Management of the Adverse Effects of Clozapine

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Abstract

Clozapine has been found to be superior to traditional neuroleptics in the treatment of refractory schizophrenia and is increasingly being used to treat schizophrenia, affective disorders, some neurological disorders, and aggression. For many patients, clozapine offers new hope for the successful pharmacological management of a disabling mental disorder. However, up to 17 percent of patients must discontinue treatment with clozapine because of adverse effects, which also limit the rate at which the dose can be increased and the maximum dose that can be tolerated. This article reviews strategies for minimizing and managing the adverse effects of clozapine, including agranulocytosis, seizures, sedation, delirium, obsessive-compulsive symptoms, hypotension, tachycardia, weight gain, sialorrhea, elevated liver enzymes, constipation, nausea, enuresis, fever, and neuromuscular effects. Incidence and morbidity are presented first. Then, the known or hypothesized pathophysiology of the adverse effects are described. Finally, nonpharmacological and pharmacological interventions are reviewed. Understanding the incidence, pathophysiology, and treatments of adverse effects is essential for a positive therapeutic outcome when prescribing clozapine.

Key words: Clozapine, atypical antipsychotics, adverse effects, side effects.

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Clozapine has been found to be superior to traditional neuroleptics in the treatment of refractory schizophrenia (Kane et al. 1988) and is increasingly being used to treat affective disorders (Zarate et al. 1995), some neurological disorders (Safferman et al. 1994), and aggression (Ratey et al. 1993; Cohen and Underwood 1994). Despite its demonstrated efficacy in psychosis and the expanding indications for its use, widespread use of clozapine has

been limited by the potential for adverse effects. In addition to the risk of life-threatening agranulocytosis, clozapine can cause seizures, hypotension, tachycardia, weight gain, sialorrhea, and many other significant adverse effects. Adverse effects also limit the rate at which the dose can be increased, as well as the maximum dose that can be tolerated by some patients. For many patients, clozapine is their best hope for successful treatment of a disabling mental illness. However, full benefit can be achieved only if the adverse effects can be controlled.

The purpose of this article is to review strategies for minimizing and managing the adverse effects of clozapine. Because the use of clozapine is on the rise, much has been published about its adverse effects, and an attempt was made to collect and organize that information. In addition, the known or hypothesized pathophysiology of these effects is described to help clinicians make rational treatment and management decisions in unique clinical situations. Increasingly, drugs are being conceptualized in terms of their pharmacodynamic and pharmacokinetic properties rather than their chemical structure (e.g., tricyclic) or their desired outcome (e.g., antidepressant). Understanding the pathophysiological mechanism of adverse effects may help the clinician prevent toxicity and determine possible treatments when those adverse effects occur. Most of clozapine's adverse effects are predictable from its pharmacological profile. Receptor-binding studies show that clozapine has a relatively high binding affinity for cortical dopamine D_4 receptors as compared to D_2 receptors (Van Tol et al. 1991). It also has significant serotonergic (5-HT$_2$), adrenergic (α_1 and α_2), muscarinic, and histaminergic (H$_1$) blocking properties (Baldessarini and Frankenburg 1991). Consequently, we know that the histaminergic and noradrenergic blocking properties of clozapine can cause sedation, and constipation is secondary to

its anticholinergic properties. Other adverse effects, such as sialorrhea and nausea have less certain etiologies. In this article, an effort has been made to group adverse effects into physiological systems (i.e., cardiovascular, gastrointestinal, etc.). Those adverse effects that represent the greatest danger to patients (such as agranulocytosis and seizures) are addressed first. The second priority is to present those adverse effects that occur most frequently. Each adverse effect is first described in terms of incidence and morbidity. Next, the pathophysiological mechanisms and related strategies of prevention are presented. Finally, nonpharmacological and pharmacological interventions are delineated.

