Maximizing Clozapine Therapy: Managing Side Effects

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Since its introduction to the United States in 1990, the benefits of clozapine use have been repeatedly validated. Clozapine remains the only antipsychotic with proven efficacy in treatment-resistant schizophrenia. Because clozapine has been part of the psychiatric pharmacopeia for considerably less time than neuroleptics, which have dominated the field for over 4 decades, its underutilization may be partly attributed to a lack of experience in managing associated side effects. Most side effects associated with clozapine are typical of antipsychotics in general, and with clozapine, these side effects are typically benign, tolerable, and manageable. It is conceivable that there remains a concern over the risk of agranulocytosis. However, the mandatory blood monitoring carried out through the Clozaril National Registry has considerably reduced the incidence of fully developed cases of agranulocytosis from premarketing values of approximately 1% to 2% to current values of 0.38% and virtually prevented mortalities. These values are likely to decrease further with the application of cytokine augmentation therapy among patients developing blood dyscrasias. Many side effects of clozapine are observed early after treatment onset and are greatly reduced by dose adjustments. Appropriate management of side effects will facilitate a maximization of the benefits of clozapine treatment. Clearly, the benefits of clozapine therapy far outweigh its risks.

(J Clin Psychiatry 1998;59[suppl 3]:38–43)

The introduction of clozapine marked the first significant advance in the pharmacotherapy of schizophrenia since the introduction of conventional antipsychotics in the 1950s.[1] As indicated by various psychiatric measures, 30% to 60% of patients who fail to respond to typical antipsychotics respond well to clozapine.[2–4] Furthermore, unlike typical antipsychotics, clozapine is not associated with acute extrapyramidal side effects (EPS), tardive dyskinesia (TD), or elevated prolactin.[5]

The significant response of neuroleptic-resistant schizophrenia patients to clozapine validates its efficacy in this patient population.[2,6] Clozapine treatment results in a clinically significant improvement in the total Brief Psychiatric Rating Scale (BPRS) score, as early as 6 weeks[2] in patients who have not responded to conventional antipsychotics for a prolonged period of time. Objective measures have indicated a marked improvement in psychopathology, as well as negative symptoms such as blunted affect, emotional withdrawal, apathy, and disorientation. However, despite these benefits, clozapine is underutilized because of its limited indication for the treatment-resistant and treatment-intolerant population (i.e., EPS/TD-prone individuals), physician uncertainty about side effect management, and, especially, the negative perceptions relating to the risk of agranulocytosis.

Most side effects associated with clozapine are typical of antipsychotic treatment in general and are usually benign and tolerable.[7] The management of the more common side effects encountered following clozapine initiation, and the uncommon drug-related agranulocytosis will be discussed. Special emphasis will be given to recent developments in side effect management.

OVERVIEW OF CLINICAL SIDE EFFECTS

Antipsychotics, whether typical or atypical, are associated with an array of potential side effects including weight gain, seizures, cardiovascular symptoms, neuroleptic malignant syndrome, antiadrenergic effects (e.g., orthostatic hypotension), and anticholinergic effects (e.g., dry mouth, mydriases and blurred vision, constipation, inhibition of sweating and temperature regulation, sexual dysfunction). Motor side effects (e.g., EPS and TD) are primarily associated with the typical antipsychotics (i.e., traditional neuroleptics).[8] TD and EPS are severely distressing side effects that can reduce compliance with drug therapy.

Unlike conventional antipsychotics, clozapine's efficacy is not attributable to a high level of dopamine D_2-receptor binding in areas of the brain (e.g., basal gan-

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Supported by an unrestricted educational grant from Novartis Pharmaceuticals Corporation.

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glia) that play a prominent role in the execution of movement.[9,10] Hence, clozapine virtually does not cause EPS or TD. In fact, numerous cases describing the improvement of TD following clozapine use have been described in the literature.[7,11–13] The side effects seen in the early stages of clozapine use are generally benign and tolerable,[7] such as hematologic changes, sedation, sialorrhea, cardiovascular and respiratory effects, weight gain, constipation, seizures, hepatic effects, urinary incontinence, and neuromuscular effects.[14–17] Slow titration and dose reduction are strategies designed to minimize these adverse effects.[18]

