CME Background

Articles are selected for credit designation based on an assessment of the educational needs of CME participants, with the purpose of providing readers with a curriculum of CME articles on a variety of topics throughout each volume. Activities are planned using a process that links identified needs with desired results.

Participants may receive credit by reading the article, correctly answering at least 70% of the questions in the Posttest, and completing the Evaluation. The Posttest and Evaluation are now available online only at PSYCHIATRIST.COM (**Keyword: June**).

CME Objective

After studying the article by Nielsen et al, you should be able to:

- Manage adverse effects of clozapine that do not warrant treatment termination

Accreditation Statement

The CME Institute of Physicians Postgraduate Press, Inc., is accredited by the Accreditation Council for Continuing Medical Education to provide continuing medical education for physicians.

Credit Designation

The CME Institute of Physicians Postgraduate Press, Inc., designates this journal-based CME activity for a maximum of 1 *AMA PRA Category 1 Credit*™. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

Note: The American Academy of Physician Assistants (AAPA) accepts certificates of participation for educational activities certified for *AMA PRA Category 1 Credit*™ from organizations accredited by ACCME or a recognized state medical society. Physician assistants may receive a maximum of 1 hour of Category I credit for completing this program.

Date of Original Release/Review

This educational activity is eligible for *AMA PRA Category 1 Credit*™ through June 30, 2016. The latest review of this material was April 2013.

Financial Disclosure

All individuals in a position to influence the content of this activity were asked to complete a statement regarding all relevant personal financial relationships between themselves or their spouse/partner and any commercial interest. The CME Institute has resolved any conflicts of interest that were identified. In the past year, Alan J. Gelenberg, MD, Editor in Chief, has been a consultant for Allergan and Forest, has received grant/research support from Pfizer, and has been a stock shareholder of Healthcare Technology Systems. No member of the CME Institute staff reported any relevant personal financial relationships. **Faculty financial disclosure appears at the end of the article.**

Termination of Clozapine Treatment Due to Medical Reasons: When Is It Warranted and How Can It Be Avoided?

Jimmi Nielsen, MD; Christoph U. Correll, MD; Peter Manu, MD; and John M. Kane, MD

ABSTRACT

Objective: To identify the outcome of potentially serious adverse effects of clozapine, particularly those frequently cited as reasons for clozapine discontinuation, and to characterize management strategies for adverse effects that do not warrant discontinuation.

Data Sources: A structured search was performed of PubMed and EMBASE from database inception until September 10, 2012, without any language restrictions, using *clozapine* as the search term. Reference lists of retrieved articles were cross-checked for additional relevant studies.

Study Selection: Included in this review were studies that reported on the frequency of the specified clozapine-related adverse effects and that either reported on the grounds for or against clozapine discontinuation or reported on management techniques to maintain patients on clozapine or enable successful clozapine rechallenge. The following side effects were considered important for this review as potential grounds for clozapine discontinuation: neutropenia or agranulocytosis, leukocytosis, thrombocytopenia, thrombocytosis, eosinophilia, leukocytosis, QTc prolongation, electrocardiogram changes, atrial flutter, tachycardia, myocarditis, cardiomyopathy, fever, syncope, diabetes mellitus, diabetic ketoacidosis, diabetic hyperosmolar coma, neuroleptic malignant syndrome, ileus, liver enzyme elevation, or seizure.

Data Extraction: Study results that supported continuation or discontinuation of clozapine or that provided information on management techniques were abstracted.

Results: Of a total of 13,385 search results, data from 81 studies were included in this review. Results suggest that prompt discontinuation of clozapine without rechallenge is indicated for agranulocytosis, myocarditis, cardiomyopathy, and a QTc interval > 500 milliseconds that is confirmed and derived using the appropriate correction method. Clozapine discontinuation with potential rechallenge (provided there is appropriate surveillance and management or prophylactic therapy) is indicated for ileus or subileus, neuroleptic malignant syndrome, venous thromboembolism, and diabetic ketoacidosis or hyperosmolar coma. Neutropenia, leukocytosis, seizures, orthostatic hypotension, severe constipation, and weight gain and metabolic abnormalities, including metabolic syndrome and its components, as well as moderately prolonged myocardial repolarization, need to be managed but do not generally warrant clozapine discontinuation. Eosinophilia, leukocytosis, drug-induced fever, and tachycardia (provided that myocarditis and neuroleptic malignant syndrome are ruled out) can be managed and should rarely lead to clozapine discontinuation.