Agranulocytosis

Agranulocytosis is defined as a granulocyte count of < 500/mm^3, and leukopenia is defined as a white blood cell (WBC) count of < 3,500/mm^3. The risk of agranulocytosis is highest in the first 3 months of clozapine treatment, and 95 percent of the cases occur within the first 6 months (Lieberman and Safferman 1992). The most recent data suggest that 0.8 percent of patients receiving clozapine develop agranulocytosis within a year (Alvir et al. 1993). This is approximately 10 times the risk found with phenothiazines (Krupp and Barnes 1989). Agranulocytosis predisposes patients to neutropenic sepsis and has a mortality rate of 3 to 4 percent of those affected (Gerson 1994). As of February 1996, 464 U.S. patients receiving clozapine have had agranulocytosis, and of those, 13 have died (J.K. Sethi—Sandoz Pharmaceuticals Company, data on file 1996). The mortality rate can be significantly decreased if agranulocytosis is discovered before signs of infection and if clozapine is immediately discontinued (Krupp and Barnes 1989). Agranulocytosis occurs slightly more often in women, the elderly, and those under 21 years of age (Alvir and Lieberman 1994).

The pathophysiological mechanism is uncertain, but there is evidence of an immunological basis (Pisciotta and Konings 1994), direct cytotoxicity of clozapine metabolites (Gerson et al. 1994), and genetic risk factors (Lieberman et al. 1990). Given the current limited understanding of the mechanism and risks of agranulocytosis, caution should be used in prescribing other medications toxic to the hematopoietic system to patients taking clozapine. Such medications include carbamazepine, captopril, propylthiouracil, and sulfonamides (Lieberman et al. 1989). Treatment with clozapine requires a weekly WBC count. A differential should be included because neutropenia occurring with a normal WBC count has been reported (Cates et al. 1992). If WBCs fall below 3,500/mm^3 or have dropped by more than 3,000/mm^3 within 3 weeks,

biweekly blood draws should be initiated. If the count falls below 3,000/mm^3 or if the absolute neutrophil count (ANC) falls below 1,500/mm^3, drug therapy should be interrupted, daily WBC counts should be obtained, and the patient should be monitored for symptoms of infection. Patients should be advised to alert their physician to new onset of fever or symptoms of infection (e.g., pharyngitis), especially during the first 18 weeks of treatment. A WBC count with differential is then indicated, and the patient's condition should be monitored closely. If any WBC count falls below 2,000/mm^3 or if the ANC falls below 1,000/mm^3, treatment should be discontinued, daily WBC counts should be obtained, and bone marrow aspiration should be considered (Sandoz Pharmaceuticals Company 1996).

The development of agranulocytosis is a medical emergency. Clozapine should be discontinued and a hematologist consulted. Management includes reverse isolation and prophylactic antibiotics, the specifics of which are beyond the scope of this article. However, recent advances in the use of granulocyte colony-stimulating factor and granulocyte-macrophage colony-stimulating factor have decreased the morbidity of this disorder and can shorten its course from a mean of 16 days to 8 days (Krupp and Barnes 1989). However, patients rechallenged on clozapine after recovering from clozapine-induced agranulocytosis invariably redevelop the condition, usually with a more rapid and malignant course (Safferman et al. 1992a). Therefore, patients who have developed clozapine-induced agranulocytosis should not be reexposed.

Other less common hematological effects associated with clozapine include benign neutropenia, which occurs in up to 22 percent of patients (Hummer et al. 1994). Patients with less than 3,500 leukocytes/mm^3 should have their WBCs checked biweekly to determine if this is transient neutropenia or the emergence of agranulocytosis (Sandoz Pharmaceuticals Company 1996). Mild leukocytosis has been reported to occur in 0.6 to 40.9 percent of patients and is usually transient and clinically irrelevant (Hummer et al. 1994). A mild asymptomatic eosinophilia occurs in 5 to 10 percent of patients. This condition appears benign but should prompt a medical workup to rule out other causes of elevated eosinophil counts (Stricker and Tielens 1991).

