Clozapine: Balancing Safety with Superior Antipsychotic Efficacy

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Abstract

Clozapine is often referred to as the gold standard for the treatment of schizophrenia and yet has also been described as the most underutilized treatment for schizophrenia supported by solid evidence-based medicine. In 2008, it was used to treat only 4.4% of patients with schizophrenia in the U.S., which is ~10–20% of those with approved indications for clozapine for which there is no alternative of equal efficacy. Its use is much higher in Scandinavian countries and China. The primary indications for clozapine are: 1) treatment-resistant schizophrenia or schizoaffective disorder, defined as persistent moderate to severe delusions or hallucinations despite two or more clinical trials with other antipsychotic drugs; and, 2) patients with schizophrenia or schizoaffective disorder who are at high risk for suicide. Concerns over a number of safety considerations are responsible for much of the underutilization of clozapine: 1) agranulocytosis; 2) metabolic side effects; and, 3) myocarditis. These side effects can be detected, prevented, minimized and treated, but there will be a very small number of fatalities. Nevertheless, clozapine has been found in two large epidemiologic studies to have the lowest mortality of any antipsychotic drug, mainly due to its very large effect to reduce the risk for suicide. Other reasons for limited use of clozapine include the extra effort entailed in monitoring white blood cell counts to detect granulocytopenia or agranulocytosis and, possibly, minimal efforts to market it now that it is largely generic. Awareness of the benefits and risks of clozapine is essential for increasing the use of this lifesaving agent.

Key Words: Schizophrenia, Clozapine, Treatment Resistant, Suicide, Agranulocytosis, Metabolic Side Effects, Myocarditis

Introduction

The primary aim of this article is to provide information about the efficacy and safety of clozapine for the treatment of schizophrenia to enable clinicians, patients, their families, and other stakeholders to make informed decisions as to when and how to use clozapine, a drug generally considered the most effective, and at the same time, the most dangerous treatment for schizophrenia and schizoaffective disorder. Mainly because of perceived dangerousness, many clinicians avoid prescribing clozapine even for those indications where there is no good alternative for patients with schizophrenia or schizoaffective disorder: 1) treatment resistance; 2) high risk of suicide; and, 3) inability to tolerate other antipsychotic drugs because of motor side effects, including moderate–severe tardive dyskinesia. Thus, although conservative estimates of the percentages of patients with schizophrenia who are treatment resistant (~30%) and who have survived a serious suicide attempt (~10%) suggest that at least 35–40% (as the two groups partially overlap) should be treated with clozapine, the latest available data in the U.S. (2008) show

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Submitted: June 28, 2011; Revised: June 12, 2012; Accepted: June 16, 2012
that clozapine has a 4.4% market share (IMS, 2010). The U.S. lags behind many other countries in the use of clozapine, especially Scandinavian and other European countries, and China. This state of affairs has been singled out as the preeminent example of the lack of use of evidence-based medicine in the treatment of schizophrenia. Horvitz-Lennon et al. noted that the FDA issuance of the indication for clozapine for use in patients deemed at high risk for suicide had no impact on the prescription of clozapine, despite the intensive marketing efforts made by Novartis, the company who funded the key research on clozapine and suicide, to educate providers and facilitate access to management tools to prescribe clozapine for this new indication (1).

Clozapine: A Brief History

A brief historical review is useful to understand the reasons for this low utilization of clozapine and to point the way to a possible increase in its use. There have been two seminal and transformational discoveries in the pharmacologic treatment of schizophrenia. The first was the discovery of chlorpromazine, serendipitously, in 1952 in Paris by Laborit, Delay and Deniker, who were the first to observe that this compound, which had been expected to be no more than a highly sedative antihistamine to relieve agitation, controlled delusions and hallucinations, and was, thus, the first antipsychotic drug (2). Little matter then, at least initially, that during ongoing treatment, many of the patients manifested a variety of motor side effects, including parkinsonism, dystonias, opisthotonus, akathisia, most likely a few cases of neuroleptic malignant syndrome (NMS) which were probably misdiagnosed as “lethal catatonia,” and eventually many cases of tardive dyskinesia or tardive dystonia. This would be especially true in elderly and post-menopausal patients. Other pharmaceutical companies sought to find other drugs which were equally effective as antipsychotics but more tolerable. Numerous drugs with a similar mechanism of action, which was quickly discovered to be a blockade of dopamine D2 receptors, were identified but, like chlorpromazaine, they too produced motor side effects. This led to the expectation that the “typical” antipsychotic drug should produce motor side effects at clinically effective doses. The motor side effects gave these drugs a class name, neuroleptics, but they are also referred to as typical or first-generation antipsychotics. The prior concern with tardive dyskinesia as a result of neuroleptic treatment is diminished to some extent now that it is so rarely seen because of the introduction of, and near ubiquitous use of, atypical antipsychotic drugs. This may be one reason why clozapine use is not as prevalent as it should be.