Conclusions: A number of side effects commonly cited as medical reasons for clozapine discontinuation do not necessarily warrant such action. Management techniques are available that allow continuation or rechallenge in relation to a number of clozapine-related side effects.

J Clin Psychiatry 2013;74(6):603–613

Submitted: *July 31, 2012; accepted January 28, 2013 (doi:10.4088/JCP.12r08064).*
Corresponding author: *Jimmi Nielsen, MD, Centre for Schizophrenia, Aalborg Psychiatric Hospital, Brandevej 5, 9210 Aalborg, N/A 9000, Denmark (jin@rn.dk).*

Clozapine remains the gold standard for treatment-resistant schizophrenia, and its impressive efficacy has been demonstrated in several clinical trials[1–4] and a meta-analysis.[5] In addition to its unique efficacy in patients with treatment-resistant schizophrenia, clozapine possesses antisuicidal[6] and antiaggressive[7] properties, and its efficacy for treatment-resistant bipolar disorder has also been documented.[8a,8b] Treatment with clozapine is highly cost-effective due to significant reductions in hospitalization.[9] Many clozapine-treated patients and their relatives report a substantial positive effect on their lives and well-being.[10] However, clozapine is also associated with a wide range of side effects, some of which are potentially fatal. The most salient among them, agranulocytosis, led to the suspension of clozapine treatment after 8 fatal cases in Finland in 1974 and demonstrated the need for the current mandatory hematologic monitoring program. Other side effects, such as myocarditis,[11] aspiration pneumonia,[12] ileus,[13] and weight gain,[14] have in fact caused more deaths than agranulocytosis. Weight gain alone has been estimated to cause 412 deaths per 100,000 patients over 10 years.[14] Although the estimate of Fontaine et al[14] remains untested in prospective samples, overall, weight gain–induced mortality is balanced by clozapine's antisuicidal properties, illustrated by 416 additional weight gain–induced deaths counteracted by saving 492 per every 100,000 patients from suicide.[14]

Because of the paucity of alternative treatments, the discontinuation of clozapine remains an issue of utmost importance. Almost half of the patients who abruptly discontinue clozapine treatment experience rapid psychotic deterioration,[15] exposing some of them to an increased risk of suicide.[16] With rates of up to 65%,[17] discontinuation is highest during the first year of treatment, but there is evidence of a 2- to 3-fold variation from study to study. There is growing evidence that psychiatrists' lack of experience with clozapine contributes to the high discontinuation rate.[16–20] A recent study[17] found that medical reasons accounted for 20% of discontinuation decisions and cited as the most common reasons seizure (45.5%), severe constipation (36.4%), somnolence (27.3%), and neutropenia (18.2%). A cause for concern is that the literature provides consistent evidence that the overwhelming majority of decisions to discontinue clozapine treatment are made on the basis of side effects, such as leukocytosis, seizures, and fever,[16–20] which, under normal circumstances, can be managed and should not lead to such a decision.

As strategies for counteracting many of the troublesome side effects are available,[21] it is highly likely that the termination of treatment is unwarranted in many cases. A lack of experience with clozapine seems to often explain why many psychiatrists are unaware of these strategies[22] and unnecessarily discontinue clozapine treatment, thus depriving patients of what could be the only effective intervention for them. Limited evidence combined with inexperience in using known remedies for side effects may thus jeopardize patients' overall well-being.

Clinical Points

- Psychiatrists should be aware that the discontinuation of clozapine treatment may exclude patients from effective treatment and can increase the risk of relapse, aggression, and suicidal behavior.
- Neutropenia, leukocytosis, seizures, orthostatic hypotension, severe constipation, weight gain, and metabolic abnormalities, including metabolic syndrome and its components, as well as moderately prolonged myocardial repolarization, need to be managed but do not generally warrant clozapine discontinuation.
- Side effects such as eosinophilia, leukocytosis, drug-induced fever without another medical cause, and sinus tachycardia can be managed and should rarely lead to the discontinuation of clozapine treatment.
- Clozapine discontinuation with potential rechallenge (providing there is appropriate surveillance and management or prophylactic therapy) is indicated for ileus or subileus, neuroleptic malignant syndrome, venous thromboembolism, and diabetic ketoacidosis or hyperosmolar coma.
  Other side effects, such as agranulocytosis, myocarditis, cardiomyopathy, and a QTc interval > 500 milliseconds that is confirmed and derived with the appropriate correction method warrant the immediate discontinuation of clozapine treatment.

