A Guide to the Management of Clozapine-Related Tolerability and Safety Concerns

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Abstract

Clozapine is a highly effective antipsychotic medication, which provides a range of significant benefits for patients with schizophrenia, and is the standard of care for treatment-resistant schizophrenia as well as for reducing the risk of suicidal behaviors in schizophrenia and schizoaffective disorder. However, clozapine is widely underutilized, largely because prescribing clinicians lack experience in prescribing it and managing its adverse events (AEs). Clozapine is associated with three uncommon but immediately dangerous AEs—agranulocytosis, myocarditis/cardiomyopathy, and seizures—as well as AEs that may become dangerous if neglected, including weight gain, metabolic syndrome and constipation, and others that are annoying or distressing such as sedation, nighttime enuresis and hypersalivation. Because of the risk of agranulocytosis, clozapine formulations are available only through restricted distribution via a patient registry, with mandatory, systematized monitoring for absolute neutrophil count using a specific algorithm. We identified articles on managing clozapine-associated AEs by searching PubMed using appropriate key words and search techniques for each topic.

A review of the prevalence and clinical characteristics of clozapine-associated AEs shows that these risks can be managed efficiently and effectively. The absolute risks for both agranulocytosis and myocarditis/cardiomyopathy are low, diminish after the first six months, and are further reduced with appropriate monitoring. Weight gain/metabolic disorders and constipation, which develop more gradually, can be mitigated with regular monitoring and timely interventions. Sedation, hypersalivation, and enuresis are common but manageable with ameliorative measures and/or medications.

Key Words: Clozapine, Adverse Events, Safety, Tolerability, Guidelines, Management, Schizophrenia

Introduction

Treatment-resistant schizophrenia (TRS) contributes significantly to the high clinical, social, and economic overall burdens of schizophrenia, adding a conservatively estimated $34 billion in direct medical costs annually in the United States (U.S.) (1, 2). TRS is believed to occur in about 30% of patients, although estimates as high as 60% have been suggested (2-4). It is generally defined as poor outcomes or functional impairment and persistent positive symptoms of at least moderate severity following at least two adequate, sequential trials of two different classes of antipsychotic drugs, including at least one atypical antipsychotic (1-5).

Clozapine, a second-generation antipsychotic, is the standard of care for TRS, as established in expert-consensus, multinational, schizophrenia-treatment guidelines (5-12) based on randomized controlled clinical

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Table 1 Serious Adverse Events (Included in Prescribing Information Black Box Warning): Characteristics

Adverse Event	Estimated Prevalence (%)	Usual Period of Onset after Treatment	Dose Related? (Y/N)	Often/Usually Transient? (Y/N)
Agranulocytosis	1.3	First 6 weeks to 6 months	N	N
Myocarditis/ cardiomyopathy	0.02–1.0	Mainly first month (see Figure 1)	N	N
Orthostatic hypotension	9	First weeks, and lasting 4–6 weeks	Y*	Y
Seizures	1.3–1.8	Nonspecific, but risk is increased with rapid upward dose titration	Y	N

*Related to dose titration.

trial data (13). Studies and meta-analyses have shown that clozapine is highly effective for reducing symptoms in 30% to 60% of patients with TRS (13-21). For patients with TRS nonresponsive to clozapine, augmentation strategies with adjunctive antipsychotic or electroconvulsive therapies with clozapine have demonstrated improved response in some studies, but remain controversial due to insufficient clinical trial evidence of their efficacy (21).

Clozapine also markedly reduces suicidality in patients with schizophrenia, schizoaffective disorder, and TRS (22-24), demonstrating a threefold decrease in suicidal behaviors (deaths and attempts) in chronically psychotic patients as compared with other antipsychotic therapies (25), and is the only medication that is U.S. Food and Drug Administration (FDA)-approved for reducing suicidal behavior in patients with schizophrenia or schizoaffective disorder (26-28). In addition, clozapine treatment for schizophrenia is associated with better continuation rates than most other antipsychotic drugs (29-35), and has been shown in double-blind, controlled studies to reduce violent and aggressive behavior in patients with schizophrenia and other psychiatric disorders (36-39). A Finnish, population-based, 11-year follow-up study (1996–2006) in patients with schizophrenia (n=66,881) also found that while long-term antipsychotic drug use was associated with lower all-cause mortality versus no drug use, clozapine was associated with significantly lower mortality compared with all other antipsychotic drugs used ($p<0.0001$) (40).

With regard to safety and tolerability, clozapine is associated with reduced risk of the variety of extrapyramidal adverse events (AEs)—including parkinsonism, dystonia, and a minimal risk of tardive dyskinesia—which occurs with first-generation antipsychotics; clozapine is considered an effective treatment for patients with tardive dyskinesia (3, 41, 42). However, clozapine is associated with a range of AEs of varying prevalence and potential danger to the patient (3, 26-28, 42, 43). These may be generally categorized as AEs that typically appear early and present an immediate danger (agranulocytosis, myocarditis/cardiomyopathy, seizures), which are listed in Table 1, and AEs with an enduring presence that may become dangerous over time (weight gain/dyslipidemia/insulin resistance, constipation), or that are generally annoying or distressing (hypersalivation, enuresis/nocturia, sedation, tachycardia), as listed in Table 2.

Because of the risk of agranulocytosis, clozapine formulations (Clozaril [clozapine] tablets [Novartis Pharmaceuticals Corporation, East Hanover, NJ], Fazaclo [clozapine] orally disintegrating tablets [Jazz Pharmaceuticals, Palo Alto, CA], and Versacloz [clozapine] oral suspension [Jazz Pharmaceuticals]) are available only through restricted distribution through a patient registry program—the Clozapine Risk Evaluation and Mitigation Strategy (REMS) Program—which was updated in September 2015 (44). The updated REMS has consolidated the previous six U.S. registries into one for U.S. clozapine prescribers; mandates systematic monitoring for absolute neutrophil count (ANC) via a detailed algorithm provided for this purpose (see Table 3), but not for white blood cell (WBC) count as previously required, prior to delivery of each supply of medication; and, provides a specific ANC monitoring algorithm for patients with benign ethnic neutropenia (BEN), a condition further discussed below (see Table 3 [44]). Routine monitoring is also strongly recommended for other AEs associated with clozapine (26-28, 42-44).

Table 2 Other Adverse Events: Characteristics

Adverse Event	Estimated Prevalence	Usual Period of Onset After Treatment	Dose Related? (Y/N)	Often/Usually Transient (Y/N)
Fever	≤55%	First 2 weeks	NR	Y
Sinus tachycardia	25%	First 2 weeks	Y	Y
Neuroleptic malignant syndrome	Rare/unknown	First 2 to 4 weeks	N	N
Weight gain and metabolic syndrome	60%–75% gain weight* 54%–62% develop metabolic syndrome	First 6 to 12 months	Y†	N
Constipation	30%	First 1 to 2 years	NR	N
Sedation	44%	First 6 weeks	Y	Y
Hypersalivation	30%–80%	First 2 weeks	Y	Y
Nighttime enuresis	21%	First 2 weeks	Y	Y

*≥10 pounds (114) and ≥10% over their baseline body weight (115); †Evidence of this relationship is equivocal.