However, in 1956, only a few years after the discovery of chlorpromazine, a drug was synthesized and characterized by Hunziker, Schmutz and Stille from the Wander Laboratories in Berne, Switzerland, which showed that antipsychotic efficacy and motor side effects could be dissociated. That drug was clozapine. In animal models, it did not cause catalepsy, an immobilized state which was shown to predict motor side effects with chlorpromazine and its congeners. Clozapine produced no motor side effects at doses in which it was effective. Indeed, it was eventually found to be tolerable in patients with Lewy Body Dementia and the L-DOPA-induced psychosis of Parkinson’s disease, who became totally immobilized when even the smallest doses of a neuroleptic able to control psychotic symptoms was administered. Thus, clozapine was atypical and, like chlorpromazaine, became the progenitor of, and eventually the clue to, discovering the pharmacologic properties needed to produce other atypical antipsychotic drugs. This article will refer to these two types of antipsychotic drugs as typical and atypical antipsychotic...
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drugs. Since clozapine does not cause catalepsy, it is incorrect to call it a neuroleptic.

Clozapine usage spread throughout Europe and, interestingly, to China, where it became almost the only antipsychotic drug used once China substituted western antipsychotic drugs for traditional medicines (3). Clozapine testing in the U.S. was just beginning when a cluster of elderly and infirm patients in Finland developed agranulocytosis, leading to eight deaths in a small geographic region (4, 5). No such clustering of deaths has been reported since, in Finland or anywhere else. The ensuing investigation rejected the conclusion that clozapine was the cause of these deaths, at least through an agranulocytosis mechanism (6). Nevertheless, these deaths led to its withdrawal from general use in all countries where it had been marketed. Subsequently, many patients who had been stabilized on clozapine relapsed severely shortly after its abrupt withdrawal (7). It was reintroduced on a very restricted basis with weekly monitoring of the white blood count so as to detect agranulocytosis within days of its emergence.

Clozapine would probably not have been reintroduced were it not for observations that it appeared to be more effective to control the symptoms of severe tardive dyskinesia and to improve psychotic symptoms in patients with tardive dyskinesia than other antipsychotic drugs (8-10). The potential of clozapine to treat schizophrenia with minimal risk of causing tardive dyskinesia was the main motivation for the willingness of Sandoz (now Novartis) and the U.S. FDA to permit a trial in patients who had failed to respond to other antipsychotic drugs or who had intolerable motor side effects, including tardive dyskinesia. Thus, the issue that is the subject of this article, balancing risk and benefit, is the main reason why clozapine was given any chance for approval in the U.S. The result was the U.S. Clozaril® study, intended to determine if clozapine was more effective in patients who had failed to respond to at least three other antipsychotic drugs. The clear superiority of clozapine over chlorpromazine in a six-week trial, in the relatively small sample of 268 patients who were treatment resistant by history and failed to respond to haloperidol at doses ≥60 mg/day for up to six weeks, led to the approval of clozapine for use in treatment-resistant and neuroleptic-intolerant patients with weekly monitoring of the white blood cell count on an indefinite basis (11). Approval by the FDA led to its eventual approval in all Western countries, but it was not until 2009 that it was approved in Japan. Worldwide experience since its U.S. approval has confirmed the greater efficacy of clozapine over not only typical but also other atypical antipsychotic drugs, at least at conventional doses in treatment-resistant patients (12, 13). Clozapine is the recommended treatment for treatment-resistant schizophrenia by the Texas Medical Algorithm Project (14), the web-based International Pharmacology Algorithm (IPAP, www.IPAP.org), and the Schizophrenia Patient Outcomes Research Team (PORT) (15). With the exception of supplemental ECT and, as will be discussed, high doses of other atypical antipsychotic drugs, there is little disagreement that clozapine is the treatment of choice once a patient with schizophrenia or schizoaffective disorder has failed two trials of adequate duration and dosage of other antipsychotic drugs. About 10% of first-episode patients fulfill this definition after a year of treatment (16), while another ~20% do so after years of responding adequately to other antipsychotic drugs (17, 18).