While the complexities of clozapine treatment, including potentially life-threatening adverse events, may cause doctors to refrain from reintroducing clozapine after witnessing serious side effects, several case reports[23] document that a rechallenge may offer patients another chance to benefit from clozapine treatment. However, the rarity of life-threatening side effects, on the one hand, and the prospect of increased risk of death following rechallenge, on the other hand, explain why this option has received only scant attention. The severe clinical consequences of discontinuation of clozapine treatment and the difficult questions facing psychiatrists have prompted this clinical overview, which aims to help psychiatrists handle the most common pitfalls in treatment with clozapine, particularly with regard to decisions on the discontinuation or continuation of clozapine treatment.

METHOD

We conducted a structured search of PubMed and EMBASE from database inception until September 10, 2012, without any language restrictions. References were imported to EndNote X4 (Thomson Reuters, New York, New York), and duplicates were removed. On the basis of review of discontinuation studies[12,20,24] and the authors' clinical experience, the following side effects were considered important for this review as potential grounds for discontinuation of clozapine treatment: neutropenia or agranulocytosis, leukocytosis, thrombocytopenia, thrombocytosis, eosinophilia, leukocytosis, QTc prolongation, electrocardiogram changes, atrial flutter, tachycardia, myocarditis, cardiomyopathy, fever, syncope, diabetes mellitus, diabetic ketoacidosis, diabetic

Table 1. Cardiac Adverse Effects: Discontinuation Rule and Management Strategies[a]

Cardiac Complication	Grounds for Discontinuation	Comments
QTc prolongation	QTc > 500 ms (extremely rare)	Confirm QT by manual reading; use Fridericia formula for heart-rate correction[25]
Myocarditis	Troponin levels 2 times the upper limit of normal, or ST-segment elevation	Rechallenge is not recommended[23]
Cardiomyopathy	Echocardiography-confirmed diagnosis	Rechallenge is not recommended[28]
Orthostatic hypotension	Continuous malignant syncopes despite counteracting strategies	Use slower up-titration or dose reduction. Rule out and address other causes, check for adequate fluid intake, and review other orthostatic medications. Use compression socks and/or fludrocortisone[21]
Idiopathic or drug-induced sinus tachycardia	Never	Exclude myocarditis and cardiomyopathy. Lower the dose or treat with cardioselective β-blockers[36]
Nonspecific electrocardiogram changes, such as ST-segment elevation or T-wave flattening or inversion	Never	Exclude myocarditis, cardiomyopathy, and other cardiac disease[38]
Atrial flutter	Electrocardiogram-confirmed atrial flutter	Discontinue and seek potential reason not related to clozapine; rechallenge if atrial flutter is related to nonclozapine reason[39]

[a]See text for detailed description.

hyperosmolar coma, neuroleptic malignant syndrome, ileus, liver enzyme elevation, or seizure. Although merely bothersome side effects may also have led to discontinuation, these are not considered here. The search term we used was *clozapine* because searches using the above-mentioned side effects in conjunction with *clozapine* did not retrieve enough articles.

Included in this review are studies that reported on the frequency of the specified clozapine-related adverse effects and that either reported on the grounds for or against clozapine discontinuation or reported on management techniques to maintain patients on clozapine or enable successful clozapine rechallenge. Review articles and meta-analyses were given precedence over case series or individual studies. Case reports were excluded unless they provided important new evidence that was not contained in prior studies or reviews. Manuscripts were reviewed manually for relevance. Reference lists of the retrieved journal articles were cross-checked for additional relevant studies.

RESULTS

Of a total of 13,385 search results, data from 81 studies were included in this review. The remaining studies were excluded upon title or abstract review or full text review because they did not provide specific information for the topic of this review. A summary of potential reasons for discontinuation of clozapine and of justifications and management techniques detailed in the text below is provided in Tables 1–4.