Utilization and Perceptions of Clozapine

Despite its indication for treatment of TRS and suicide risks, clozapine has historically been underutilized in patients with schizophrenia, with rates in the U.S. varying widely by region and healthcare system, and ranging from as low as 2% to almost 25% among inpatients in state-operated hospital systems in recent years (45-51). A 2014 registry study including 550 patients with schizophrenia, schizophreniform, or schizoaffective disorder, at treatment centers in various U.S. regions, reported that 21.4% were receiving clozapine (52). However, the percentage of all patients with schizophrenia with either of the two indications for clozapine—TRS and risk for suicidal behaviors—is conservatively estimated at 35% to 40% (3). Higher rates of clozapine utilization have been reported in other countries, including New Zealand (32.8% of all patients with schizophrenia [53]), the United Kingdom (54% of patients with TRS [54]), and Austria (34% of all hospitalized patients with schizophrenia at discharge [55]), suggesting increased acceptance of schizophrenia-treatment guidelines (7, 9, 11, 12).

Unwarranted delay of treatment with clozapine has also been observed in studies in the U.S. and other countries (50, 56-58). A 2001 study at four hospitals in London, England (n=112), for example, found that clozapine prescription was delayed a mean of five years following its indication, and after a mean of nine other trial drug prescriptions (56). Major reasons for underutilization and delay of clozapine may include physician or patient excessive apprehension regarding AEs or efficacy (43, 58), physician unfamiliarity with clozapine prescribing or financial limitations (56, 59), and cumbersome prescribing requirements, logistical difficulties with laboratory follow-up, and lack of access to the medication (45).

A literature review study found that while clozapine treatment should be discontinued for agranulocytosis, myocarditis, cardiomyopathy, and QTc interval >500 milliseconds, physicians often discontinue treatment for other AEs that can be pre-emptively managed (see Table 4 [43]).

Moreover, clozapine registry data indicate that monitoring for agranulocytosis has reduced the rate of this AE by estimates of up to fivefold, and related deaths up to tenfold, as detailed below (60). An estimated three times more clozapine-related deaths are now due to constipation complications than agranulocytosis (43, 61).

Discontinuation of clozapine is associated with rapid worsening of psychotic symptoms, functional status, and quality of life, exposing some patients to increased risk of suicide (43, 58, 62, 63). Conversely, increased clozapine usage in New Zealand was associated with low discontinuation rates, increased duration of treatment, higher occupational activity and independent living, and lower rates of compulsory treatment and hospitalization (30). The limited data available on patient perspectives also suggest that patients with schizophrenia feel the benefits of clozapine outweigh its disadvantages (64, 65). In addition, studies suggest that even when clozapine treatment is discontinued,

Table 3 Clozapine Monitoring Recommendations Based on Absolute Neutrophil Count (ANC) for the General Population (A) and Patients with Benign Ethnic Neutropenia (B) (44)

A. MONITORING FOR THE GENERAL PATIENT POPULATION

ANC LEVEL	CLOZAPINE-TREATMENT RECOMMENDATIONS	ANC MONITORING*
Normal Range: (≥1,500 mL)	• Initiate treatment • If treatment interrupted <30 days, continue monitoring as before • If treatment interrupted ≥30 days, monitor as if new patient	• Weekly from initiation to 6 months • Every 2 weeks from 6 to 12 months • Monthly after 12 months
	• If treatment discontinued for reasons other than neutropenia	• See section 2.4 of clozapine prescribing information document (26-28)† below
Mild Neutropenia: (1,000 to 1,499/μL)	• Continue treatment	• Three times weekly until ANC ≥1,500/μL • Once ANC ≥1,500/μL, return to patient's last Normal Range ANC monitoring interval
Moderate Neutropenia: (500 to 999/μL)	• Recommend hematology consultation • Interrupt treatment for suspected clozapine-induced neutropenia • Resume treatment once ANC ≥1,000/μL	• Daily until ANC ≥1,000/μL, then 3 times weekly until ANC ≥1,500/μL • Once ANC ≥1,500/μL, check ANC weekly for 4 weeks, then return to patient's last Normal Range ANC monitoring interval
Severe Neutropenia: (<500/μL)	• Recommend hematology consultation • Interrupt treatment for suspected clozapine-induced neutropenia • Do not rechallenge unless prescriber determines benefits outweigh risks	• Daily until ANC ≥1,000 μL, then 3 times weekly until ANC ≥1,500/μL • If patient rechallenged, resume treatment as a new patient under Normal Range monitoring once ANC ≥1,500/μL

B. MONITORING FOR PATIENTS WITH BENIGN ETHNIC NEUTROPENIA (BEN)

ANC LEVEL	CLOZAPINE-TREATMENT RECOMMENDATIONS	ANC MONITORING*
Normal BEN Range: (established ANC baseline ≥1,000/μL)	• Obtain at least 2 baseline ANC levels before initiating treatment • If treatment interrupted <30 days, continue monitoring as before • If treatment interrupted ≥30 days, monitor as if new patient	• Weekly from initiation to 6 months • Every 2 weeks from 6 to 12 months • Monthly after 12 months
	• Discontinuation of treatment for reasons other than neutropenia	• See section 2.4 of Clozapine prescribing information document (26-28)† below
BEN Neutropenia: (500 to 999/μL)	• Recommend hematology consultation • Continue treatment	• Three times weekly until ANC ≥1,000/μL or ≥patient's known baseline • Once ANC ≥1,000/μL, or at patient's known baseline, check ANC weekly for 4 weeks, then return to patient's last Normal BEN Range ANC monitoring interval
BEN Severe Neutropenia: (<500/μL)	• Recommend hematology consultation • Interrupt treatment for suspected clozapine-induced neutropenia • Do not rechallenge unless prescriber determines benefits outweigh risks	• Daily until ANC ≥500/μL, then 3 times weekly until ANC ≥ than patient's baseline • If patient rechallenged, resume treatment as a new patient under Normal Range monitoring once ANC ≥1,000/μL or at patient's baseline

*Confirm all initial reports of ANC <1,500/μ/L with a repeat ANC measurement within 24 hours if clinically appropriate; †Section 2.4 of the clozapine prescribing document (PI) states:

2.4 Discontinuation of Treatment

Method of treatment discontinuation will vary depending on the patient's last ANC: • See Tables 2 or 3 (of PI; these are combined into Table 3 above) for appropriate ANC monitoring based on the level of neutropenia if abrupt treatment discontinuation is necessary because of moderate to severe neutropenia. • Reduce the dose gradually over a period of 1 to 2 weeks if termination of clozapine therapy is planned and there is no evidence of moderate to severe neutropenia. • For abrupt clozapine discontinuation for a reason unrelated to neutropenia, continuation of the existing ANC monitoring is recommended for general population patients until their ANC is ≥1500 μL and for BEN patients until their ANC is ≥1000/μL or above their baseline. • Additional ANC monitoring is required for any patient reporting onset of fever (temperature of 38.5ºC or 101.3ºF or greater) during the 2 weeks after discontinuation (see WARNINGS AND PRECAUTIONS [5.1]). • Monitor all patients carefully for the recurrence of psychotic symptoms and symptoms related to cholinergic rebound such as profuse sweating, headache, nausea, vomiting, and diarrhea.