Hematologic Side Effects

Agranulocytosis is a hematologic condition involving a severe reduction in the number of mature myeloid cells and normal erythroid and megakaryotic cells.[19] Agranulocytosis is clinically defined as a granulocyte count of less than 500/mm^3, whereas neutropenia is defined as a neutrophil count of less than 1000/mm^3 and leukopenia as a white blood cell (WBC) count of less than 3500/mm^3.[5] The cause of agranulocytosis is yet undetermined, but a recent in vivo analysis of immune-inflammatory markers in the plasma indicate that clozapine appears to have a complex immunomodulatory effect associated with activated T cells, pro-inflammatory effects, and immunosuppressive activities.[20] The presenting symptoms of the early stages of this hematologic disorder include lethargy, weakness, fever, and sore throat. Premarketing data indicated an incidence of 1% to 2%,[5,21] but, primarily due to the efficient blood monitoring procedures of the Clozaril National Registry (CNR), the actual incidence is at a low 0.38%.[22] During the period between 1990–1994, with CNR blood-monitoring procedures in place, the agranulocytosis-related death rate in the United States was at a low 3.1%, a dramatic reduction from a rate of over 50% in the early phases of clozapine use (circa 1966–1975).[22] Data from a patient monitoring system in the United Kingdom and Ireland during the same period (1990–1994) reported that fatal agranulocytosis occurred in 0.03% of patients.[23]

Since clozapine is clinically superior to chlorpromazine, it was useful to determine whether patients at risk for agranulocytosis could be identified prior to clozapine treatment. Risk factors for clozapine-associated agranulocytosis include increasing age, female sex, and coadministration of certain other drugs that may lead to agranulocytosis.[21,24] Other risk factors for agranulocytosis include genetic susceptibility: patients of Ashkenazic Jewish descent with the HLA-B38 phenotype appear to be at higher risk, and African Americans have been shown to have an approximately 2-fold greater mortality risk following agranulocytosis than white patients.[21,24]

Among individuals who are at risk, the critical period of developing agranulocytosis is within the first 6 months following clozapine initiation.[21] In relation to this finding, the Food and Drug Administration (FDA) advisory committee recommended, in July 1997, that mandatory weekly blood monitoring be modified to a lower frequency (e.g., every 2 weeks) after 6 months. A definitive ruling on the frequency of hematologic monitoring required after 6 months is still pending.

Most hematologic adverse effects (i.e., early abnormalities that could progress to agranulocytosis) following clozapine initiation are transient and manageable.[25] Transient neutropenia and leukopenia have also been described after treatment with other psychotropic agents, such as phenothiazines and carbamazepine.[26,27] If the WBC count falls to below 3000/mm^3 or the absolute neutrophil count to below 1500/mm^3, therapy with the suspected agent (e.g., clozapine) should be interrupted immediately. Recent developments in cytokine research present the possibility of a concomitant clozapine-cytokine treatment regimen to manage drug-induced agranulocytosis.[19,28,29] With this augmentative treatment strategy, cytokine-mediated recovery of blood precursor cells could reverse, or possibly even prevent, the progression of early phases of blood dyscrasias to a potentially lethal stage, i.e., agranulocytosis. Because the incidence of clozapine-related agranulocytosis is so rare, it is not feasible to conduct a large clinical study on the therapeutic efficacy of granulocyte colony-stimulating factor (G-CSF) or granulocyte-macrophage colony-stimulating factor (GM-CSF). However, isolated case studies indicate that this recombinant technology may decrease the occurrence and/or duration of agranulocytosis.[19,28,29] G-CSF and GM-CSF have been shown to prevent the development of agranulocytosis by stimulating precursor cells in the bone marrow[30] and induce a return of the number of precursor cells to near normal state within 5 to 8 days.[19,29] Subcutaneous administration of 75–150 mg b.i.d. of GM-CSF and 300 μg/day of G-CSF safely and effectively decreased the duration of clozapine-related agranulocytosis by facilitating a replenishment of WBC precursors in the bone marrow.[19,29]

Sedation

Drowsiness/sedation is the most common side effect of clozapine therapy, appearing in at least 39% of patients, although it is usually mild and transient in the initial stages of therapy.[31] Sedation may often be experienced as dizziness, perhaps associated with hypotension.[5] Certain precautions to minimize clozapine-associated sedation include use of a minimal drug dose, bedtime drug administration, use of caffeinated substances, and avoidance of other CNS antidepressants (Table 1) (e.g., benzodiazepines).[6,31]

Preliminary evidence suggests that methylphenidate may help control clozapine-associated sedation. Case reports suggest that morning (or morning and afternoon) administration of methylphenidate with clozapine is well tol-