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Other benefits for clozapine that have to be considered to evaluate its benefit-to-risk ratio for specific patients include, in order of importance and identifying the initial reports of efficacy: 1) reducing the risk for suicide (19); 2) improvement in some domains of cognition (20); and, 3) blocking L-DOPA-induced psychosis in patients with Parkinson’s disease without worsening motor symptoms (21). On the other hand, the early safety issues with clozapine, which included major motor seizures, pulmonary embolism, and tachycardia, have been expanded as evidence for metabolic side effects, including type II diabetes mellitus and major weight gain for some patients (22, 23), myocarditis, cardiomyopathy and sudden death (24, 25) has accumulated.

Evaluating the Benefits of Clozapine

Efficacy in Treatment-Resistant Schizophrenia

As mentioned in the Introduction, the first indication of the superiority of clozapine over other antipsychotic drugs in patients with schizophrenia was the advantages for positive and negative symptoms in treatment-resistant patients who participated in the six-week, double-blind, randomized U.S. Clozaril trial (11). Three issues that need to be clearly delineated to make the decision to recommend clozapine over other treatments, including other atypical antipsychotic
drugs such as olanzapine and risperidone, for treatment-resistant patients are: 1) the definition of treatment resistance, which includes which symptoms of schizophrenia are to be targeted; 2) the dose of clozapine to be used during a trial; and, 3) duration of the trial.

The definition of treatment-resistant schizophrenia which is appropriate for consideration whether or not to begin a clozapine trial is: the subgroup of poor (or functionally impaired) outcome schizophrenia which has persistent positive symptoms of at least moderate severity after two or more trials of other antipsychotic drugs, typical or atypical. Approximately 30% of patients with schizophrenia meet these criteria for treatment resistance (12, 26). There is no evidence that this percentage has diminished since the substitution of atypical for typical antipsychotic drugs as first-line treatment, as these two classes of drugs are equal in efficacy for the treatment of positive symptoms in nontreatment-resistant patients and, at ordinary doses, the atypicals are no better than typical antipsychotic drugs in treatment-resistant patients (27, 28; see Meltzer [29] for further discussion). Not all schizophrenia patients with poor outcome have severe positive symptoms, and those that do not are not as likely to have a superior response to clozapine as those who do (have persistent positive symptoms). The proportion with poor outcome is estimated to be upwards of 50% (30). The causes of poor outcome in those with minimal to moderate positive symptoms, assuming they have been compliant with treatment, may be severe, persistent negative symptoms, cognitive impairment, substance abuse, inadequate psychosocial treatment and economic support, both of which may be exacerbated in difficult economic conditions such as those affecting the U.S. and other countries since 2008 (12).

While clozapine may be more effective for negative symptoms than other treatments, especially to the extent that the negative symptoms are secondary to positive symptoms and those positive symptoms respond to clozapine, the benefits to be expected in such patients and, hence, the efficacy-to-safety ratio, may be less than those with moderate-to-severe positive symptoms (11, 12, 31). Clozapine has been shown to have advantages over other atypical antipsychotic drugs for overall psychopathology, including general symptoms, in poor-outcome patients (32), but this effect is weaker than that for positive symptoms. Thus, it is the subset of poor outcome patients who have persistent moderate-to-severe positive symptoms, along with those who are highly suicidal, whether or not they have moderate-to-severe positive symptoms, for which a trial of clozapine is most clearly justified.

