

Review and Management of Clozapine Side Effects

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Clozapine has demonstrated superior efficacy in relieving positive and negative symptoms in treatment-resistant schizophrenic patients; unlike other antipsychotics, it causes minimal extrapyramidal side effects (EPS) and has little effect on serum prolactin. Despite these benefits, the use of clozapine has been limited because of infrequent but serious side effects, the most notable being agranulocytosis. In recent years, however, mandatory blood monitoring has significantly reduced both the incidence of agranulocytosis and its associated mortality. The occurrence of seizures appears to be dose-related and can generally be managed by reduction in clozapine dosage. Less serious and more common side effects of clozapine including sedation, hypersalivation, tachycardia, hypotension, hypertension, weight gain, constipation, urinary incontinence, and fever can often be managed medically and are generally tolerated by the patient. Appropriate management of clozapine side effects facilitates a maximization of the benefits of clozapine treatment, and physicians and patients alike should be aware that there is a range of benefits to clozapine use that is wider than its risks.

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Clozapine was first marketed in the United States in 1990 and is indicated for the management of severely ill schizophrenic patients who fail to respond adequately to standard antipsychotic drug treatment. Clozapine has demonstrated superior efficacy in relieving the positive and negative symptoms in treatment-refractory schizophrenic patients; it causes minimal extrapyramidal side effects (EPS), produces no tardive dyskinesia, and has little effect on prolactin. The underutilization of clozapine is likely related to uneasiness on the part of physicians in managing the side effects, particularly agranulocytosis, and a reluctance on the part of patients to submit to frequent blood sampling. However, side effects associated with clozapine are generally tolerated by the patient (Table 1), and appropriate medical management facilitates a maximization of the benefits of clozapine treatment.

A major benefit of clozapine treatment is the relative lack of drug-induced EPS. In an effort to keep the early clozapine/comparator studies blind, anticholinergic agents were often administered with traditional antipsychotics, which undoubtedly influenced the various results. In the study comparing clozapine-treated patients and those treated with chlorpromazine plus benztropine,² there was

no rating scale evidence of EPS difference between the 2 groups. In another study,³ there was no significant difference in EPS between clozapine-treated patients and those treated with haloperidol plus benztropine. On the other hand, the premarketing data—i.e., an accumulation of data from various clinical trials (using different methodologies) that were compiled for submission to the Food and Drug Administration—that compared clozapine with traditional antipsychotics without anticholinergics demonstrated a lower rate for all EPS in patients treated with clozapine.⁴ In a later review of 8 published studies describing the effects of clozapine on tardive dyskinesia, approximately 43% of the patients—particularly those with dystonic features—improved after clozapine treatment.⁵ A short-term 18-week investigation of the efficacy of clozapine in neuroleptic-resistant chronic schizophrenic patients also demonstrated improvement rates of 74% for tardive dyskinesia, 69% for parkinsonism, and 74% for chronic akathisia.⁶ In general, clozapine reduces dyskinesic movements, and there have been no confirmed cases of tardive dyskinesia directly attributable to clozapine treatment. Clozapine produces slight and transient elevations only in serum prolactin levels,⁷⁻¹⁰ and unlike other antipsychotics, particularly the traditional antipsychotics, prolactin levels remain low even after long-term clozapine use. Despite superior efficacy, minimal EPS, and lack of hyperprolactinemia, clozapine has generally been underutilized because of the associated serious side effects.