Cardiac Adverse Effects (Table 1)

QTc prolongation. Prolongation of the QTc interval to levels > 500 milliseconds has been associated with an increased risk of developing life-threatening polymorphic ventricular arrhythmia, or torsade de pointes. The QTc interval is a measure of the time from the beginning of ventricular depolarization to the end of repolarization obtained from surface electrocardiogram.[25] However, since a heart rate elevation has the effect of narrowing the QT interval, a correction formula is used.

While a blockage of the fast rectifier potassium channel causes many antipsychotics to prolong the QTc interval[25,26] (an effect most pronounced for ziprasidone and sertindole, with mean prolongation up to 20 milliseconds), QTc intervals above 500 milliseconds that should lead to discontinuation are rarely seen during clozapine treatment. In fact, the extent to which clozapine is capable of prolonging the QTc interval remains largely unknown, as no studies have taken account of 2 important pitfalls: (1) tachycardia is common during treatment with clozapine and (2) the Bazett formula is valid only for heart rates below 80 bpm; since most machines use this formula for correcting the QT interval, overcorrections are likely to occur.[25]

For heart rates exceeding 80 bpm, the Fridericia formula offers a more reliable correction.[25] Two sets of scores illustrate the widening gap between the results for the 2 correction formulas: for a QT interval of 420 milliseconds, corrected figures of 454 milliseconds and 442 milliseconds are elicited at a heart rate of 70 bpm using the Bazett and Fridericia formulas, respectively. At the elevated heart rate of 90 bpm, the corresponding figures are 514 milliseconds and 481 milliseconds. The conclusion is that, very likely, a high number of cases with a QTc > 500 milliseconds during treatment with clozapine represents an artifact of the Bazett formula rather than the Fridericia formula being employed.

Another pitfall in clozapine treatment is presented by occasional changes in nonspecific T-wave morphology, in particular, flattening.[27] This occurrence complicates both automatic and manual reading of the QT interval and is best controlled for by using manual readings based on a determination of the QT interval in the lead where the T-wave exhibits the greatest amplitude.[25] Termination of clozapine treatment on the grounds of QTc prolongation is rarely warranted; other causes of prolongation, such as concomitant medications or unrecognized cardiac disease, should therefore be sought.

Table 2. Hematologic Adverse Effects: Discontinuation Rule and Management Strategies[a]

Hematologic Complication	Grounds for Discontinuation	Comments
Eosinophilia	Never	Exclude other diagnoses, eg, myocarditis and neutropenia[42,43]
Neutropenia	ANC < 1,500/μL; for patients with benign ethnic neutropenia, ANC < 1,000/μL has been proposed	Pausing until ANC is normalized may resolve the problem. Lithium may be used in case of rechallenge[23,49]
Agranulocytosis	ANC < 500/μL	Rechallenge is not recommended[23]
Thrombocytopenia	Thrombocyte count of < 50,000/μL	Extremely rare, often transient. Pause until thrombocytes normalize, and attempt rechallenge[61]
Thrombocytosis	Thrombocyte count of > 750,000/μL to 1,000,000/μL	May be transient. Pause until thrombocytes normalize, and attempt rechallenge[65]
Leukocytosis	Never, in and of itself; rule out infection	Benign phenomenon. Exclude other diagnoses, eg, agranulocytosis, neuroleptic malignant syndrome, infection, and myocarditis[66]

[a]See text for detailed description.
Abbreviation: ANC = absolute neutrophil count.

Myocarditis. The absolute risk of clozapine-induced myocarditis is 0.015%–0.188%.[28] Myocarditis occurs within the first months of treatment and is diagnosed by ST-segment elevation and tachycardia using an electrocardiogram or by increased troponin levels (troponin levels twice the upper limit of normal warrant discontinuation).[29] Flu-like symptoms, fever, fatigue, and dyspnea are the most common symptoms.[28] A recent study found that, in most cases, patients had no symptoms of myocarditis before death, which raises the question of whether weekly monitoring of troponin levels is warranted.[29,30] Clozapine should be discontinued immediately in case of myocarditis, and rechallenge is not recommended.[23] Although, in a report[31] of 4 cases, clozapine rechallenge was successful in 3 patients, a publication bias is likely. Moreover, with the addition of 8 additional cases published recently,[32] 4 of which were successful, clozapine rechallenge would still not be recommended according to the metrics published by Manu et al[23] for recommending rechallenge.