Dosage of clozapine in treatment-resistant patients with schizophrenia is usually between 300–600 mg/day (11, 12). Both lower and higher doses may be sufficient or necessary to achieve efficacy and tolerability. Nontreatment-resistant patients usually respond at doses of 150–400 mg/day (see [29] for discussion). The latter corresponds to doses of risperidone of 4–6 mg/day and olanzapine 10–20 mg/day. There is some evidence that at higher doses of olanzapine (e.g., 25–45 mg/day or higher) positive symptoms in treatment-resistant patients with schizophrenia or schizoaffective disorder will respond as well as to higher doses of clozapine. At six months, both high-dose olanzapine and clozapine improved multiple measures of psychopathology with no significant difference between them, but the improvement in Global Assessment of Functioning score was significantly greater with clozapine (p=0.01). There were no significant differences in motor side effects, but weight gain was significantly greater with high-dose olanzapine (p=0.05; [33]). There are few trials with higher doses of other atypical antipsychotic drugs to compare with clozapine in the higher dose range. More such trials are needed with other atypical antipsychotic drugs to investigate the possibility that clozapine is more effective than other atypicals because its low motor side effect profile persists throughout a very wide dose range. There is no question that high dosages of typical antipsychotic drugs do not improve their efficacy for treatment-resistant patients. A recent report showing that ziprasidone, at ordinary doses, showed comparable efficacy to clozapine in treatment-resistant patients requires independent replication (34).

Partly because the U.S. Clozaril trial (11) was of short duration—six weeks—and was sufficient to show advantage for clozapine over chlorpromazine, it has been assumed by some that this is a sufficient duration for all trials with clozapine. Other comparative studies have produced similar results (31, 35-38). However, there is considerable evidence that improvement in positive symptoms with clozapine for individual patients may require up to six months of treatment, and that some patients will show no advantage to clozapine during the first three months of treatment, or even longer, and yet have a marked response. Clozapine differs from typical antipsychotic drugs in this regard. The evidence for this comes from open trials (39, 40), retrospective studies (41), and the double-blind trial which compared clozapine and high-dose olanzapine previously mentioned (33). Significant improvement in measures such as relapse and social function, even after more prolonged treatment with clozapine, has been reported by Joffe et al. (41). A longer time period of a trial with clozapine does increase the risk for agranulocytosis, which peaks within the first six months, but given the limited treatment options for treatment-resistant patients it would appear that it is prudent to recommend the longer trial rather than failing to identify all or nearly all patients...
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patients who are responders. However, others have suggested that trials of clozapine should last no more than 3–4 months (42, 43).

It can be estimated from the effects of clozapine on suicide attempts and the proportion of attempters who complete suicide that at least one-third of the approximately 5,000 patients per year with schizophrenia or schizoaffective disorder who commit suicide in the U.S. would not do so had they been treated with clozapine.

Suicide Reduction with Clozapine: Impact on Overall Mortality

Suicide is the major contributor to premature death among patients with schizophrenia (44). Overall, approximately 30–50% of patients with schizophrenia attempt suicide, while 5% actually die from suicide, a fivefold greater rate than the lifetime risk for suicide in the general population of the U.S. (45, 46). There is now extensive evidence of various types that clozapine markedly reduces suicidal behavior in patients with schizophrenia and schizoaffective disorder, regardless of treatment-resistance status. The first evidence for this effect of clozapine was a two-year mirror image study of 88 patients with treatment-resistant schizophrenia which showed an 85% decrease in attempts following switching to clozapine (19). An epidemiologic study of 67,000 cases of clozapine-treated patients in the U.S. between 1989 and 1996, adjusted for age, sex, and race, found that all-cause mortality was lower during the period of clozapine use than during nonuse. The longevity-enhancing effect of clozapine was mainly the result of a dramatic decrease in suicide in clozapine users (47). This was confirmed in a subsequent mirror image study from Europe (48). These studies could not rule out the possibility that more frequent clinic visits during clozapine treatment may have accounted for the advantage. To address this issue, a multicenter, randomized, international, two-year follow-up study—the International Suicide Prevention Trial (InterSePT)—was conducted to compare the risk for suicidal behavior in patients at high risk for suicide who were randomized to clozapine or olanzapine (49). Patients randomized to clozapine attempted suicide significantly less than those in the olanzapine group (p=0.03). This led to clozapine being approved by the FDA for the indication of suicide reduction but, as noted in the Introduction, this had no discernable impact on the use of clozapine for this purpose. Clearly, some knowledgeable physicians are making their patients aware of this treatment option, but many fewer than need to.