MANAGEMENT OF SERIOUS SIDE EFFECTS

The clozapine side effect that causes the greatest concern is agranulocytosis—i.e., granulocyte count less than

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Table 1. Side Effects of Clozapine

Serious Side Effects	Common Side Effects
Agranulocytosis	Sedation
Cardiovascular/respiratory arrest	Hypersalivation
Seizures	Tachycardia
	Hypotension
	Hypertension
	Weight gain
	Constipation
	Hepatic effects
	Urinary incontinence
	Fever

500/mm³. On the basis of premarketing experience and accumulated data from abroad, an intrinsic rate of agranulocytosis of 1% to 2% was estimated; postmarketing data suggest an incidence of 0.38%.¹¹ A review of data from the Clozaril Patient Management System showed that the majority of cases of agranulocytosis occurred within 3 months after the start of clozapine treatment, with the greatest risk peaking in the third month.¹² Only 3 cases occurred after 6 months of clozapine treatment, and 1 case occurred after 1.5 years. From 1990 to 1994, the agranulocytosis-related death rate in the United States in clozapine-treated patients was approximately 3% compared with a rate of greater than 50% during the early years of clozapine use. Clearly, the monitoring system has been effective in reducing both the incidence of clozapine-related agranulocytosis and the associated mortality rate. As a result, the requirement for blood sampling has decreased to every 2 weeks in patients who have maintained acceptable white blood cell (WBC \geq 3000 mm³ and absolute neutrophil count \geq 1500/mm³) counts during the first 6 months of continuous clozapine therapy.¹

The risk of agranulocytosis in clozapine-treated patients increases with age and is higher in women than in men.¹² There also appears to be a genetic susceptibility for the complication among Ashkenazic Jews with the HLA-B38 phenotype.¹³ Because the mechanism behind clozapine-related agranulocytosis is unknown, combining clozapine with other drugs that have the potential for suppressing the bone marrow (e.g., carbamazepine and neuroleptics) should be limited.¹⁴ Although it is undetermined whether African Americans have an increased incidence of clozapine-associated agranulocytosis, they seem to have a high mortality rate when the complication occurs.

Persons suffering from agranulocytosis are exceedingly endangered by infections for up to 4 weeks until hematologic recovery occurs.¹⁵ Therefore, any treatment that reduces this critical time period should also decrease the risks of clozapine treatment. Although controlled studies are lacking, hematopoietic glycoprotein growth factors¹⁵⁻¹⁷ such as G-CSF (human granulocyte colony-stimulating factor) and GM-CSF (granulocyte-macrophage colony-stimulating factor) have been shown to prevent the development of agranulocytosis and decrease the duration of

clozapine-related agranulocytosis by facilitating a replenishment of precursors of granulocytes and macrophages in the bone marrow.

Patients should be advised to notify their physician if they experience clinical signs of infection (i.e., fever, chills, sore throat, urinary frequency or burning). If a patient develops a fever or other signs of infection, a WBC count and differential should be checked immediately to rule out agranulocytosis.

Rare instances of respiratory and/or cardiac arrest during clozapine treatment have also been reported.^{1,18} Some of the patients receiving clozapine treatment who collapsed and had a subsequent cardiorespiratory arrest were concurrently receiving benzodiazepines; however, similar events have also been reported in patients taking other psychotropic drugs or clozapine alone.¹⁹ Clinicians should be aware that clozapine may have important central depressant and hypotensive actions, and caution is advised when the drug is initiated in patients taking benzodiazepines or other psychotropic drugs.

Although estimates vary, the overall incidence of seizures in clozapine-treated patients is approximately 3% and appears to be dose-related.²⁰ At doses less than 300 mg/day, patients taking clozapine are at the same seizure risk as those taking traditional antipsychotics (1%–2%), and at doses of 300 to 600 mg/day, the seizure risk is 3% to 4%. At doses of 600 to 900 mg/day, the seizure risk is 4% to 6%, and the majority of seizure events has been reported in patients taking the drug in doses greater than 600 mg/day. Other factors that may increase seizure activity are rapid dose titration, the concurrent use of other epileptogenic agents, and a previous history of neurologic abnormalities. Approaches that minimize the seizure risk include gradual upward titration and electroencephalographic monitoring for ictal activity if the dose of clozapine is to exceed 600 mg/day. Another strategy is to keep the clozapine dosage below 300 mg/day—with an attendant seizure risk of 1%. However, some patients will have seizures even at a lowered dose, and others may require higher doses for maximal antipsychotic efficacy. If a seizure does occur, the dose of clozapine should be decreased by half, an anticonvulsant such as valproate initiated, and a gradual upward titration of clozapine resumed until a clinical response is reached.