Table 1. Management of Side Effects Associated With Clozapine

Side Effect	Management Options
Sedation	Minimal drug dose Bedtime drug administration Use of caffeinated substances Avoidance of other CNS antidepressants
Hypersalivation	Amitriptyline Clonidine patch Benztropine mesylate Trihexyphenidyl hydrochloride Pirenzepine
Tachycardia	Peripheral β-blocker Propafenone
Hypotension	May resolve in time Dihydroergotamine
Weight gain	Nutrition counseling Exercise Serotonin selective reuptake inhibitor
Constipation	High-fiber diet Increased fluid intake Laxatives
Seizures	EEG before ≥ 600 mg/day dose Gradual titration Cut dose in half Valproate
Hepatic effects	Usually resolve in time Reduce dose More gradual dose titration
Urinary incontinence	Ephedrine dDAVP

erated and reduces sedation, which may be a sufficiently distressing effect to result in noncompliance.[31] Methylphenidate should be used with caution due to its risk of exacerbating movement disorders, as well as its potential for abuse.[32]

Hypersalivation

While hypersalivation is the second most common side effect experienced by patients taking clozapine, some studies paradoxically show no significant difference in average saliva flow rates between patients taking clozapine and controls.[16,33] The reported incidence varies dramatically, from 0% to 80%, with a 31% rate reported in premarketing testing.[16,34] Oddly, subjective complaints of hypersalivation in clozapine-treated patients may not correlate with measured salivary flow rates.[34] Effective treatment of hypersalivation is achieved with amitriptyline, a clonidine patch, benztropine mesylate, or trihexyphenidyl hydrochloride.[35–37] Fritze and Elliger[38] also reported successful control of hypersalivation using pirenzepine, at daily doses of 25 mg to 100 mg (Table 1).

Cardiovascular and Respiratory Effects

Tachycardia (25%) and hypotension (9%) are the most common cardiovascular side effects of clozapine. Although it may be related to hypotension, clozapine-associated tachycardia is believed to result from the drug's anticholinergic properties and its elevation of plasma norepinephrine.[5] Tachycardia can be transient,[39] but may require treatment with a peripheral β-blocker if persistent.[5] Torsades de pointes is a specific type of rapid ventricular tachycardia, characterized by a changing polarity of the QRS axis. This often self-limiting condition may transpose into ventricular fibrillation, resulting in cardiac arrest.[40] The multiple-acting antiarrhythmic drug propafenone is helpful in preventing ventricular tachycardia by prolonging QRS duration during sinus rhythm (Table 1).[41]

Hypotension is often related to the frequency and intensity of clozapine dose titration. It is often self-limiting and is affected by the drug's antiadrenergic actions. Orthostatic hypotension can occur with or without syncope and is more likely to occur during the first few days of clozapine therapy. Dihydroergotamine, a headache treatment, may help to alleviate orthostatic hypotension.[8] There have been rare reports of respiratory arrest and also of cardiac arrest in patients receiving clozapine, but it is unclear if these reactions result from clozapine or its interaction with other drugs (Table 1).[5]

There are a handful of reported cases of clozapine-associated cardiomyopathy. One such case was reported in a patient with an established history of schizophrenia but no prior cardiac problems, although clozapine may have exacerbated a previously undiagnosed cardiomyopathy. The literature review for this case noted that cases of cardiac adverse effects during clozapine treatment often involved other concurrent medications (e.g., benzodiazepines, which often depress respiration), further complicating interpretation of any causal relationship between clozapine and cardiorespiratory complications.[42] Recurrent cardiac arrest, cardiogenic shock, and coma were observed in one man who developed agranulocytosis after 11 weeks of clozapine therapy and died the next week, despite hospitalization and aggressive care; the man was an Ashkenazic Jew, often considered a high-risk category for clozapine-associated agranulocytosis.[43]

Weight Gain

Weight gain is a side effect associated with many antipsychotics.[44,45] Drug-induced increases in weight should be carefully monitored since obesity is well known as a risk factor for conditions such as cardiovascular disease, diabetes mellitus, and some types of cancer. Medication noncompliance may also occur as a patient's way of halting the source of the weight gain.[46] Patients experiencing a drug-induced weight increase may experience depression or anxiety about their appearance, thereby exacerbating psychosocial health.