Table 4 Summary Recommendations for Clozapine Adverse Event Management Based on a Literature Review (43)

Adverse Event	Management Outcome
Agranulocytosis, myocarditis, cardiomyopathy, and a QTc interval >500 milliseconds	Immediate discontinuation without rechallenge
Ileus or subileus, NMS, venous thromboembolism, and diabetic ketoacidosis or hyperosmolar coma	Discontinuation with potential rechallenge (with appropriate surveillance and management or prophylactic therapy)
Neutropenia, seizures, orthostatic hypotension, severe constipation, weight gain and metabolic abnormalities, including metabolic syndrome and its components, as well as moderately prolonged myocardial repolarization	Generally, discontinuation not necessary; need of intensive management
Eosinophilia, leukocytosis, CAF, and tachycardia (provided that myocarditis and NMS are ruled out)	Generally, discontinuation not necessary; usually easily managed

CAF=clozapine-associated fever; NMS=neuroleptic malignant syndrome.

the reason is rarely poor therapeutic response, but most commonly noncompliance or AEs (66-68).

Hence, it is essential to pre-emptively monitor and manage clozapine AEs in order to provide its substantial benefits and avert its risks (43). This review was conducted to clarify the prevalence and clinical characteristics of clozapine-associated AEs and provide a rational, evidence-based approach to the management of them (see Table 5).

Methods

Evidence cited for this review was gathered chiefly via research of the complete prescribing information documents for clozapine and other agents mentioned in this article, and published articles in the National Library of Medicine/MEDLINE PubMed database (http://www.ncbi.nlm.nih.gov/pubmed/), with use of appropriate search terms for clozapine efficacy, safety, utilization, and AE prevalence and management. Original research articles were selected for inclusion on the basis of their power and methodology, and review articles for their depth and breadth of evidence, with preference overall for those providing the most recent and comprehensive data, and offering practical tips and suggestions for clinical management. Since this article is expressly intended to be a practical guide to clozapine AE and safety management, the clinical experience and judgments of the authors were also applied to all topics discussed and are included in the evaluation of all research evidence presented in this article.

Clozapine-Associated Adverse Events: The Facts

Serious/Rare Adverse Events

Agranulocytosis

Agranulocytosis is defined as an ANC <500/mm^3 (see Table 3 [26, 27]). Risk of clozapine-induced agranulocytosis is approximately 1.3% overall (26-28, 69), and is elevated in older patients, women, African-American and Asian ethnic groups, and people of Ashkenazi Jewish descent with the haplotype human leukocyte antigen (HLA)-B38, DR4, DQw (42).The risk is not dose related (42). The period of highest risk is between weeks 6 and 18 of treatment (42), with incidence decreasing markedly thereafter (70, 71). In one U.S. study, the risk of agranulocytosis was 0.70/1,000 patient-years in the second 6 months of clozapine treatment and dropped to 0.39/1,000 patient-years after the first year (70). Agranulocytosis is a medical emergency requiring immediate discontinuation of therapy and consultation with a hematologist (43) (see Tables 3 and 5). Rechallenge with clozapine is contraindicated in cases of severe leukopenia and/or severe granulocytopenia (ANC <1,000/mm^3) or agranulocytosis (ANC <500/mm^3) (see Table 3 [26-28]).

Detection of agranulocytosis is achieved via:

- strict adherence to the ANC monitoring protocol (see Table 3)
- new onset of fever or symptoms of infection (e.g., pharyngitis), reported by patients/caregivers, or at prompting and/or observation of the physician, particularly during the first 6 months of treatment, during which weekly ANC monitoring is mandated (3, 72) (see Table 3).

With falling ANC levels, interruption of therapy is indicated as per the clozapine monitoring protocol (see Table 3 [26, 27]). The course of neutropenia is unpredictable, with some cases resolving within 2 to 8 days following clozapine cessation while more severe cases may progress to agranulocytosis within several days of the ANC reaching <1,500/mm^3, even after stopping clozapine (42, 43). The mechanistic correlation of agranulocytosis and neutropenia remains

Table 5 Clozapine Adverse Event Management Options

Adverse Event	Evaluations/Testing	Dosage Adjustment or Interruption/Rechallenge?	Adjunctive Medications/ Therapies	Behavioral Modifications/ Other Interventions
Agranulocytosis	• Mandatory ANC monitoring protocol (see Table 3 [44]) • Encourage patients to report symptoms of fever and/or infection (e.g., pharyngitis) and promptly evaluate them if present	• For moderate neutropenia* recommend hematology consultation and interrupt treatment, as per protocol (see Table 3 [44]) • May rechallenge at recovery of ANC to levels indicated by protocol† (see Table 3 [44]); if rechallenged, monitor as indicated by protocol (see Table 3 [44]) • In case of severe neutropenia‡ discontinue treatment without rechallenge unless prescriber determines benefits outweigh risks	N/A	• In cases of late neutropenia or agranulocytosis, discontinue concomitant therapies that may cause blood dyscrasias† • Conduct ANC testing ≥2 hours after patient has awakened in the morning to reduce risk of elevated counts by diurnal variation
Myocarditis/ Cardiomyopathy (M/C)	• History & PE; baseline measure of eosinophils (e.g., CRP, CK-MB); referral to cardiologist as needed • Common symptoms: dyspnea, palpitations/ tachycardia, fever, fatigue, chest pain • Nonspecific symptoms: sore throat, cough, vomiting, diarrhea, headache, neck pain, dizziness, faintness • Weekly (first 4 weeks) lab evaluation of peripheral eosinophils, CRP, CK-MB, troponin, and/or WBC levels (consult proposed detailed protocols for M/C monitoring) • If lab results show elevations, ECG/echocardiogram are indicated • Diagnosis by echocardiographic evidence of reduced EF and ECG disturbance	• Interruption if symptoms/lab tests indicate possible M/C • Rechallenge possible in carefully selected and monitored patients, with appropriate concomitant CV therapies (but not generally recommended)	• CV therapies as needed for treatment • Concomitant CV therapies in cases of rechallenge	N/A
Orthostatic hypotension	• Evaluate symptoms of dizziness, lightheadedness, and/or syncope • Take standing and sitting BP at treatment initiation and dose changes	• Moderate dose titration	N/A	• Rise slowly from sitting or lying position • Drink plenty of fluids • Consume adequate dietary salt • Use of support stockings • Tilt head of bed slightly upward at night
Seizures	Prior to seizure, evaluate for risk factors including: • History of head trauma or seizure • Concomitant use of other drugs that lower seizure threshold • Discontinuation of concomitant drugs that raise the seizure threshold (e.g., benzodiazapines) • Asian race • Recent stopping of smoking Following seizure, evaluate for nonclozapine causes, including: • Drug toxicity • Withdrawal of benzodiazapines or antiepileptics • Electrolyte abnormalities • Diabetic ketoacidosis • Organic brain disorders • History of febrile convulsions • Sleep deprivation following prior seizure	• To reduce risk, slow upward dose titration and maintenance of lowest effective dose • Reduce dose in patients who have stopped smoking • In case of seizure, 50% dose reduction	• In case of seizure, preferred antiepileptic agents include levetiracetam, lamotrigine	• If possible, discontinue other drugs that lower seizure threshold