A second major epidemiologic study confirmed that clozapine markedly reduces all-cause mortality compared to all other antipsychotic drugs and that a major contributing factor is the reduction in death by suicide (50). Using national record-based data on medication prescription and deaths in 66,881 patients with a schizophrenia-related diagnosis from 1996 to 2006, it was found that the lowest risk for overall mortality was present in patients treated with clozapine. Compared to the reference treatment, perphenazine, the risk was reduced 26% (relative risk=0.74, confidence interval=0.60 to 0.91, p=0.0045). Clozapine was superior to all other antipsychotic drugs in reducing death due to suicide as well (p<0.0001). The risk of death from suicide on clozapine, adjusted for risk factors, was 0.34, compared to 1.0 for perphenazine and 1.58 for quetiapine. No other drug had a lower risk for suicide than any other. As will be discussed, there was no offsetting increase in mortality due to ischemic heart disease with clozapine. Tiihonen et al. (50) recommended a reconsideration of clozapine as a first-line treatment based upon their data and other available data supporting the efficacy of clozapine for reducing suicide. This conclusion was challenged by De Hert et al. (51) but none of the issues raised could possibly change the overall findings. For example, they raise the possibility that because the lower mortality rate was highly likely to be driven by the ability to reduce the risk for suicide, a conclusion they accept, that there is a survivor bias in the overall mortality rate, on the assumption that patients early in their course made a suicide attempt and were prescribed clozapine and remained on it, noting that discontinuation from clozapine is less frequent than other drugs. However, there are no data available which indicate the proportion of patients who are treated with clozapine in Finland which is due to a prior suicide attempt. Treatment resistance would be much more common as a reason for prescribing clozapine.

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Clozapine Advantages in Cognition and Broad Outcome Measures

Improvement in positive and negative symptoms, general psychopathology, cognition, suicidality/mood, and fewer extrapyramidal side effects (EPS) contribute to clozapine having broader advantages that most probably represent the integrated sum of these effects. These include improvement in work and social function, quality of life, lower relapse rate and rehospitalization. Much of this depends upon improvement in cognitive function. Clozapine has been reliably shown to improve some domains of cognition in schizophrenia. These include verbal fluency, declarative memory, attention, and speeded mental functions (20, 52-54).

Some have claimed that this is simply a practice effect (55) or that typical antipsychotic drugs are as effective (56). We have found that verbal fluency in 25% of patients treated with clozapine improved at least one standard deviation, which is unlikely to be a practice effect. Improvement of this magnitude was not observed in patients treated with typical antipsychotic drugs (Meltzer and Sumiyoshi, to be submitted). As with improvement in positive symptoms, it may take up to six months for improvement in cognition to become evident and maximal (20). There is abundant evidence for the failure of typical antipsychotic drugs to improve cognition (see Meltzer and McGurk [22] for review). The reasons for these discrepancies in views on clozapine and other atypicals on cognition go beyond the scope of this article to discuss in detail. It is important to note that preclinical studies of the effects of typical and atypical drugs on certain models of cognitive impairment, such as impaired novel object recognition due to subchronic phencyclidine (PCP) administration in rodents, have demonstrated that atypicals can reverse the deficit due to PCP while typical antipsychotics are ineffective (57). The importance of cognitive improvement to functional outcome in schizophrenia is sufficiently well established to warrant utilizing the possible benefits conveyed by clozapine over typical antipsychotic drugs in the consideration of whether or not to treat a patient with it.