Adverse Central Nervous System Effects

Seizures. A review of all patients exposed to clozapine during the first 6 months after marketing found the incidence of tonic-clonic seizures during that time to be 1.3

percent (Pacia and Devinsky 1994). Seizures tend to occur during the upward titration phase of treatment or at doses greater than 600 mg per day. In Europe, lower total doses have generally been used with equal efficacy and fewer seizures (Fleischhacker et al. 1994a). However, the use of clozapine in Europe has been less restrictive and the patients may not be as refractory or require such high doses. The risk of seizures ranges from 1 to 3 percent at low doses, 100 to 300 mg, and up to 5 percent at high doses, 600 to 900 mg (Sandoz Pharmaceuticals Company 1995). The incidence of abnormal electroencephalograms (EEGs) rises sharply for doses above 600 mg/day (Gunther et al. 1993). Patients with a prior history of seizures or head trauma are at increased risk for seizures on low doses soon after the initiation of therapy (Haller and Binder 1990). Other drugs that lower the seizure threshold may increase the risk of clozapine-induced seizure. Drugs such as benzodiazepines that raise the seizure threshold may also increase the risk of seizure if discontinued during clozapine treatment. Drinking alcohol may also increase the risk of seizure.

Experiencing a clozapine-induced seizure is not an absolute contraindication to continued treatment. In one study, 78 percent of the patients who experienced seizures were successfully able to continue treatment with clozapine after a dose reduction, a more gradual dose titration, or the addition of an anticonvulsant (Pacia and Devinsky 1994). If a seizure occurs, an EEG and a neurology consultation should be considered. Clozapine should be temporarily held and reinstituted at a dose approximately 50 percent of that at which the seizure occurred (Lieberman et al. 1989). If clozapine is held for more than a few days, treatment should be restarted at initial doses because patients lose their tolerance to the adverse effects. The dose should be increased more slowly and a reduction in target dose should be considered. A clozapine blood level may help the clinician determine the lowest possible effective dose (Simpson and Cooper 1978).

Several recent studies have shown an association between therapeutic response and plasma threshold concentrations of 350 to 420 ng/mL (Perry et al. 1991; Potkin et al. 1994; Kronig et al. 1995). If a patient experiences a seizure and has a plasma clozapine level above this threshold concentration, a lower daily dose may still be able to provide an adequate therapeutic response. Seizures may be related to peak blood level and a divided dosing strategy may minimize seizure risk (Jann et al. 1993; Chengappa et al. 1994a). An anticonvulsant should also be considered as a prophylaxis against seizures. Valproate is less likely than other anticonvulsants, such as phenytoin and carbamazepine, to alter the metabolism of clozapine (Centorrino et al. 1994; Jerling et al. 1994). In addition, the generalized polyspike- and spike-wave activity found

on EEGs of patients taking valproate suggests that valproate may be the best antiseizure agent for them (Pacia and Devinsky 1994). Because carbamazepine is also associated with neutropenia, it should be avoided when using clozapine (Gerson et al. 1991).

Sedation. Sedation is the most frequently reported adverse effect of clozapine, occurring in approximately 39 percent of patients (Safferman et al. 1991). It appears early in treatment and patients gradually develop tolerance, usually within 4 to 6 weeks of treatment (Marinkovic et al. 1994). The knowledge that the sedation will eventually diminish is frequently enough for patients to endure this effect. Other sedating medications can exacerbate the sedative qualities of clozapine. Giving the major portion of the dose at night and titrating up slowly sometimes helps, but a dose reduction may be necessary. Dextroamphetamine, methylphenidate and L-dopa have been successfully used to decrease sedation (Cohen 1992; Burke and Sebastian 1993; Meltzer 1995). However, these stimulants may exacerbate psychosis and should be reserved for severe, persistent sedation and used with caution.

Delirium. Susceptible patients, such as the elderly or those with organic cognitive deficits, may become delirious or confused when treated with clozapine. This condition has been temporarily reversed by the use of intravenous physostigmine, suggesting that the delirium is caused by the anticholinergic properties of clozapine (Schuster et al. 1977). One study found delirium most likely to occur in patients receiving other anticholinergic or central nervous system's depressant medications (Gaertner et al. 1989). Therefore, the use of these drugs should be minimized. If delirium occurs, the clozapine dose should be decreased, the rate of dose escalation slowed, and consideration given to limiting the absolute dose (Szymanski et al. 1992).