Table 5 Clozapine Adverse Event Management Options - continued

Adverse Event	Evaluations/Testing	Dosage Adjustment or Interruption/Rechallenge?	Adjunctive Medications/ Therapies	Behavioral Modifications/ Other Interventions
NMS	Evaluate symptoms including: • Fever and rigidity • Hypertension or hypotension • Shock • Diaphoresis • Tachycardia and/or tachypnea • Sensory disturbances • Altered consciousness/delirium • Leukocytosis • CK levels well above 1,000/uL • Often severe parkinsonism	• Interruption and treatment until symptoms resolve • Rechallenge may be attempted after symptoms resolve, with slower titration	• Hydration, cooling, antibiotic therapy • Electroconvulsive therapy in severe and refractory cases	N/A
Fever	• Persistent fever with other symptoms of possible M/C should prompt evaluation for M/C (see above) • Fever may also be an early sign of infection and/or agranulocytosis, NMS, or immunologic conditions and other infections, depending on concomitant symptoms	• No interruption or dose adjustment for transient fever; fever due to underlying infection or condition to be treated accordingly	N/A	N/A
Sinus tachycardia	• Persistent tachycardia of >100 bpm for ≥24 hours following initiation of clozapine accompanied by other signs of cardiac dysfunction should prompt evaluation for M/C or other disorders • ECG in case of sustained, isolated sinus tachycardia (>4–6 weeks)	• Dose reduction	• If dose reduction is unsuccessful, use of a beta blocker, preferably a cardioselective beta blocker in patients with asthma or diabetes • Ivabradine in case of nonresponse to, or intolerance of, a beta blocker	• Discourage consumption of caffeinated beverages
Weight gain and metabolic syndrome	Measurement at baseline and regularly thereafter of: • Weight and waist circumference • BP, blood glucose, lipids	• Use of lowest effective dose • In case of severely increased fasting glucose levels not managed with rehydration and lowering of blood sugar, interruption of clozapine • In case of diabetic ketoacidosis: discontinuation and careful rechallenge	• Extended-release metformin • Aripiprazole	• Patient counseling on need for proper diet and exercise for weight and glucose control
Constipation	• Query patients regularly about their defecation frequency, with intervention if frequency is <4–5 times per week	• Dose reduction, although the dose relation has not been clearly established	If defecation frequency <4–5 times per week: • Orlistat • Polyethylene glycol 3350 with lactulose	• High-fiber diets • Adequate hydration • Regular exercise • Stool softeners and laxatives • Compensate for altered pain sensitivity in schizophrenia patients by coordinating with team members to enhance monitoring and observation of patient
Sedation	• Query patients about fatigue or sedation, particularly early in treatment	• Dose reduction • Administration of most or all of dose at night • Slower upward dose titration	• Fluvoxamine to raise clozapine serum levels and enable lower clozapine dose	• Reassure patients symptoms usually resolve after 6–12 weeks • Avoiding other sedating medications • Practice good sleep hygiene

Table 5 Clozapine Adverse Event Management Options - continued

Adverse Event	Evaluations/Testing	Dosage Adjustment or Interruption/Rechallenge?	Adjunctive Medications/ Therapies	Behavioral Modifications/ Other Interventions
Hypersalivation	• Query patients about hypersalivation	• Dose reduction may be helpful	• Glycopyrrolate • Anticholinergic agents (e.g., trihexyphenidyl, biperiden) • Ophthalmologic drops with anticholinergic properties (e.g., atropine) • Alpha-2 adrenergic receptor agonists (e.g., clonidine, lofexidine, guanfacine) • Diphenhydramine • Botulinum toxin injection • Sulpiride	• Chewing gum to promote swallowing • Elevation of head and sleeping on side • Covering the pillow with a towel
Nighttime enuresis	• Query patients about nighttime enuresis, bearing in mind embarrassment may inhibit response or voluntary mention	• Splitting bedtime dose during the day • If symptoms persist, dose reduction	• Desmopressin • Anticholinergics (e.g., trihexyphenidyl, oxybutynin) • Alpha-1 agonists (e.g., ephedrine, pseudoephedrine) • Antidepressants	• Avoid intake of diuretics • Avoid excessive fluid intake at night • Stop fluid intake at 3 hours before bedtime • Completely empty bladder before sleep

*ANC 500 to 999/μL general population (this ANC category is not applicable for BEN); †ANC ≥1,000/μL; ‡ANC <500/μL for both general population and BEN. ANC=absolute neutrophil count; BEN=benign ethnic neutropenia; BP=blood pressure; bpm=beats per minute; CK=creatine kinase; CK-MB=creatine kinase-MB; CRP=C-reactive protein; CV=cardiovascular; ECG=electrocardiogram; EF=ejection fraction; M/C=myocarditis/cardiomyopathy; N/A=not applicable or not available; NMS=neuroleptic malignant syndrome; WBC=white blood cell count.

unclear, in part because the observed risk factors for each condition are inconsistent (73). A low baseline WBC count and Black race have been associated with neutropenia, but neither factor has been correlated with increased risk of agranulocytosis (73, 74). Moreover, increasing age is associated with greater risk of agranulocytosis but decreased risk of neutropenia (73, 74). Nonetheless, data from the Clozaril National Registry over five years in almost 100,000 patients showed that discontinuation of clozapine according to the ANC testing protocol (see Table 3) reduced the rate of agranulocytosis cases from an estimated 1% to 2% without monitoring, based on historical data, to 0.38%, and the number of deaths to 12 from a projected estimate of up to 149 (60).

However, certain factors bear consideration when monitoring WBC levels, including:

- *BEN:* as noted above, patients with BEN must be monitored for ANC levels via a specific algorithm designed for this population (see Table 3 [44]). BEN describes the phenomenon wherein the low end of the normal WBC count range in African-American patients is 2,800/mm^3 versus 3,600/mm^3 for white patients, but is not accompanied by adverse health consequences such as chronic or severe infections (42, 73, 75). As noted above, neither low baseline WBC levels nor Black race have been associated with increased risk of agranulocytosis (73-75). Nonetheless, this racial difference in normal WBC ranges presents the potential for many African Americans to be incorrectly considered neutropenic (42, 75). Indeed, clozapine utilization in African-American patients is reported to be one-third to two-thirds lower, and discontinuation two times higher, compared with white patients (42, 75, 76), a disparity the updated clozapine ANC algorithm may help rectify (44). BEN has also been observed in some Middle Eastern ethnic groups (73).
- *diurnal variation in WBC and absolute neutrophil:* multiple reports have documented patient WBC levels that were substantially lower in the morning than in the afternoon (77-79). One study found that WBC levels had increased substantially after a minimum 2-hour period of wakefulness and movement following nighttime sleep (79). Therefore, taking WBC readings later in the morning or in the afternoon may reduce the risk of a low reading and interruption of clozapine treatment as per guidelines (see Table 3).
- *neutropenia caused by concomitant medications:* late onset of neutropenia or agranulocytosis (≥6 years of clozapine treatment) has been reported in clozapine-treated patients taking concomitant therapies that also carry risks for blood dyscrasia, including val-

proic acid, haloperidol, olanzapine, or risperidone (42). These reports pose the question of whether the events were clozapine-induced or associated with the concomitant drug and/or their combination with clozapine (42). Additional medications associated with agranulocytosis include ticlopidine hydrochloride; antithyroid drugs; auto-immune response suppressants such as infliximab and auranofin; spironolactone; carbamazepine; sulfonamides; and, beta-lactam antibiotics, among others, although with estimated attributable incidences of generally less than 1:1 million (80-82). Overall, drugs independently associated with blood dyscrasias should be used with caution and increased vigilance for agranulocytosis in patients also taking clozapine (72).