Improvement in measures of quality of life also reflects advantages of clozapine over typical antipsychotic drugs (58, 59). In the European Schizophrenia Outpatients Health Outcomes (EU-SOHO) study, a three-year observational study of outcomes associated with antipsychotic treatment for schizophrenia in an outpatient setting involving a total of 9,340 patients, olanzapine and clozapine were associated with important health-related quality of life benefits at endpoint, most of which occurred during the first six months (60). Other broad outcome measures of clinical and pharmacoeconomic importance in which clozapine is advanta-
Evaluating the Risk of Clozapine

Agranulocytosis

The risk of developing granulocytopenia or agranulocytosis during clozapine treatment is between 0.7–1.0% (70). Most cases occur between six weeks and six months. The chance in the second six months of treatment is 0.70/1,000 patient-years and, after the first year, 0.39/1,000 patient-years (71). Mandatory monitoring of white blood cells or neutrophils permits early detection of granulocytopenia and cessation of clozapine before full agranulocytosis occurs. As a result, very few cases of full agranulocytosis occur any more. Data from the U.S. clozapine registry covering the first five years of use showed that, with monitoring, there were 382 cases of agranulocytosis in 99,502 patients (0.38%) and 12 deaths (0.01%). If agranulocytosis occurs, treatment with granulocyte colony-stimulating factor is effective to restore normal white blood cell levels in most cases, before infections develop. Treatment with antibiotics is usually effective in those cases, so the mortality due to agranulocytosis is in the range of 1/10,000. Given the mortality from other causes of patients with clozapine, and the limited choices open to patients who are treatment resistant or highly suicidal, it would seem to be a relatively easy decision to balance the benefits from clozapine against this small risk of fatality. According to Schulte, even with no monitoring of clozapine after six months, the mortality due to agranulocytosis is comparable to other drugs with no monitoring (e.g., mianserine or phenylbutazone) and with life in general. While it is a real risk, it is not so great a risk that it overrides the benefit for those patients who respond poorly to other antipsychotic drugs. With appropriate monitoring, the rate of fatal agranulocytosis should be in the range of 1 per 10,000 patients. This has to be compared with the reduced risk of suicide. Both the epidemiologic studies noted above demonstrate that mortality in schizophrenia is significantly less with clozapine than any other antipsychotic drug. Between 4–8% of African Americans and people of Middle Eastern origin have chronically low white blood cell counts (e.g., 2,500–3,500), with absolute neutrophil counts of 1,300–1,700 (72). These individuals are not at any greater risk for agranulocytosis than are those with typical white cell counts of 4,500–8,000. It is important not to deny such patients a trial of clozapine or to stop clozapine when it might be chanced upon by another clinician.

Metabolic Side Effects of Clozapine

Clozapine and olanzapine are comparable to one another in risk of causing marked weight gain, glucose dysregulation leading in some cases to type II diabetes mellitus and diabetic ketoacidosis, and lipid increases (23, 73, 74). These metabolic changes result from insulin resistance (75). African Americans and Hispanic people may be at greater risk than Caucasians (22). Both olanzapine and clozapine are more likely to produce these changes than any other atypical or typical antipsychotic drug and, for this reason, would be avoided compared to those which are atypical but which produce infrequent and mild insulin resistance (e.g., ziprasidone and aripiprazole) (74). However, it is important to recall that factors such as lifestyle, including diet, and intrinsic vulnerability to metabolic problems present in schizophrenia may minimize the differences between clozapine and other antipsychotic treatments with regard to adverse metabolic consequences (76). For some patients who develop type II diabetes, it will be a particularly difficult decision to continue clozapine as long-term renal, peripheral vascular, and ocular side effects may be such that patients will prefer not to risk their development. Those patients with the most adverse metabolic effects of clozapine should be counseled about the need for diet and exercise. However, an interesting feature of weight gain with clozapine is that weight gain with clozapine predicts clinical response (77, 78). Thus, because of increased efficacy, the decision to stop clozapine treatment may be more complicated. In addition, relapse following termination of clozapine treatment may be rapid and severe (79). Therefore, treatments to counteract the metabolic side effects of clozapine may be of particular interest. Metformin treatment has been found to be useful to reduce a wide range of the adverse metabolic effects of clozapine (80). There is extensive investigation of genetic markers for the risk for developing metabolic syndrome. It is possible that these will become sufficiently sensitive to allow identification of those patients most likely to develop metabolic effects (81), and enable consideration of the value of the trial relative to this added risk or permitting some preventive actions such as diet and exercise.
**Motor Side Effects and Tardive Dyskinesia**