Obsessive-Compulsive Symptoms. It has been estimated that up to 10 percent of patients treated with clozapine develop obsessive-compulsive symptoms (Baker et al. 1992). Only one formal study on this phenomenon has been published, and it was unable to establish a definitive relationship between clozapine and obsessive-compulsive symptoms (Ghaemi et al. 1995). That study reported a retrospective chart review of 142 patients and may have been limited by underreporting by both patients and clinicians. Still, multiple case reports describe this phenomenon. It has been hypothesized that clozapine's antiserotonergic effects are responsible for the emergence of obsessive-compulsive symptoms (Patil 1992), which have been reported to abate spontaneously after 1 to 3 weeks (Patil 1992) or to respond to a decrease in dosage

(Levkovitch et al. 1995). Others report that adding serotonin re-uptake inhibitors effectively treats these symptoms (Cassidy and Thaker 1993; Patel and Tandon 1993).

Adverse Cardiovascular Effects

Tachycardia. Tachycardia from clozapine occurs in approximately 25 percent of patients, with a mean increase of 10 to 15 beats per minute (Safferman et al. 1991). Tolerance generally develops within 4 to 6 weeks (Marinkovic et al. 1994) but may limit the rate at which the dose can be raised. Tachycardia appears to be related to vagal inhibition by the anticholinergic properties of clozapine, and not simply reflex tachycardia secondary to hypotension (Rechlin et al. 1994).

If sustained or symptomatic tachycardia occurs, an electrocardiogram (EKG) can be obtained. Sinus tachycardia is the most common EKG abnormality caused by clozapine. Nonspecific ST–T segment changes, T-wave flattening, and inversions are sometimes seen but are usually not clinically significant. If tachycardia persists or distresses the patients, a lower dose or slower upward titration should be considered. Alternatively, beta-blockers can be used. A noncardioselective beta-blocker, such as propranolol, can also prevent the orthostatic hypotension associated with alpha-blockade (Cleophas and Kauw 1988). Atenolol may be preferable in patients with asthma or diabetes because it is relatively cardioselective. In addition, atenolol is less lipophilic than propranolol and is less likely to cross the blood-brain barrier and cause fatigue and other central nervous system effects (Wadworth et al. 1991). The use of beta-blockers can slow atrio-ventricular conduction and cause bradycardia and hypotension, so therefore it should be monitored carefully.

Orthostatic Hypotension. Orthostatic hypotension is defined as a drop in blood pressure when rising from sitting to standing of at least 25 mm Hg systolic and 10 mm Hg diastolic (Schatz 1984). Approximately 9 percent of patients receiving clozapine experience orthostatic hypotension (Safferman et al. 1991). It usually occurs at the initiation of treatment or with dosage increases, and patients gradually develop tolerance, usually within 4 to 6 weeks of treatment (Marinkovic et al. 1994). Patients with orthostatic hypotension secondary to clozapine may describe dizziness or lightheadedness and are prone to syncope. In rare cases (1/3,000), orthostatic hypotension has been associated with collapse and respiratory and/or cardiac arrest (Sandoz Pharmaceuticals Company 1995). Although benzodiazepines are commonly used in combination with clozapine without adverse effects, rare cases of cardiovascular/respiratory collapse have been reported

(Sandoz Pharmaceuticals Company 1995). Orthostatic hypotension can be monitored by taking sitting and standing blood pressures regularly when therapy is initiated or when dosage increases.

Orthostasis is caused predominantly by the antiadrenergic properties of clozapine. It can be minimized if patients are advised to rise slowly from a sitting or lying position, especially in the morning and after meals. Increased fluid and salt intake may help by increasing blood volume. If these steps are ineffective, support stockings can be tried. Tilting the head of the bed slightly upward at night may produce some relief by reducing renal artery pressure and increasing renin production, thereby increasing blood volume (Cleophas and Kauw 1988).