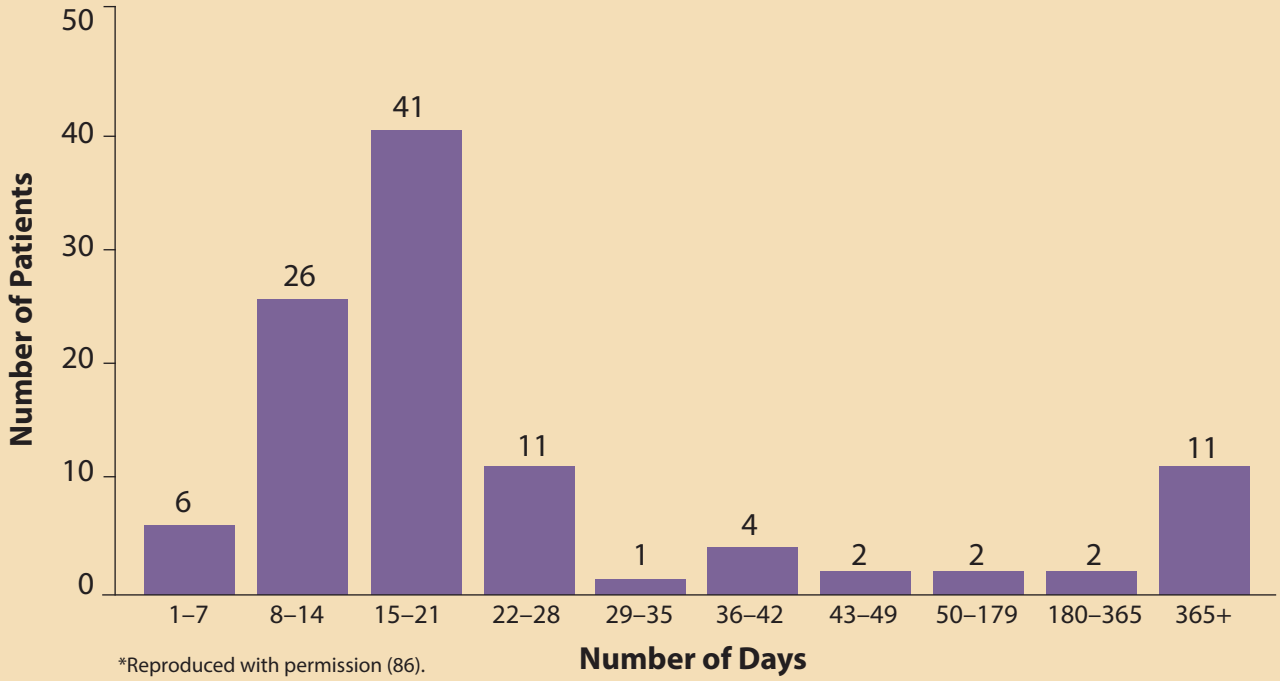
Myocarditis and Cardiomyopathy

Estimates of the absolute risk of clozapine-induced myocarditis or cardiomyopathy from regulatory or registry data have generally ranged from approximately 0.01% to 0.19% (83-85), although rates as high as 0.7% to 1.2% have been reported in large cohorts (86). The variation in these estimates may be due in part to substantial underreporting of cases to regulatory agencies (85) and to increasing physician awareness and recognition of this AE, suggesting the higher estimates may be more accurate (87). Reported case fatality rates have also ranged widely, from approximately 10% to 46% (83, 84, 86, 88, 89), with delayed diagnosis resulting in worse outcomes (90). Diagnosis of myocarditis/cardiomyopathy is cause for immediate discontinuation of clozapine therapy (43, 85).

Myocarditis typically occurs within the first 6 months after clozapine initiation, with 85% to 90% of cases estimated to occur within 8 weeks (42, 85, 87). A particularly high incidence in the third week of treatment has also been reported (see Figure 1 [86]). However, some authors believe it may occur very rarely later during treatment (42, 43, 85). Cardiomyopathy is typically of dilated type and may frequently feature electrocardiogram (ECG) P-wave and T-wave abnormalities (43). Clozapine-associated myocarditis/cardiomyopathy has not been found to be dose dependent, occurring at standard and even very low doses (85, 87). Little is known about its pathophysiology, but it is hypothesized to be a type 1 hypersensitivity reaction and possibly involving clozapine-induced anticholinergic blockade of M2 receptors resulting in cardiotoxicity, release of pro-inflammatory cytokines, or increased serum catecholamine levels, among other proposed mechanisms (42, 90, 91). Additional medications associated with hypersensitivity myocarditis include lithium, thyroxine, and sulfonamides, among others (90).

Although there are no classic manifestations of clozapine-induced myocarditis, the most common symptoms include dyspnea, palpitations or tachycardia, fever, fatigue, chest pain, and other nonspecific symptoms, which could include flu-like symptoms, sore throat, vomit-

Figure 1 **Number of Days Receiving Clozapine before Onset of Suspected Clozapine-Induced Myocarditis among 106 Patients in Australia from 1993 to 2003***



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ing, diarrhea, headache, and neck pain (85, 87, 90, 92). Because symptoms like tachycardia and fever also appear in isolated, transient, and benign forms with clozapine treatment, as discussed below, they should primarily arouse suspicion of myocarditis when concomitant with other symptoms. Narrowed pulse pressure (i.e., <40 mm Hg difference between systolic and diastolic blood pressures) and peripheral edema are also potential indications of clozapine-induced myocarditis, among multiple other cardiac signs as reviewed elsewhere (42, 43, 85, 87).

Monitoring for potential myocarditis/cardiomyopathy may include weekly (for the initial 4 weeks, perhaps at the time of the mandated ANC monitoring [see Table 3]) checks for these clinical symptoms and signs along with laboratory evaluation of peripheral eosinophils, C-reactive protein, and creatine kinase-MB, and/or WBC levels (42, 87, 88). Assessment of levels of troponin I or T—markers of myocardial injury—has been advocated as part of a proposed monitoring protocol (87, 88), but this is not universally accepted (42, 85).

Elevated levels of the blood parameters, suggesting potential myocarditis/cardiomyopathy, indicate pausing of clozapine and further evaluation via echocardiogram or ECG or both. Based on these findings, a referral for cardiology consultation may be indicated. Diagnosis is determined primarily by echocardiographic evidence of reduced ejection fraction; supportive ECG findings include ST-segment elevation and tachycardia (43, 85). More detailed discussions of cardiovascular (CV) evaluation for clozapine-induced myocarditis/cardiomyopathy have been published (85, 87, 88). Rechallenge with clozapine following resolved clozapine-induced myocarditis/cardiomyopathy has been seldom attempted, but may be successful in carefully selected patients with echocardiographic monitoring and appropriate concomitant CV therapies (85).