The difference between clozapine and neuroleptic drugs such as haloperidol and perphenazine with regard to motor side effects in rodents and humans was the basis for the second stage in the evolution of antipsychotic drug treatment discussed in the Introduction. As noted in the Introduction, the high prevalence of tardive dyskinesia in the U.S. in the 1980s (26), clearly the result of neuroleptic drug treatment, led to the revival of clozapine after it had been banned due to its risk for agranulocytosis. According to Kane et al. (26), tardive dyskinesia developed in about 5% of patients with each year of cumulative neuroleptic exposure. The incidence in older individuals is markedly higher. While this high rate may have been due to the high doses that were common in that era, there is no indication that lower doses of neuroleptics when given for prolonged periods produce rates comparable to the atypical antipsychotic drugs (82). Clozapine clearly has a lower likelihood to cause tardive dyskinesia than typical neuroleptics and is among the least likely of the atypicals to cause tardive dyskinesia (82). Thus, clozapine should be considered for patients with severe tardive dyskinesia and given extra consideration as a treatment in patients who show signs of developing tardive dyskinesia and who require continuing antipsychotic drug treatment. The lower mortality rate with clozapine (50) plus the emerging tardive dyskinesia provides more rationale for using clozapine even in nontreatment resistant and nonsuicidal patients.

The motor side effects of neuroleptics are an established factor in noncompliance with antipsychotic drug treatment and relapse (83). The near complete absence of motor side effects contributes to the low rate of discontinuation with clozapine. The desire to find other antipsychotic drugs which were as free of motor side effects as clozapine but did not cause agranulocytosis or have some of the other side effects specific to clozapine, such as hypersalivation and major motor seizure, stimulated the development of risperidone, olanzapine, quetiapine, and subsequent atypical antipsychotic drugs. Because some patients with clozapine have special vulnerability to develop motor side effects, very rare cases of tardive dyskinesia and NMS have been reported. Long-term clozapine usage as the primary, if not only, antipsychotic drug is needed to evaluate its risk for causing tardive dyskinesia. A study from China of 101 patients who received clozapine as a primary antipsychotic drug since their first episode, with a mean follow up of 12±6 years, showed a prevalence of tardive dyskinesia of 3.96%. The tardive dyskinesia was mild and orolingual in nature (84).

Clozapine is tolerable in patients who have had NMS from prior antipsychotic drugs but can also rarely be a precipitating factor, usually in patients with concurrent treatment with mood stabilizers or with a history of NMS from other drugs (85). The greater tolerability of clozapine in patients with Parkinson’s disease who require antipsychotic drug treatment because of the development of psychosis following L-DOPA compared to all other antipsychotics, with the exception of quetiapine, provides strong evidence that it and quetiapine have the least likelihood of causing tardive dyskinesia of all antipsychotic drugs (86). It also can suppress tardive dyskinesia (9, 87). Other atypical antipsychotics can do so as well, but clozapine may be more effective in some patients (82). Thus, for patients who experience motor side effects sufficiently on other antipsychotic drugs that it is a factor in their adherence to treatment or leads to motor side effects such as dystonias or NMS, clozapine's benefits would justify the increased risk of agranulocytosis.

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**Clozapine and Cardiovascular Risk**

Clozapine is associated with a low (0.015% to 0.188%) risk of potentially fatal myocarditis or cardiomyopathy (88). A higher rate of suspected myocarditis (0.7% and 1.2%) was identified in Australia. The condition developed within a median 17 days (mean 171.7 days, ±530.9 days) and 12 (10.3%) died. The outcome was unknown in the rest. Clozapine is not associated with prolongation of the QTc interval or sudden death due to torsades de pointes (89).