Cardiomyopathy. Clozapine-induced cardiomyopathy is a serious medical condition. Typically, it is of dilated type, and sinus tachycardia may be accompanied by fatigue, dyspnea, and tachypnea.[28] Electrocardiogram signs are typically nonspecific but frequently include T-wave and P-wave abnormalities and signs of left ventricular hypertrophy. A cardiomyopathy diagnosis confirmed by echocardiography should lead to prompt discontinuation of clozapine.

Orthostatic hypotension. Especially during up-titration of clozapine, orthostatic hypotension may cause problems. The mechanism is extensive antagonism at the noradrenergic α_1 receptor and is probably exacerbated by the sedating properties of clozapine.[21] Slower up-titration may solve the problem, but if orthostatic hypotension is present in long-term treatment, patients are advised to drink plenty of fluid and eat a salt-containing diet. If this recommendation does not solve the problem, compression socks and/or fludrocortisone may help.[33,34]

Sinus tachycardia. Sinus tachycardia is a frequent side effect of clozapine. It is most pronounced at the start of treatment and during the up-titration phase. Clozapine-induced sinus tachycardia is usually harmless but could be the first sign of life-threatening conditions, such as myocarditis, cardiomyopathy, or neuroleptic malignant syndrome. Newly occurring sinus tachycardia in a patient who has been in stable and unchanged treatment for at least a month should raise suspicion of cardiomyopathy.

Dose reduction should be attempted in case of idiopathic sinus tachycardia; if this attempt proves ineffective or if psychotic symptoms preclude dose reduction, a cardioselective β-blocker may be tried after cardiomyopathy and myocarditis, as well as neuroleptic malignant syndrome, have been ruled out.[35] Treatment with a β-blocker should not be initiated within the first months of clozapine treatment because tolerance to the heart-rate inducing effect of clozapine is likely to develop after 4 to 6 weeks of treatment.[36] Moreover, the use of β-blockers may complicate the diagnosis of myocarditis. Ivabradine may also be used in case of lack of response to or intolerability of β-blockers.[37] In conclusion, idiopathic or drug-induced sinus tachycardia should not lead to clozapine discontinuation.

Other cardiac complications. Nonspecific electrocardiogram changes, such as ST-segment elevation, T-wave flattening, or T-wave inversion, have been reported during treatment with clozapine in which no connection to cardiac disease was found. Provided that cardiac disease can be excluded, such symptoms appear to be of no clinical importance.[27,38] Atrial flutter of unknown origin has also been reported and should lead to the discontinuation of clozapine or relevant medical treatment.[39]

Hematologic Adverse Effects (Table 2)

Eosinophilia. An increase in eosinophil production may indicate allergic reactions and is therefore considered to be a predictor of other clozapine-induced side effects such as myocarditis,[11] agranulocytosis,[40] and toxic hepatitis.[41] Clozapine-induced eosinophilia is not predictive of other side effects, but, since many of these potentially life-threatening side effects are accompanied by concomitant eosinophilia, a thorough examination should be performed.[42] Eosinophilia (eosinophil level > 3,000/μL) is usually transient and occurs mainly during the first year of treatment. The manufacturer of clozapine recommends discontinuation and eventually

restarting when the level of eosinophils is below 1,000/μL.[43] Continuous eosinophilia (> 3,000/μL) is extremely rare, and the consequences remain unclear. It is our opinion that the potential consequences of discontinuation of clozapine outweigh this risk if all other medical conditions are excluded.[43]