Seizures

The overall estimated incidence of seizure with clozapine treatment is 1% to 2% after 6 months, 3% to 5% after 1 year, and 10% after 3.8 years (93-95). While other first- and second-generation antipsychotics also increase seizure risk, clozapine is associated with the highest risk among these medications (95, 96). A study in 1,418 patients between 1972 and 1988 showed that clozapine-induced seizure risk was dose dependent, rising from 1.0% at doses <300 mg/day to 2.7% at doses 300 to 600 mg/day, and 4.4% of patients at doses >600 mg/day (97). However, clozapine 6-months postmarketing data for 5,629 patients and a 2011 review of all published literature on this association failed to show a significant correlation of clozapine dose with seizure risk (93, 94). Researchers have suggested that the inconsistency of these data may be attributed to multiple patient factors and variables in treatment such as dose titration, which cause variation in per-dose clozapine plasma levels, the underlying factor influencing seizure risk (93-95). Although data on the direct relationship between clozapine plasma levels and seizure risks are limited, some evidence suggests a substantially increased risk at clozapine levels >1,300 μg/L (94, 95).

Patient factors that appear to increase clozapine serum levels include age older than 45 years and female gender, although the direct correlation with these factors and seizure risk is unclear (95). Some evidence suggests that Asians may be slow metabolizers of clozapine and, thus, at risk for higher per-dose clozapine plasma levels (94). In addition, smoking cessation by patients may result in marked elevation of clozapine plasma levels and, thus, increased risk of seizure; this may occur because the polycyclic aromatic hydrocarbons found in cigarette smoke induce clozapine metabolism, thereby reducing clozapine plasma levels by up to 50% and often necessitating higher doses for therapeutic efficacy in smokers (nicotine replacements have no effects on these changes) (94, 98). Additional patient risk factors for clozapine-induced seizures include a history of head trauma or seizures; discontinuation of drugs during clozapine use that raise the seizure threshold, such as benzodiazepines; and, drinking alcohol (72, 95).

Co-administration of drugs that may interfere with clozapine metabolism, such as cytochrome P450 isoenzyme 1A2 inhibitors, which include ciprofloxacin and fluvoxamine, may also raise clozapine plasma levels and, thus, seizure risk (95). Several reports have also been published of seizures occurring with co-administration of clozapine with medications that independently lower the seizure threshold, including erythromycin, haloperidol, and lithium (95).

If a seizure occurs, or electroencephalographic activity indicating an epileptiform focus is present, a 50% clozapine dose reduction is advisable, along with evaluation of other possible causal factors, such as drug toxicity, withdrawal of antiepileptics or benzodiazepines, electrolyte abnormalities, diabetic ketoacidosis, organic brain disorders, history of febrile convulsions, or sleep deprivation following a previous seizure (43). The clozapine 6-months postmarketing data for 5,629 patients found that of the 71 (1.3%) patients who experienced a seizure, 37 (52.1%) were rechallenged with clozapine, of whom 29 (78%) were able to continue the treatment with dose reduction and gradual dose titration, or the addition of an antiepileptic medication (93).

Suggested measures to lower seizure risk include slow upward titration of the clozapine dose and maintenance of the lowest effective dose (72) (see Table 5). The antiepileptic drug (AED) valproate has been suggested as prophylaxis or remedial therapy for seizures, although the optimal timing

and role of this treatment in patients receiving clozapine remains unclear (94, 95); in addition, pharmacokinetic data have shown that valproic acid may induce clozapine metabolism, with an incremental effect beyond that of smoking (99). Alternative AEDs would preferentially include agents that do not depress WBC, such as levetiracetam or lamotrigine.

Neuroleptic Malignant Syndrome

Neuroleptic malignant syndrome (NMS) is a rare but potentially life-threatening condition that may occur with clozapine treatment (43). Multiple reviews have found approximately 20 reported cases of clozapine-associated NMS in the literature (100); another review that critically examined all published cases of NMS against formal diagnostic criteria reported that 12 cases had occurred between 1986 and 2005 (101). Patient risk factors for NMS may include physical exhaustion or dehydration, heat exposure, malnutrition, alcohol use, iron deficiency, trauma, thyrotoxicosis, and brain disorders including dementia, delirium, tumor, or encephalitis (102). However, the main risk for NMS is exposure to neuroleptic drugs (i.e., first- and second-generation antipsychotics) and the concurrent use of multiple neuroleptics or of neuroleptics with other medications that may also raise the risk of NMS (102). These may include non-neuroleptics with antidopaminergic activity such as metoclopromide, tetrabenazine, and reserpine; dopaminergics, such as levodopa, dopamine agonists, and amantadine; and, other agents, including lithium, phenelzine, dosulepin, desipramine, and trimipramine, which have been rarely associated with NMS (102).

Symptoms typically occur within 2 to 4 weeks of treatment initiation, the most commonly reported being tachycardia, mental status changes, and diaphoresis (103). Hypertension, hypotension, diaphoresis, tachypnea, fever, leukocytosis, and often severe parkinsonism may also be present (43, 103). Appearance of these symptoms and suspicion of NMS should prompt testing for creatine phosphokinase (CPK) levels; elevated CPK levels well above 1,000 U/L support a diagnosis (43, 103). On suspicion of NMS, clozapine should be paused and the patient sent to the emergency room for treatment, which may include hydrating until symptoms fully resolve, and electroconvulsive therapy in severe and refractory cases (43) (see Table 5). Rechallenge with clozapine can be attempted, with slower titration recommended (43).

Less Serious/More Common Adverse Events

Common clozapine-associated AEs, which do not generally require discontinuation, include fever, sinus tachycardia, orthostatic hypotension, weight gain and metabolic syndrome, constipation, sedation, hypersalivation, and nighttime enuresis. They are addressed in order of symptoms that could indicate one of the more serious conditions discussed above (fever, sinus tachycardia), present inherent risks such as falling (orthostatic hypotension), become dangerous over time (weight gain and metabolic syndrome, constipation), or are chronic problems that may be annoying and distressing to the patient (sedation, hypersalivation, and nighttime enuresis).

Fever

Clozapine-induced fever has been reported to occur in 0.5% to 55% of patients; this wide variation may be partly explained by varying thresholds used for fever (43, 104). Studies using a fever threshold of 37.5°C or 38.0°C (99.5° or 100.4°F) in clozapine recipients have reported fever prevalence in the 14% to 44% range (105-107). Clozapine-related fevers typically rise to approximately 38° to 39°C (~100° to 102°F), occur within the first 2 weeks to month of treatment initiation, and last between 2 and 4 days, with no need for clozapine discontinuation provided the fever is not an indication of another, more serious condition (42, 105-108). One study of 93 clozapine-treated patients found that the 19 (20.4%) patients who experienced fever had no increased risk for developing a severe reaction, or for discontinuation, after 1 year of treatment (105). However, fever can be an early sign of agranulocytosis with infection, myocarditis, neuroleptic malignant syndrome, or immunologic conditions such as pancreatitis, polyserositis, and colitis, or other infections (43); therefore, monitoring for concomitant symptoms of such conditions with fever is advisable. Persistent fever with cardiac symptoms such as tachycardia should prompt full evaluation for myocarditis, as outlined above (e.g., chest x-ray, ECG, C-reactive protein, creatine kinase-MB, B-type natriuretic peptide, and WBC [42]) (see Table 5).

Sinus Tachycardia

Clozapine-induced sinus tachycardia, with a mean increase of 10 to 15 beats/min and characterized by 100 to 120 beats/min, typically begins at the start of treatment and during the upward dose-titration phase, occurring in these early stages in up to 50% of patients, and may subside after 4 to 6 weeks (43, 109). It is commonly asymptomatic and has been associated with use of additional concomitant antipsychotic medications (109). Although prevalence data are limited, one study in a sample of 98 patients reported asymptomatic tachycardia in 34% of patients (109). This AE is usually benign, but could be an early sign of myocarditis, cardiomyopathy, or NMS (43). A persistent sinus tachycardia of >100 beats/min for ≥24 hours (symptomatic or asymptomatic) ac-

companied by other signs/symptoms of cardiac dysfunction may indicate risk for myocarditis that should prompt further evaluation (92).