MANAGEMENT OF COMMON SIDE EFFECTS

Sedation is the most common side effect reported in clozapine-treated patients.^{18,21} Although premarketing data indicated a 44% incidence of sedation,⁴ the condition is usually mild and transient and occurs in the initial phase of treatment. VanderZwaag et al.²² reported that clozapine serum concentrations and sleepiness were significantly correlated at week 6; at week 12, the relationship was no longer significant, suggesting that tolerance develops. In

the Breier et al.³ study, the condition was separated into mild or moderate/severe sedation. Although 37% of patients taking clozapine or a combination of haloperidol and benztropine complained of a mild sedative effect initially, none reported moderate or severe sedation with either regimen at 10 weeks. Management of sedation includes giving the lowest possible dose of clozapine—the majority of which should be given at bedtime—and avoiding other central nervous system depressants.²³ Some clinicians have used methylphenidate to reduce the sedative effects of clozapine, which may be of sufficient distress to cause noncompliance.²¹ However, methylphenidate should be used with caution due to the possibility of worsening movement disorders and exacerbating psychoses.²⁴

Although the frequency is difficult to determine—with an incidence varying from 0% to 80%—hypersalivation is probably the second most common side effect of clozapine treatment.²⁵ Since hypersalivation commonly occurs at night, a history can often be elicited by asking if the patient's pillow is wet upon arising. Research indicates that subjective complaints of hypersalivation may not correlate with salivary flow rates.^{26,27} In one study,²⁶ salivary flow rates in individuals with schizophrenia taking clozapine were no different from normal controls. In another study,²⁷ there was no correlation between salivary flow rate and daily clozapine dosage. Because the severity and prevalence of the complaint is greater at night, the possibility of an altered circadian rhythm of salivation has been suggested.²⁶ Since hypersalivation is apparently unrelated to salivary flow rate, anticholinergic agents are generally ineffective. Management of hypersalivation includes administering the lowest possible effective dose of clozapine, a clonidine patch, or pirenzepine.²⁸

Clozapine-related cardiovascular side effects include tachycardia, hypotension, and hypertension. Approximately 25% of clozapine-treated patients will have tachycardia,²⁸ and although the increase in heart rate may be associated with the hypotensive effect, the major cause appears to be the anticholinergic activity of clozapine and its elevation of plasma norepinephrine.¹⁸ Tachycardia may be transient and related to rapidity of titration; if it is persistent, treatment with a peripheral β -blocker may be required. Clozapine-related hypotension (9%)²⁸ is related to the α -adrenergic antagonistic property of clozapine; it is usually transient and often occurs at the beginning of treatment.¹⁸ Prevalence and severity of the hypotension is significantly influenced by the rate and magnitude of clozapine dose titration. Patients generally develop tolerance, although hypotension can persist in some patients and be a limiting factor in the rate of dose escalation and the absolute dose of clozapine that can be tolerated. Isolated episodes of hypertension have also been reported but these usually occur early in the course of treatment and are related to rapidity of titration.²⁹ Tolerance usually develops without clinical intervention, although caution should be

exercised in patients with preexisting abnormal blood pressure or cardiovascular disease.