**Optimizing the Benefits of Clozapine**

A few considerations on how best to administer clozapine will be mentioned here. The importance of initial titration, dosage and adequate duration of treatment, and avoidance of additional add-on antipsychotic drugs until monotherapy has been tried are important general principles. It is critical at the outset of treatment with clozapine to educate patients and significant others as to why a trial with clozapine has been suggested, whether it be for treatment resistance or suicide risk reduction, how evidence has accumulated that for the right patient benefits outweigh risks, how the risk will be minimized with white blood cell monitoring, what will happen if the white count falls below the thresholds for granulocytopenia and agranulocytosis, and the wide range of annoying side effects, including sedation,
hypersalivation, tachycardia, weight gain, lipid changes, myoclonic jerks and seizures. This group of side effects can generally be effectively managed, although the weight gain less so. They should rarely be the cause for discontinuation in patients who require clozapine because of treatment resistance or suicide. A discussion of reduction in any current extrapyramidal side effects and reduced risk of tardive dyskinesia, the necessity for compliance and not stopping the medication in order to avoid a relapse, should also be part of this discussion.

Achieving adequate plasma levels of clozapine (≥350 ng/ml), which may require periodic measurement at the early phase of treatment and utilization of doses up to 900 mg/day, will enhance the benefit-to-risk ratio. If the patient is on another antipsychotic drug when clozapine is initiated, it should be discontinued shortly after adequate dosage has been achieved. Monotherapy trials should last for six months whenever possible. As discussed above, for some patients a second antipsychotic drug may sometimes be effective. There is controversy about the value of adding risperidone (90, 91). Some selective serotonin reuptake inhibitors, including paroxetine and fluoxetine (but especially fluvoxamine), impair the metabolism of clozapine so that reducing the dose of clozapine is usually appropriate. Sertraline and citalopram do not interfere with the metabolism of clozapine (92). Valproic acid may also increase plasma levels of clozapine, warranting reducing the dosage (92). Smoking leads to induction of cytochrome P450 CYP1A2 which will lead to lower plasma clozapine levels. Conversely, smoking cessation may markedly elevate clozapine plasma levels (93). Plasma levels of clozapine should be monitored for at least 3–6 months after smoking cessation and dosage adjustments made as needed. Patients receiving clozapine will need psychosocial treatment to maximize the benefits from the improvement in psychosis, negative symptoms and cognitive impairment which may emerge in the months after starting clozapine. Family and group therapy, cognitive behavioral treatment, supportive employment, and activity therapy have all been used with considerable success to enhance improvement with clozapine.

Conclusions

Despite the risk of agranulocytosis, metabolic side effects, and a variety of cardiovascular problems, including myocarditis, the specific advantages of clozapine with regard to efficacy can still make it a prudent choice for as many as 30–40% of patients with schizophrenia or schizoaffective disorder. The following advantages are well established: 1) superiority for positive symptoms in treatment-resistant patients; 2) lower risk for suicide; 3) lower risk for tardive dyskinesia and suppression of established tardive dyskinesia; 4) improvement in cognition contributing to better work and social function; 5) higher quality of life and longer time to discontinuation; and, 6) decreased relapse. On the other hand, there are serious risks: 1) agranulocytosis; 2) insulin resistance with increased risk of type II diabetes, weight gain, and various vascular complications; and, 3) myocarditis. There are also other unpleasant side effects, such as hypersalivation and increased risk of seizures. The results from the U.S. (47) and Finnish (50, 67) epidemiologic studies suggest that none of the potentially life threatening risks, as managed in the “real world,” have enough of an impact to negate the advantages which come from clozapine. Whether this will remain true after even longer term use of clozapine cannot be known for sure. However, clozapine has been available for twenty years in the U.S. now, and there is no evidence that mortality in the clozapine patients who have been taking it for this extended period is increasing. The success of clozapine in terms of time to discontinuation and fewer relapses than almost any other drug suggests that once patients get started on clozapine, their subjective experience is sufficiently favorable that they prefer it to other treatments.

Disclosures

HY Meltzer has been a consultant or grantee of Sandoz, Novartis, Azur, Teva, ACADIA, BioLineRx, BioVail, Cephalon, Dainippon Sumitomo, Eli Lilly, EnVivo, Janssen, Merck, Pfizer, Roche, and Schering-Plough.

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