Management measures for sinus tachycardia include:

- dose reduction as the first adjustment (43) (see Table 5), particularly if clozapine plasma levels are relatively high
- if dose reduction is unsuccessful, use of a beta blocker, preferably a cardioselective agent such as atenolol in patients with diabetes or asthma, or ivabradine in case of nonresponse or intolerance of a beta blocker (43, 61, 72, 109, 110)
- ECG for evaluation if the symptoms are sustained (72, 109).

Orthostatic Hypotension, Bradycardia, and Syncope

Orthostatic hypotension is defined as a drop in blood pressure (BP) of ≥20 mm Hg systolic or 10 mm Hg diastolic when rising from a sitting to standing position (111). Clozapine-related orthostatic hypotension occurs in approximately 9% of patients, usually at treatment initiation, is related to dose titration, and is usually transient; in rare cases it has been associated with collapse and respiratory and/or cardiac arrest (41, 72). Although patients generally develop tolerance within 4 to 6 weeks, hypotension may persist in some individuals, limiting the maximum dose they can tolerate (41). Patients may describe dizziness or lightheadedness, and are prone to syncope (72).

Monitoring for orthostatic hypotension includes taking standing and sitting BP measurements at treatment initiation and dose changes, although such measures have limited diagnostic sensitivity (72, 112) (see Table 5). To reduce risks and discomfort of orthostatic hypotension, potential measures include:

- moderation of dose titration (72)
- advising the patient/caregiver to rise slowly from a sitting or lying position, especially in the morning and after meals (72)
- drinking plenty of fluids, and consuming a diet with adequate salt (72)
- use of support stockings and tilting the head of the bed slightly upward at night (72)
- for persistent cases, consultation with an internist.

Weight Gain and Metabolic Syndrome

Second-generation antipsychotics are generally associated with weight gain, particularly olanzapine and clozapine, and with related risks of metabolic disturbances such as insulin resistance, type 2 diabetes, dyslipidemia, and diabetic ketoacidosis (3, 43, 113). Studies show that the majority of patients gain ≥10 pounds (114) and ≥10% over their baseline body weight (115) during the first 6 to 12 months of clozapine treatment, with the greatest gains occurring in patients with younger baseline age and lower body mass index (BMI) (116-118). Clozapine dose was positively associated with weight gain in a randomized, double-blind, 16-week study in 50 patients (118), but had no relationship to weight in a 5-year medical records study in 82 patients (119). Although the physiology of antipsychotic-induced weight gain is unclear, hypothetical mechanisms include drug effects on regulators of appetite and weight, including serotonergic, histaminergic, adrenergic, and dopamine signaling, as well as insulin and leptin levels (120).

Despite the relatively strong association of clozapine with weight gain, mounting evidence suggests clozapine has no greater effect on metabolic disease risks than other antipsychotics. A university-based study in 307 patients with schizophrenia found no significant differences between patients treated with clozapine for a mean 7.6 years (n=96) versus those treated with one or more other antipsychotics (n=211) on all metabolic parameters studied, including: mean BMI (31 vs. 32); rates of type 2 diabetes (17% vs. 18%), dyslipidemia (35% vs. 38%), hypertension (32% vs. 39%), and obesity (48% vs. 54%), respectively (121). A database study in 1,686 patients also showed no significant difference in CV mortality between patients aged <55 years treated with clozapine (n=1,084) or risperidone (n=602) after a 6- to 10-year follow-up, although results were unclear for patients who started clozapine at age ≥55 years (122). In addition, a Finnish, population-based cohort, 11-year follow-up study among 66,881 persons with schizophrenia (also noted in the Introduction) found that the risk for death due to ischemic heart disease was similar for clozapine, compared with other commonly used antipsychotic agents (40). Nonetheless, metabolic syndrome (using National Cholesterol Education Program or International Diabetes Federation 2007 criteria) occurred in 53.8% to 61.6% of patients receiving clozapine in studies (123, 124), and at significantly higher rates than population-based controls matched for age, BMI, and race/ethnicity (123).

Expert-consensus recommendations for monitoring and reducing risks for diabetes associated with antipsychotic drug treatment include measurement of weight, waist circumference, BP, blood glucose, and lipids performed at baseline and regularly thereafter in all patients receiving antipsychotic medications (125) (see Table 5). Researchers in this field have also suggested use of the lowest effective clozapine dose (43) and patient counseling on the need for proper diet and exercise, particularly considering clozapine-induced sedation and fatigue, which can lead to a sedentary lifestyle (3, 126, 127).

A meta-analysis of 10 trials involving 482 patients found that nonpharmacologic/behavioral interventions for antipsychotic-induced weight gain achieved significant mean reductions in weight gain versus treatment as usual (2.56 kg [5.6 lb]; p=0.001), and BMI (0.91 kg/m^2; p=0.001) (126). Mean percentage weight reduction ranged from 1.9% to 4.0%, which the authors suggested could result in decreased morbidity and mortality risks for some patients (126). However, a more recent meta-analysis of 40 trials representing 19 distinct interventions for antipsychotic-induced metabolic AEs in patients with schizophrenia found that nonpharmacologic approaches alone were insufficient (128).

The most well-studied pharmacotherapy for antipsychotic-induced weight gain is extended-release metformin, which has demonstrated significant weight loss, with a mean difference versus placebo of approximately 3.2 kg (7.1 lb) across 10 studies (129). Clinically relevant weight loss (e.g., ≥7% of total weight) was also significantly more frequent with metformin versus placebo, with a number needed to treat (NNT) of 3, across 4 studies reporting this outcome (129). In addition, metformin is associated with decreased leptin levels, insulin, and triglyceride to high-density lipoprotein–cholesterol (HDL-C) ratio, and a significant increase in HDL-C (compared with placebo) in clozapine-treated patients (128, 129). Randomized, placebo-controlled studies have also demonstrated the efficacy of concomitant aripiprazole and clozapine (130, 131), with a differential weight loss in one 16-week trial of -2.15 kg (4.7 lb) versus placebo (-2.53 vs. -0.38, respectively; p<0.001) (131); 15% of patients given aripiprazole experienced a clinically relevant weight loss of ≥7% from baseline versus 3.0% in the placebo group (p<0.001), for an NNT of 9. Total and low-density cholesterol levels were also significantly reduced in the aripiprazole group.

Antipsychotic-induced glucose and lipid changes may occur even without significant weight gain, and with different effects based on ethnicity (132). In cases of severe increased levels of fasting glucose not managed with rehydration and lowering of blood sugar, clozapine should be interrupted and appropriate antidiabetic management implemented until adequate glucose control is achieved (43). In cases of diabetic ketoacidosis, a rare but potentially fatal AE, clozapine should be discontinued immediately with transfer to an emergency department or other facility where intravenous treatment and appropriate monitoring can be performed (43). Careful rechallenge with clozapine accompanied by sustained diabetic management and intensive glucose monitoring is reasonable following resolution (43).