Despite the lack of a dose-dependent relationship, a mean 12-kg (26-lb) weight increase has been observed in patients given clozapine.[46] In one review of 82 patients receiving clozapine for at least 3 months, 73% of the patients gained a mean of almost 12 lb (5.4 kg), and 20%

gained over 10% of baseline body weight.[47] In some cases, a positive correlation has been drawn between weight gain and the therapeutic efficacy of clozapine in schizophrenia symptom reduction.[48] Nutrition counseling could be provided to educate patients who tend to have poor dietary habits (Table 1).[36] In addition, an SSRI such as fluoxetine may be effective in ameliorating clozapine-induced weight gain.[49]

Constipation

The gastrointestinal system is a common site for adverse drug effects, largely, but not exclusively, due to oral administration. Gastric disturbance may result from a myriad of drugs, from aspirin to controlled substances. Many opiates and anticholinergic drugs induce constipation, and perhaps the latter quality is responsible for clozapine-associated constipation.[5] Constipation is experienced in about 14% of patients on clozapine therapy. A high-fiber diet, adequate intake of fluids, and use of laxatives (bulk and nonbulk) are ways to manage constipation (Table 1).[47]

Seizures

The occurrence of seizures appears dose-related in patients taking clozapine: at doses less than 300 mg/day, patients taking clozapine are at the same risk of seizures as those taking typical antipsychotics, i.e., about 1% to 2%; between doses of 600 mg to 900 mg/day, seizure risk reaches 5%. The majority of case studies reporting seizures in clozapine patients revealed doses over 600 mg/day.[50] One review noted that the factors that appear to increase seizure risk include rapid dose titration and previous history of neurologic abnormalities, simultaneous use of epileptogenic drugs, and preexisting seizure disorders.[49] Suggested guidelines to minimize seizure risk in clozapine patients include administering an EEG before elevating the dose above 600 mg/day; gradual titration (e.g., elevating clozapine dose by 12.5 mg to 25 mg every 2 to 4 days), and minimizing the clozapine dose.[5,50]

Valproate, an anticonvulsant, may prevent seizures in clozapine-treated patients. Coadministration of valproate and clozapine has not been associated with seizures.[51]

Hepatic Effects

Clozapine commonly increases hepatic enzyme levels. This effect is usually both small and temporary, but substantial and lasting changes may occur and result in asymptomatic hepatitis.[5] One analysis of 238 patients receiving clozapine revealed a higher elevation of certain hepatic enzymes than was observed with haloperidol; however, since most of the increases dissipated within 13 to 18 weeks of treatment onset, the authors suggest that this is a transient effect in most patients (Table 1).[52] If elevation of liver function tests (i.e., LFTs) persists, dose titration can be made more gradual or treatment withheld until hepatic enzymes normalize. Therapy can then resume at a lower dose and more gradual titration.

Table 2. Receptor Subtypes, in Vitro Affinities, and Possible Clinical Correlates Associated With Clozapine Binding*

Receptor Subtype	In Vitro Affinity and Action	Possible Clinical Correlates
5-HT_2	High antagonist	Thermoregulation; low EPS incidence; antipsychotic effect
D_4	Moderate antagonist	Antipsychotic effect
α-Adrenergic	High antagonist	Sedation; hypotension; hypersalivation; tachycardia; urinary incontinence
Muscarinic	High antagonist	Tachycardia; dry mouth; urinary incontinence; constipation
Histaminic	Moderate antagonist	Sedation
D_2	Low antagonist	Low EPS/TD incidence; TD; akathisia; antipsychotic effect

*Adapted from references 5, 56, and 57.

Urinary Incontinence

Urinary incontinence, although not usually a health risk, is a major negative influence on a patient's quality of life and could lead to noncompliance. Its incidence is about 1%, but it may be underreported because of the embarrassing nature of this adverse effect. Although clozapine may cause urinary incontinence through a variety of mechanisms, it is generally thought to be due to its adrenergic antagonism.[53] Adrenergic blockade could result in urinary incontinence through a mechanism leading to a decreased internal bladder sphincter tone.[54] This physiologic mechanism is validated by the finding that ephedrine, an approved commercially available α-adrenergic agonist, was effective in preventing urinary incontinence in patients who were taking clozapine (Table 1).[53] Desmopressin (dDAVP)[55] administered intranasally can be used for symptomatic treatment.