Neutropenia or agranulocytosis. Agranulocytosis indicates a condition in which the absolute neutrophil count is below 500/μL, whereas neutropenia is characterized by absolute neutrophil counts between 500/μL and 1,500/μL.[44] The risk of agranulocytosis is 0.7%; the risk of neutropenia is approximately 3%. The current mandatory monitoring system has made fatal agranulocytosis extremely rare, with incidences as low as 0%–0.03%.[19] Occurrence of neutropenia typically provokes concern that the absolute neutrophil count will continue to drop and reach the agranulocytosis level, a development that is unpredictable. As clozapine treatment is generally terminated for safety reasons, the elucidation of this question is difficult. As a practical but unreliable rule of thumb, it can be assumed that neutropenia can occur at any time during treatment with clozapine, whereas agranulocytosis tends to develop predominantly during the first 6 months of treatment.[17,45–48] The problem is particularly pronounced with the so-called leukocyte and granulocyte "dips," which can occur at any time during treatment with clozapine. Although the absolute neutrophil count may have been stable for months to years, it may suddenly drop and reach neutropenia levels, in which case clozapine should be interrupted. The treatment may be resumed under increased surveillance when the absolute neutrophil count returns to normal levels.[49]

Moreover, clinicians should be aware of the potential for morning pseudoneutropenia, a physiologic state that can be attributed to increased neutrophil demargination as plasma cortisol levels reach their morning peak. However, morning pseudoneutropenia is no cause for concern; blood sampling should merely be transferred to midmorning[50] or the afternoon.[51] In patients of African and Middle Eastern descent, benign ethnic neutropenia may be present with a low baseline count, a biological variation in which increased infection rates have not been recorded.[52] In general, a low baseline absolute neutrophil count is a risk factor for neutropenia but not for agranulocytosis.[19] In Great Britain, adjusted thresholds have been proposed and used for neutropenia in patients with benign ethnic neutropenia that are 500/μL lower than in the general guidelines, recommending clozapine discontinuation only if the absolute neutrophil count is < 1,000/μL.[52] However, severe cases of ethnic neutropenia may require concomitant treatment with granulocyte colony–stimulating factor, and a long-acting preparation of pegfilgrastim administered subcutaneously every 14 days has been shown to be effective.[53]

Lithium may be used to raise the neutrophil count in patients with a history of neutropenia as it stimulates the bone marrow and is a frequent cause of leukocytosis.[54] The dosage should be therapeutic, ie, > 0.4 mmol/L (12-hour value); after administration, a period of at least 1 to 2 weeks should follow before the reinitiation of clozapine, if it was deemed necessary to discontinue clozapine. Despite the widespread use of this regimen, no investigation of its effect on infection rate has been undertaken. Lithium inhibits myeloperioxidase, which may reduce the aggressiveness of neutrophils, thereby masking the problem.[55] Despite this fact, several studies report the successful use of lithium to boost neutrophils, and it is a recommended strategy in case of leukopenia.[23,56,57] Other bone marrow–stimulating drugs, such as filgrastim, have also been tried successfully.[58]

Agranulocytosis should always lead to prompt discontinuation of clozapine. Rechallenge should not be attempted in patients with a history of agranulocytosis.[23,54]

Some patients have their clozapine treatment discontinued because they refuse to follow the hematologic monitoring. After 6 months of treatment, the risk of agranulocytosis with clozapine is similar to other drugs used in psychiatry, such as mianserin. For this reason, and if the patient accepts the potential risk, an option may be to accept longer intervals between blood sampling or to draw blood only whenever an infection is suspected.[59] Another option may be to introduce hematologic monitoring with a point-of-care device, which may facilitate continuous monitoring on-site using capillary blood.[60]

Thrombocytopenia. Low thrombocyte counts may occur in isolation or accompanied by other cell line changes.[61,62] The sequelae of thrombocytopenia are petechiae and increased risk of bleeding. Clozapine-induced thrombocytopenia is usually transient and rarely merits a discontinuation of clozapine. Persistent thrombocytopenia is rare.[63] Thrombocyte counts below 50,000/μL should lead to discontinuation. The problem may be resolved by pausing until values return to a normal level. Lithium may also increase the thrombocyte count.[64] It is currently being debated whether mandatory thrombocyte monitoring should be introduced.[61]

Thrombocytosis. While extremely rare, elevated thrombocyte counts have been reported during clozapine treatment.[65] Although thrombocytosis predisposes to thrombosis, mild, transient thrombocytosis should not lead to discontinuation, but thrombocyte levels > 750,000/μL to 1,000,000/μL warrant the discontinuation of clozapine.