Fludrocortisone, a potent mineralocorticoid, has been used to treat clozapine-related hypotension (Testani 1994). Fludrocortisone works by increasing sodium retention and potassium excretion in the kidney. The usual starting dose is 0.1 mg/day and can be increased by increments of 0.1 mg every 5 to 7 days. Maintenance doses range from 0.1 to 1.0 mg/day. Fludrocortisone may cause hypertension, hypokalemia, marked fluid retention, and congestive heart failure in up to 30 percent of patients (Rechlin et al. 1994), so it should be reserved for cases in which more conservative measures have failed. The alpha-adrenergic agonist ephedrine has also been used to treat orthostatic hypotension (Patterson 1992); the typical dose ranges from 25 to 150 mg/day. Dihydroergotamine, at doses of 10 mg/day, has been shown in a double-blind, placebo-controlled study to prevent orthostatic hypotension in patients treated with psychotropic medications (Thulesius and Berlin 1986).

Weight Gain

Weight gain is a frequent side effect of neuroleptic treatment. Recent studies have suggested that the weight gain associated with clozapine is more common than previously thought and may be even more common than with conventional neuroleptics (Leadbetter et al. 1992). One study found that 75 percent of patients gained at least 10 pounds over a 6-month period (Lamberti et al. 1992). Over a 3-year period, more than 80 percent of patients increased their weight by 10 percent and over 38 percent increased by at least 20 percent, thus posing a significant long-term health risk (Umbricht et al. 1994).

The mechanism of clozapine-related weight gain is uncertain, but as with conventional neuroleptics, its etiology is likely to be multifactorial. Clozapine affects the histaminergic, cholinergic, endocrine, and metabolic systems, all of which may affect weight (Lamberti et al.

1992). In addition, serotonin antagonists like clozapine stimulate carbohydrate cravings and cause weight gain (Bernstein 1988). Diet, exercise, and nutritional education are recommended. Currently, there are no known pharmacological interventions that may effectively limit weight gain. One group observed that lithium, which influences serotonin transmission, tended to protect patients from weight gain (Leadbetter et al. 1992).

Adverse Gastrointestinal Effects

Sialorrhea. Sialorrhea occurs to some degree in most patients treated with clozapine, and tolerance does not usually develop (Lieberman and Safferman 1992). Although hypersalivation is generally a benign side effect, patients sometimes describe a choking sensation at night and may even aspirate excess saliva. In addition, drooling can be socially embarrassing. The pathophysiology of sialorrhea is not clear. Salivary glands respond to both cholinergic and adrenergic stimulation. A case report of a barium swallow study done on one patient with severe hypersalivation found decreased laryngeal peristalsis (Pearlman 1994). Instruction in swallowing two or three times without inhaling (by compression of nostrils) alleviated the sensation of choking without affecting the sialorrhea. Patients can be encouraged to chew sugar-free gum during the day so that the frequent need to swallow will be less noticeable (Bourgeois et al. 1991). A towel placed on the pillow at night can be used to absorb excess saliva.

The use of anticholinergic drugs has been reported to be effective in reducing sialorrhea. Amitriptyline at doses of 75 to 100 mg/day (Copp et al. 1991) and benztropine at 1 to 2 mg/day (Bourgeois et al. 1991) have been used. However, anticholinergic drugs increase the already potent anticholinergic properties of clozapine and are not generally recommended (Lieberman et al. 1989). Pirenzepine, a selective muscarinic$_1$ antagonist that does not pass the blood-brain barrier, was used successfully in 120 patients to control sialorrhea (Fritze and Elliger 1995), but this agent is not currently available in the United States. The alpha$_2$-adrenergic agonist clonidine has been effective, suggesting an adrenergic role in hypersalivation. A clonidine patch, 0.1 to 0.2 mg/day applied weekly, has been recommended to allow a more sustained delivery of the drug (Grabowski 1992). Clozapine, a potent alpha-adrenergic antagonist, tends to block the antiphypertensive effect of clonidine, a potent alpha-adrenergic agonist (Markowitz et al. 1995). Nonetheless, patients' blood pressure should be monitored carefully when initiating this combination.