RELATIONSHIP OF PHARMACOLOGY TO SIDE EFFECTS

Clozapine influences many neurotransmitter receptor subtypes (Table 2); it has strong antagonist activity at serotonergic 5-HT_2 receptors, high activity at α-adrenergic, cholinergic, and histaminic receptors, and low affinity for the D_2 receptors, with preferential D_1 and D_4 actions.[5,56,57] The more diverse receptor profile of clozapine confers a molecular distinction from the traditional antipsychotics, whose mode of action hinges primarily on strong D_2 receptor blockade. The unique pharmacology of clozapine challenges the tenet that the D_2 receptor is the chief modulator of antipsychotic efficacy. Dopamine blockade by clozapine may predominantly occur in limbic (predominantly D_4), rather than basal ganglia (predominantly D_2) neurons, which may partially account for its antipsychotic effect with few EPS.[57] Clozapine and some traditional antipsychotics share high anticholinergic and antiadrener-

gic activity, possibly underlying the observed sedation and orthostatic hypotension. The 5-HT_2 antagonism, in addition to clozapine's low D_2 affinity, may mediate its low EPS incidence.[57]

BENEFIT-TO-RISK ASSESSMENT

Historically, the inclusion of clozapine in the psychiatric pharmacopeia has been somewhat controversial.[22] Its superior efficacy in the treatment-resistant population has been remarkable, and its unique pharmacology has revolutionized the definition of an antipsychotic (i.e., reduction of the positive and negative symptoms of schizophrenia need not be associated with EPS or TD). However, the morbidity associated with agranulocytosis has mandated weekly blood monitoring during the course of clozapine treatment. Since the introduction of clozapine in the United States in 1990, there has been a dramatic reduction in the incidence of agranulocytosis-related deaths. Meanwhile, the efficacy of clozapine among treatment-resistant schizophrenic patients has been repeatedly validated, and wider applications for this medicine in schizophrenia have been elucidated.[58] Clozapine improves some behavioral aspects of schizophrenia that are usually associated with illness chronicity. It has also been shown to reduce substance abuse,[59–61] violence and persistent aggression,[62–64] and suicide.[65,66]

The mortality rate of schizophrenic individuals, the excess of which is largely due to suicide, is at least twice that of the general population.[66,67] The risk of suicide among schizophrenic individuals is 9% to 13%. It is estimated that for every 10,000 patients with schizophrenia, there would be 1000 to 1300 suicides; in contrast, there would be only 1.5 deaths due to clozapine-related agranulocytosis.[65]

Clozapine remains the prototype atypical antipsychotic drug. It is an important treatment modality for the 30% to 60% of schizophrenic individuals who fail to derive appreciable benefits from traditional neuroleptics and other antipsychotics. The symptom reduction and improvement in overall psychiatric state give treatment-resistant and chronically ill schizophrenic patients an opportunity to integrate into society. These benefits should be weighed against the associated side effects which, for the most part, are benign, tolerable, and manageable.

CONCLUSIONS

Many of the side effects relating to clozapine treatment (e.g., sedation, tachycardia, orthostatic hypotension, weight gain, seizures, and urinary and hepatic effects) are associated with antipsychotic treatment in general and usually arise during treatment initiation. Typically, dose adjustments eventually result in relief from these side effects while optimizing treatment. Periodic blood monitoring is a requirement for clozapine prescription renewal. This procedure, which is done through the CNR, is a safeguard against agranulocytosis, a rare blood dyscrasia that may develop in individuals who are at high risk for developing immune-system–related disorders. Augmentative treatment strategies are also available. Recent developments in cytokine recombinant therapy (e.g., G-CSF and GM-CSF) may be utilized in patients with developing blood dyscrasias to circumvent a progression toward agranulocytosis. Appropriate management of side effects facilitates a maximization of the benefits of clozapine treatment.

Physicians and patients should be aware that there is a wider range of therapeutic benefits to clozapine use compared with its associated risks. Clozapine maintains its superiority over other antipsychotics in treatment-resistant schizophrenia. Recent clinical studies have also shown that it has wider usefulness in schizophrenia (i.e., reduction of substance abuse, suicide, and violence). Physicians and patients should assess the benefit-to-risk ratio of clozapine. By and large, the risks of schizophrenia-related morbidity alone (e.g., due to suicide) far exceed the risk of agranulocytosis.

Drug names: amitriptyline (Elavil and others), benztropine (Cogentin and others), carbamazepine (Tegretol and others), chlorpromazine (Thorazine and others), clonidine (Catapres), clozapine (Clozaril), fluoxetine (Prozac), haloperidol (Haldol and others), methylphenidate (Ritalin), propafenone (Rythmol), trihexyphenidyl (Artane and others).

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