Gastrointestinal side effects secondary to clozapine treatment include weight gain and constipation. Weight gain is a troublesome side effect and an important management issue in clozapine-treated patients. Only 3% of subjects in the premarketing trials complained of weight gain during the 6-week trials.⁴ Cohen et al.³⁰ reported that 6 of 7 patients treated with clozapine in premarketing studies at their site gained from 6 to 69 lb (mean = 24.7 lb) over 2 to 9 months. John et al.³¹ reported that 73% of patients treated with clozapine for at least 3 months gained a mean of 5.4 kg, and 20% of the patients gained greater than 10% of baseline weight. Leadbetter et al.³² measured weekly weights of 21 patients for 12 weeks prior to starting clozapine and for 16 weeks during clozapine treatment. During the 16 weeks of clozapine treatment, 38% of the patients experienced marked weight gains, and 29% had moderate weight gains. To focus on true weight gain, the absolute weight at the start of clozapine treatment was compared with the weight at week 16 of treatment, and a total of 14 (67%) of the 21 patients gained more than 5% of baseline body weights. They found a significant positive correlation between weight gain and decrease in psychopathology as measured by the total Brief Psychiatric Rating Scale score. Although weight gain may be linked to clinical improvement in clozapine-treated patients, observations suggest that the longer the duration of treatment, the greater the weight gain. Management includes careful monitoring of drug-induced weight gain and nutritional counseling to educate patients who may have poor dietary habits.²⁸

Clozapine is a potent anticholinergic agent, which may explain its association with constipation.³⁰ Anticholinergic agents are also associated with symptomatic gastric motor dysfunction leading to delayed gastric emptying and subsequent nausea, vomiting, bloating, and abdominal pain. The problem is usually managed effectively with a high-fiber diet, adequate hydration, and the use of bulk laxatives and stool softeners. On rare occasions, clozapine-related constipation has led to more serious complications of obstipation, ileus, and bowel obstruction.³³

An increase in serum hepatic enzymes occurred in approximately 2% of clozapine-treated patients in premarketing trials⁴ compared with approximately 0.5% of chlorpromazine-treated patients.² Occasionally, the increase in hepatic enzymes can lead to a drug-induced hepatitis,¹⁸ but, more commonly, the findings are transient and clinically insignificant.

Urinary incontinence is probably underreported because of the patient's embarrassment and the social stigma of incontinence. Because some patients are hesitant to discuss the problem, the history must occasionally be elicited from family members or caregivers. Urinary incontinence is estimated to occur in approximately 1% of patients treated with clozapine and is thought to be related to

α -adrenergic antagonism leading to decreased internal bladder sphincter tone.³⁴ Treatment includes the reduction of fluid intake during evening hours and the use of an α -adrenergic agonist (ephedrine) taken at bedtime. Administration of dDVAP (desmopressin) intranasally has also been used as symptomatic treatment.²⁸

In premarketing data,⁴ fever was reported in 4% to 13% of clozapine-treated subjects contrasted with 1% to 4% in chlorpromazine-treated subjects.² The peak incidence of fever commonly occurs within the first 3 weeks of treatment. Although fever in a clozapine-treated patient is usually benign, transient, and responds to antipyretics, underlying infection and agranulocytosis are always major clinical concerns that must be ruled out. If a patient develops a fever over 102°F, a neuroleptic malignant syndrome must also be ruled out.

CONCLUSION

Mandatory blood monitoring has significantly reduced the incidence and associated mortality of clozapine-related agranulocytosis. The appropriate management of other clozapine side effects facilitates a maximization of the benefits of clozapine treatment. Physicians and patients alike should be aware that there is a range of benefits to clozapine use that is wider than its risks.

Drug names: benztropine (Cogentin and others), carbamazepine (Tegretol and others), chlorpromazine (Thorazine and others), clonidine patch (Catapres-TTS), clozapine (Clozaril), ephedrine (Quadrinal and others), haloperidol (Haldol and others), methylphenidate (Ritalin and others).

Disclosure of off-label usage: The author of this article has determined that, to the best of his knowledge, these agents are not approved by the U.S. Food and Drug Administration for these indications: clonidine patch for hypersalivation and ephedrine for urinary incontinence. Pirenzepine is not approved for use in the United States.

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