Elevated Liver Enzymes. Elevations in liver enzymes are usually mild and transient. One study found that up to

31 percent of patients experienced increases in liver enzymes to at least twice the baseline values. The highest reported values were a 22-fold increase in alanine aminotransferase and a 12-fold increase in aspartate aminotransferase without clinical sequelae (Gaertner et al. 1989). In the absence of signs and symptoms of hepatotoxicity, elevated liver function tests are considered a biochemical abnormality rather than a necrotic liver injury (Eggert et al. 1994). However, at least one case of toxic hepatitis secondary to clozapine has been described (Kellner et al. 1993), and patients should be observed for jaundice and other signs of hepatotoxicity. Liver function tests should be obtained before initiating therapy and monitored periodically, particularly during the initial phases.

Constipation. Constipation occurs in 14 percent of patients treated with clozapine and can be severe. Three deaths from severe ileus and obstipation have been reported (Hayes and Gibler 1995). It is most likely due to the anticholinergic properties of clozapine, and other medications with anticholinergic properties may exacerbate it. Patients can be encouraged to eat a diet high in fiber, drink plenty of fluids, and exercise. Fiber supplements such as psyllium or unprocessed bran are safe and effective in cases of mild constipation. For more distressing symptoms, stool softeners and laxatives such as docusate sodium and milk of magnesia can be used. Stimulant cathartics such as senna, phenolphthalein, and bisacodyl can be used in more severe cases. Because long-term use of stimulant cathartics can result in degenerative changes in colonic muscles and nerves, short-term treatment is recommended. If necessary, an enema can be used (Lennard-Jones 1993).

Nausea. Nausea tends to develop later in the course of treatment and affects 11 percent of patients (Marinkovic et al. 1994). The pathophysiological basis for this symptom is uncertain but may involve the anticholinergic effect of delayed gastric emptying, increased salivation, and food intake, or direct effects on the hypothalamus (Bourgeois et al. 1991). Metoclopramide has been used with some success (Lieberman et al. 1989). Other treatments that have been successfully used include antacids and H$_2$ blockers (Lieberman and Safferman 1992). Cimetidine should be avoided because it inhibits the hepatic microsomal P-450 system and can raise the blood level of clozapine (Jann et al. 1993).

Enuresis

Estimates of the incidence of urinary incontinence have ranged from 0.23 percent (Aronowitz et al. 1995) to 30 percent (Konicki et al. 1995). This wide variation may be

due to underreporting of this symptom by embarrassed patients. Therefore, direct inquiry should be made about the possible presence of this adverse effect. The mechanism of enuresis is unknown, but suggestions include excessively deep sleep related to clozapine's sedating properties, and urinary retention with subsequent overflow related to clozapine's anticholinergic properties (Aronowitz et al. 1995). The alpha-adrenergic antagonist properties of clozapine have also been implicated (Konicki et al. 1995).

Patients can be told to avoid fluids in the evening and to void before going to bed. Scheduled middle-of-the-night awakenings to empty the bladder can be practiced. If necessary, an enuresis alarm can be used.

A recent study using the alpha-adrenergic agonist ephedrine successfully treated 15 out of 16 patients with clozapine-related enuresis (Konicki et al. 1995). The starting dose of 25 mg was titrated upward until the enuresis resolved or side effects intervened. The maximum dose used was 150 mg. These data implicate the alpha-adrenergic antagonist properties in the pathophysiology of enuresis secondary to clozapine.

Desmopressin has also reportedly been used to successfully treat clozapine-related enuresis (Steingard 1994). This synthetic analog of the antidiuretic hormone vasopressin can be given as an intranasal spray, 20 to 40 mcg before sleep. Caution is recommended because there are case reports of seizures secondary to desmopressin-related water intoxication (Beach et al. 1992).

Oxybutynin, an anticholinergic agent with antispasmodic properties, used at doses of 5 to 15 mg/day, has been reported to help in both enuresis and urinary urgency (Frankenburg et al. 1996).

Adverse Thermoregulatory Effects

A benign fever occurs in about 5 percent of patients during the initial phase of clozapine treatment. It usually lasts only a few days and rarely goes above 100 °F. However, a persistent rise in temperature raises concern about the possibility of agranulocytosis and infection.