Constipation

Constipation occurs in an estimated 30% of patients receiving clozapine (61), which is similar to the estimated rate of 36% for all antipsychotics (133), although some clozapine studies have reported prevalence as high as 60% (61). Complications of clozapine-induced constipation can be serious. An Australian sample of 15 cases of clozapine-related constipation, for example, included 9 cases that were described as severe, including 4 of fecal impaction, 2 of subacute bowel obstruction, 1 of rectal prolapse requiring ileostomy, and 1 death that occurred in a case of previously unreported constipation (134). A French sample of 30 patients with constipation included 3 (10%) cases of intestinal obstruction requiring laparotomy, of which one was a fatality (135). Reported fatalities from clozapine-associated constipation have involved cases of fecal peritonitis, aspiration of feculent vomitus as a result of bowel obstruction, bowel necrosis, and bowel ischemia (136-138). As noted above, an estimated three times more deaths are caused by clozapine-induced constipation complications than by agranulocytosis (43, 61).

Because constipation is hypothesized to be a side effect of clozapine's anticholinergic action, some clinicians believe dose reduction (within therapeutic ranges) may be helpful (136). Management may also include high-fiber diets, adequate hydration, regular exercise, and use of stool softeners and laxatives (61). Patients and caregivers should be queried about their defecation frequency, with intervention if frequency is <4 or 5 times per week (43). Use of orlistat (61, 139) or polyethylene glycol 3350 combined with lactulose may also be helpful. Physicians should also be aware that schizophrenic patients may have altered sensitivity to, or difficulty communicating, pain, which is usually the central symptom of acute abdomen (136). These factors emphasize the need for a team approach with other healthcare providers to enhance patient monitoring and treatment (136).

Sedation

Sedation is perhaps the most common clozapine-associated AE, occurring in about 44% of patients (41), and is among the most common AEs mentioned by patients/caregivers (64, 65). The few available data for this AE suggest that sedation increases with higher clozapine serum levels, appears early in treatment, and may resolve within 6 to 12 weeks (41, 140). Management options include assuring patients the sedation is likely to diminish; avoidance of other sedating medications; dose reduction; administration of most or all of the clozapine dose at night and/or slower upward dose titration; and, practice of good sleep hygiene (e.g., regular sleep/wake schedules, avoiding caffeine and nicotine at night, drinking alcohol in moderation, relaxation before bed, keeping bedroom quiet and cool) (41, 72, 141). A randomized, placebo-controlled pilot trial of concomitant modafinil and clozapine showed no effect on sedation symptoms (142). Although other stimulants have been used to counter sedation in patients with schizophrenia, such thera-

pies may exacerbate psychosis and carry a risk of abuse (141, 142).

Hypersalivation

Reported rates of clozapine-associated hypersalivation have ranged widely, from 30% to 80% of patients (41, 61), and is a common reason for stopping treatment due to distress caused by embarrassment, social problems, withdrawal, and reduced self-esteem (61). Symptoms appear to be dose related, occur early in treatment and during both the daytime and night sleep, and can lead to secondary problems such as skin damage, inflammation, sleep disturbance, respiratory problems secondary to aspiration, painful swelling of salivary glands, daytime sleepiness, wet clothing, unpleasant odors, and associated social stigma and embarrassment (61, 143). Some ameliorative measures for the patient include:

- chewing gum to promote swallowing (61)
- elevation of the head and sleeping on the side to reduce the risks for aspiration and secondary pneumonia (61)
- covering the pillow with a towel to soak up the saliva (61)
- use of anticholinergic medications such as trihexyphenidyl and biperiden, or ophthalmologic drops with anticholinergic properties, such as atropine, as a mouthwash before bedtime (61)
- treatment with centrally acting alpha-2 adrenergic receptor agonists, such as clonidine, lofexidine, guanfacine; diphenhydramine; botulinum toxin injection; and, sulpiride (144).

A 2011 literature review of 13 clinical trials (6 double blind) and 13 case reports of therapies for clozapine-induced hypersalivation found there was only weak evidence for the efficacy of antimuscarinic agents (144); however, glycopyrrolate demonstrated significant efficacy versus biperiden for clozapine-associated hypersalivation (biperiden was also effective versus baseline) in a 12-week, randomized, double-blind, crossover, fixed-dose study (144, 145).

Nighttime Enuresis

Reported rates of clozapine-associated nighttime enuresis have ranged from 0.23% to 44%, with underreporting likely due to patient embarrassment or physician omission (42, 61, 146). An observational cohort study in 606 patients taking a variety of second-generation antipsychotics found that enuresis occurred in 20.7% of patients taking clozapine (n=82) versus <10% each for olanzapine, quetiapine, and risperidone (147). Significant risk factors for enuresis among all patients were use of a second antipsychotic and a history of childhood bedwetting.

Enuresis symptoms have been reported to occur most commonly at initiation and titration phases, and to subside thereafter in most patients, based on clinical observation and case series data (42, 148, 149). However, a study in 61 clozapine-treated inpatients found that enuresis occurred in 27 (44.3%) patients and was persisting in 15 (55.6%) after 3 months (146). Management options may include:

- splitting bedtime clozapine dose during the day
- avoiding intake of diuretic substances (e.g., coffee and alcohol) and excessive intake of fluids at night (e.g., stopping fluid intake at 3 hours before bedtime other than small amounts for taking medication) (61)
- completely emptying bladder before sleep (42)
- if symptoms persist, clozapine dose reduction (42).

A range of medications including desmopression (with careful medical supervision advised to avoid hyponatremia), anticholinergics (trihexyphenidyl, oxybutynin), alpha-1 agonists (ephedrine), and antidepressants (amitriptyline) have also been described in case reports and case series for managing this AE (42, 43, 148, 150). Ephedrine was shown to be both effective and well tolerated in one open-label study in 16 patients with clozapine-associated urinary incontinence (149), and pseudoephedrine was effective in a randomized trial in 9 patients with primary nocturnal enuresis (151).

Expert Opinion—Preparing Patients, Families, and Caregivers

Patients and their families or caregivers should be informed orally and/or with handouts before treatment with clozapine is started that: 1) clozapine has adverse effects that can be dangerous; some of these can be mitigated (e.g., preemptive use of fiber and a stool softener to reduce risk for constipation) and others can be detected early before serious injury occurs (e.g., blood monitoring to detect the first signs of myocarditis); 2) when clozapine is started, several other medications may be started as well to mitigate potential adverse effects, which might include metformin to limit weight gain and insulin resistance, aspirin to reduce risk for venous thromboembolism, and a stool softener; 3) if other adverse effects appear they should be brought to the clinician's attention for management; and, 4) the clinicians' goal is for the patient to be comfortable on clozapine. Discussion of healthy eating and exercise, and ways to deal with increased appetite, is recommended. Review of the blood draw schedule and providing support to get blood work, if needed, may also be helpful.

Conclusions

An estimated 30% of patients with schizophrenia are treatment resistant, and clozapine, a second-generation an-

tipsychotic, is the standard of care for TRS and for reducing the risk of suicidal behaviors in schizophrenia and schizoaffective disorder. While clozapine has been generally underutilized in the U.S., largely due to its AEs and monitoring requirements, recent data show it can be used successfully with proper monitoring and AE management. Greater and earlier use of clozapine when indicated, and pre-emptive management of AEs, is essential to the successful treatment of TRS.

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