging,[38] early, accurate identification of the treatment-resistant patient and initiation of clozapine enhances the therapeutic efficacy.

Since risperidone was approved in 1994, many patients have been switched from clozapine to risperidone. The reported results of these switches suggest that risperidone is not necessarily an effective therapy for patients who have responded to therapy with clozapine.[30,34,39–41] After some of these patients were switched back to clozapine from risperidone, they did not respond well and required higher dosages of clozapine than they had needed initially.[30]

Lacey and associates[42] reported that 80% of their patients who had been switched from clozapine to risperidone experienced relapses within 4 weeks. In another study of inpatients with treatment-resistant schizophrenia who had been crossed over from clozapine, Still and colleagues[34] reported that after the switch to risperidone, none of the patients improved, and 50% terminated therapy because of an exacerbation of their psychosis or the occurrence of adverse events.

Fewer reports exist about the effects of switching from clozapine to olanzapine, since olanzapine was only approved in 1996. Nonetheless, preliminary reports suggest that although olanzapine is biochemically similar to clozapine, it is not as effective as clozapine, at least in the population of patients with treatment-resistant schizophrenia. A relapse rate as high as 80% within 4 weeks of switching from clozapine to olanzapine recently has been reported.[20]

There is a chance of noncompliance when a patient is switched from one medication to another. This, combined with the potential lack of efficacy of the alternative treatments that are tried, considerably increases the risk of a relapse, and a relapse of schizophrenia is costly. Lack of efficacy of treatment and noncompliance with the treatment regimen account for 60% and 40%, respectively, of the costs of rehospitalization.[43]

Adverse Effects of Treatment

Drug-related side effects such as drowsiness, weight gain, dizziness, anergia, seizures, myoclonus, and urinary disturbance sometimes are associated with antipsychotic treatment in general and are often present during treatment with clozapine. Careful adjustment of the dosage of clozapine will reduce many of these side effects, particularly dizziness, anergia, and myoclonus. The likelihood of seizures also can be reduced by careful attention to dosing.[44] Weight gain and persistent somnolence, however, can be more severe with clozapine than with other antipsychotic agents and can lead to a medical necessity to discontinue treatment.

The most serious adverse effect associated with clozapine is agranulocytosis, although the risk is low, estimated to be 0.38% in clozapine-treated patients.[18] If agranulocytosis or severe leukopenia develops during treatment with clozapine, the treatment should be discontinued, and the patient should not be rechallenged with the drug. During the era before blood monitoring, the agranulocytosis-related death rate was as high as 50%.[45] Since the clinical introduction of clozapine in 1990, increased prescriber awareness, mandatory weekly blood monitoring, and the institution of safety measures such as the CNR (which ensures that patients who develop agranulocytosis or severe leukopenia stop taking the drug and not be rechallenged with it) have lowered the agranulocytosis-related death rate markedly. The new rate was estimated to be 3.1% during the years 1990 through 1994.[18] Thus, based on recent agranulocytosis-related fatalities,[46] the overall death rate from agranulocytosis today in clozapine-treated patients is probably about 2.5 per 10,000.

We now know that extremes of age and the use of adjunctive drugs that suppress the bone marrow are risks for death if agranulocytosis develops. Aggressive medical management of susceptible patients and avoidance of polypharmacy during treatment with clozapine will be effective in lowering the agranulocytosis-related death rate. Also, the development of recombinant cytokines has allowed for the effective treatment of agranulocytosis in many cases. The use of filgrastim, a human granulocyte–colony-stimulating factor (G-CSF), safely reduces the duration of clozapine-induced agranulocytosis by 50%.[47]

Lamberti et al.[47] have reported that the white blood cell count of 1 patient increased from 2000/mm^3 to 5400/mm^3 within 6 days of treatment with filgrastim.

DETERMINING AN ADEQUATE DOSAGE OF CLOZAPINE

Assessing the Time to Response

Individualized dosage titration is one effective means of optimizing treatment and minimizing side effects that is particularly useful with clozapine. Guidelines for the initial titration of the dosage of clozapine have been suggested by a working panel of the American Psychiatric Association.[5] These guidelines say that treatment should be initiated at a low dosage (12.5 to 25.0 mg/day) and, if the drug is tolerated, the dosage should be increased gradually (by no more than 25 to 50 mg/day) over 2 weeks until the target dosage is reached. At the starting dosage, patients should be monitored for respiratory depression, sedation, tachycardia, and orthostatic hypotension.[5] Further increases in the dosage should be made with increments of no more than 100 mg once or twice weekly.