If a patient develops a fever of 100 °F without specific symptoms, a routine workup, including a physical examination, a WBC count with differential, and a urinalysis, should be performed (Nitenson et al. 1995). A chest X-ray and blood cultures should be obtained if clinically indicated. A determination of serum creatinine phosphokinase level should be considered, although clozapine has rarely been associated with neuroleptic malignant syndrome. We reported a case of transient allergic reaction to clozapine manifested as a fever (102.4 °F) and eosinophilia, which did not preclude continued treatment with clozapine (Druss and Mazure 1993).

Mild hypothermia is seen in approximately 87 percent of clozapine-treated patients (Safferman et al. 1991). This is similar to the frequency found with chlorpromazine and has no known clinical significance.

Adverse Neuromuscular Effects

Akathisia. Akathisia has been reported in 6 percent (Marinkovic et al. 1994) to 39 percent (Cohen et al. 1991) of patients treated with clozapine. This stands in contrast to reports of the use of clozapine as an effective treatment for patients unable to tolerate traditional neuroleptics because of severe akathisia (Wirshing et al. 1990; Levin et al. 1992). Instead of clozapine's directly causing akathisia, it has been suggested that tardive akathisia is revealed as patients are titrated off conventional antipsychotics (Safferman et al. 1992b). One study found that patients who had akathisia also had continuing symptoms of tardive dyskinesia (Chengappa et al. 1994b). Moreover, another study found that patients who did not have akathisia at baseline did not develop it during treatment with clozapine (Safferman et al. 1993). In two studies, patients with akathisia at baseline exhibited a reduction in their symptoms over the course of treatment with clozapine (Safferman et al. 1993; Stanilla et al. 1995). These studies suggest that continued treatment with clozapine may be indicated for treatment-emergent akathisia.

Myoclonus. Myoclonus occurs in approximately 2 percent of patients treated with clozapine (Lieberman and Safferman 1992). In a series of five cases, these episodes were described as primarily orofacial, alternating between both sides of the face, and were sometimes associated with weakness of the extremities (Bak et al. 1995). These symptoms improved when clozapine was discontinued or the dose reduced, or when an anticonvulsant was added. Several authors have suggested that the movements described above represent myoclonic seizures, and several cases of myoclonus have progressed to grand mal seizures (Berman et al. 1992; Gouzoulas et al. 1993; Meltzer and Ranjan 1994). Because myoclonus can herald the onset of tonic-clonic seizures, a reduction of clozapine dose or addition of an anticonvulsant may be indicated. Both valproate (Meltzer and Ranjan 1994) and carbamazepine (Bak et al. 1995) have been reported to be effective, although valproate may be the preferred agent for the reasons described in the "Seizures" section of this article.

Establishing the Dose

It is well known that to minimize the adverse effects of pharmacological agents, the lowest possible dose should

always be used (Mazure et al. 1992). However, no formal clozapine dose-response relationship studies have been done to establish guidelines for the lowest therapeutic dose. Furthermore, there is a fivefold to eightfold variance in plasma levels among patients receiving the same daily dose (Baldessarini and Frankenburg 1991). Although the association between blood levels and the therapeutic and toxic effects of clozapine has not yet been firmly established, knowledge of blood levels may have some utility in managing side effects. Several recent studies have shown an association between therapeutic response and plasma threshold concentrations of 350 to 420 ng/ml (Perry et al. 1991; Potkin et al. 1994; Kronig et al. 1995). If a patient is having an adequate therapeutic response but experiencing intolerable adverse effects, the plasma clozapine level can be a rough guide as to whether a lower dose of medication is likely to be effective; this same strategy has been established with traditional neuroleptics (Mazure et al. 1990).

Conclusion

For many patients, clozapine offers new hope for successful pharmacological management of a disabling mental disorder. However, up to 17 percent of patients must discontinue treatment because of adverse effects (Grohmann et al. 1989). The percentage of patients given suboptimal doses or an inadequate trial duration of clozapine because of adverse effects is unknown. Managing these unwanted effects may be essential to a therapeutic outcome. Furthermore, compliance with clozapine can be significantly enhanced if patients are adequately informed about the nature and risks of its adverse effects and if the clinician recognizes and attempts to treat them (Fleischhacker et al. 1994*b*).

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