Although the total time required to obtain the optimal response to treatment with clozapine remains controversial,[48] we have found that patients who respond to clozapine typically do so within 8 weeks of a change in dosage.[26] If clozapine fails to show clinical benefit at any given dosage, its use should not be prolonged much beyond this 8-week interval. In our study of 50 inpatients with treatment-refractory schizophrenia, 68% had a clinical response at a mean dosage of 468 mg/day, and the mean time to a response was 82 days. A total trial period of 12 to 18 weeks identified about 90% of the patients who responded to clozapine. We found no "late responders" in follow-up of as long as 75 weeks.[26] Of course, patients who begin to respond to clozapine may continue to accrue benefits over a longer period.

We have now modified our proposed schedule for optimal titration of clozapine[26] to include blood-level monitoring. Once patients have shown clinical improvement with clozapine, we measure a plasma level. In patients who have plasma levels of greater than 350 ng/mL, we reduce the dosage to achieve optimal plasma levels of 200 to 350 ng/mL. This usually corresponds to a daily dose of 200 to 400 mg, although dosage must be individualized. We have done this successfully in 12 patients now with no loss of efficacy. In 6 patients who did not respond to dosages of 700 to 900 mg/day, we determined plasma levels and found that 4 patients had levels of less than 300 ng/mL. These patients were tolerating clozapine well, with no side effects. All were inpatients and were observed to be compliant with the medication regimen. We increased the dosage in each of these 4 patients. Two responded, 1 at 1050 mg/day, and 1 at 1175 mg/day. At the time of their response, these patients had blood levels of 425 ng/mL and 390 ng/mL, respectively. The other 2 patients did not respond to higher dosages of as high as 1200 mg/day, with corresponding blood levels of 437 ng/mL and 475 ng/mL. This experience showed that a full exploration of the possibility of response to monotherapy with clozapine is useful and effective, but daily oral dosages of more than 900 mg should be administered with extreme caution and tried only in patients who tolerate the drug well.

MAINTAINING THERAPY WITH CLOZAPINE

In a study of 56 inpatients who had chronic schizophrenia, VanderZwaag and colleagues[27] found that patients who had plasma levels of clozapine in the ranges of 200 to 300 ng/mL and 350 to 450 ng/mL responded better than did those who had plasma levels in the range of 50 to 150 ng/mL. There was no incremental advantage to having plasma levels of 350 to 450 ng/mL compared with 200 to 300 ng/mL, and patients at the higher end of the dosing continuum tended to experience more sedation.[27] Response should be evaluated at the dosage plateaus of 200 to 400 mg/day and 500 to 600 mg/day. Only patients who have minimal side effects should have their dosages titrated to more than 600 mg/day.[4]

SUMMARY

The efficacy of clozapine in reducing symptoms in treatment-resistant schizophrenia remains unparalleled despite the availability of other novel antipsychotic agents. Treatment with clozapine may be optimized by tailoring the dosage for each individual, thereby minimizing side effects while maximizing the benefits. Treatment should be initiated at a low dosage (12.5 to 25 mg/day) and increased gradually to the target dosage, provided it is tolerated. The benefits of therapy with clozapine include improvement in both positive and negative symptoms (without inducing EPS or tardive dyskinesia), cognitive function, and overall quality of life. When patients respond well to clozapine, they should be maintained on this treatment regimen unless interruption of therapy is medically warranted. Abrupt withdrawal of clozapine has been shown to result in a cholinergic rebound, which is characterized by somatic symptoms and, in some cases, return of symptoms. Switching the patient to treatment with other atypical agents such as risperidone and olanzapine may lead to a relapse, suggesting that these antipsychotic agents are not as effective as clozapine in patients who respond to it.

The safety measures that surround the use of this drug are largely responsible for the marked increase from the 1970s to the 1990s in the benefit-risk ratio associated with the use of clozapine. If agranulocytosis develops, clozapine needs to be discontinued immediately. The use of

filgrastim may shorten the duration of agranulocytosis. A national registry of clozapine-treated patients (the CNR) ensures that patients who develop agranulocytosis are not rechallenged with the drug. It will be important to provide the same high level of safety monitoring when generically produced clozapine is marketed.

Drug names: chlorpromazine (Thorazine and others), clozapine (Clozaril), filgrastim (Neupogen), haloperidol (Haldol and others), olanzapine (Zyprexa), quetiapine (Seroquel), risperidone (Risperdal), sertindole (Serlect).

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