Leukocytosis. Paradoxically, clozapine may cause not only leukopenia, but also leukocytosis. The sparse work done in relation to leukocytosis has failed to uncover the underlying mechanism, but the condition is viewed as benign in relation to clozapine treatment and should not lead to discontinuation.[66–68] An unreplicated study found an increased risk of acute myeloid leukemia associated with clozapine, but the incidence was extremely low.[69] Obviously, clinicians should rule out any non–clozapine-related reason for the elevated leukocyte count, including neuroleptic malignant syndrome (see later section on neuroleptic malignant syndrome), but, if there is none, then leukocytosis should not lead to clozapine discontinuation. Leukocytosis occurs very often transiently in the first weeks of treatment, and, in this period, additional medical examination is usually not warranted in comparison to the development of leukocytosis after years of treatment.

Table 3. Cardiometabolic Adverse Effects: Discontinuation Rule and Management Strategies[a]

Cardiometabolic Complication	Grounds for Discontinuation	Comments
Weight gain	Almost never	Behavioral weight management[72]; adjunctive treatment with metformin or topiramate[73]; adjunctive aripiprazole[74]; consider addition of approved antiobesity treatments
Arterial hypertension	Almost never	Exercise, weight loss, salt restriction; usual antihypertensive management[70]
Dyslipidemia	Almost never	Exercise, low-fat diet, weight loss; usual antilipidemic management[70]
Diabetes mellitus	Fasting glucose levels > 350 mg/dL or significant clinical symptoms, eg, syncope, lethargy, confusion	Try managing diabetes first; identify and correct other diabetogenic conditions or medication effects. Generally, diabetes is manageable[79]
Metabolic syndrome	Almost never	Treatment of individual components of metabolic syndrome, according to general medical guidelines, as above[70]
Diabetic ketoacidosis or diabetic hyperosmolar coma	Dehydration, fruity-smelling breath, shortness of breath, lethargy, confusion, seizures, coma	Stop clozapine; identify and manage other potential reasons for diabetes; rechallenge carefully only after stabilization of diabetes and with ongoing, tight glucose monitoring[79]

[a]See text for detailed description.

Cardiometabolic Adverse Effects (Table 3)

Weight gain, arterial hypertension, dyslipidemia, and metabolic syndrome. Clozapine is among the antipsychotics with the strongest liability for weight gain and lipid and glucose abnormalities. Although most antipsychotics can lower blood pressure via blockade of α_1 adrenergic receptors and although clozapine can be associated with orthostatic hypotension (as described in the section on cardiac adverse effects), the often-severe weight gain can offset this effect, raising the risk for elevated blood pressure over time. Clozapine is among the antipsychotics with the greatest risk for the development of metabolic syndrome, a constellation of at least 3 of the following 5 cardiovascular risk factors: abdominal obesity, arterial hypertension, hypertriglyceridemia, low high-density lipoprotein cholesterol, and elevated blood glucose.[70]

Metabolic syndrome or its components should generally not lead to clozapine discontinuation. Although these cardiometabolic risk factors are of clinical concern, they should each and all be managed appropriately during ongoing clozapine treatment by following general medical guidelines. Healthy lifestyle guidance should be offered as early as possible when initiating clozapine treatment, but clearly when cardiometabolic side effects emerge.[71] Since weight gain and metabolic abnormalities may be at least to some degree dose-related,[70,71] the lowest effective clozapine dose should be used. Behavioral weight-management treatment[72] should be initiated when cardiometabolic adverse effects worsen. When behavioral interventions fail or patients cannot adequately comply with them, adjunctive treatment with metformin or topiramate[73] or with aripiprazole[74] should be considered. These options have the best evidence base for weight loss in patients treated with clozapine. Novel approved drugs for obesity, such as lorcaserin, the combination of phentermine plus topiramate, or naltrexone plus bupropion, could also be attempted, although no data currently exist for patients with antipsychotic-induced weight gain and metabolic abnormalities.

If arterial hypertension, dyslipidemia, or hyperglycemia emerge, common medical guidelines should be followed for the management of these conditions, which should generally be managed by a medical specialist in conjunction with the psychiatric health care team.[70]

Diabetes mellitus, diabetic ketoacidosis, and diabetic hyperosmolar coma. Diabetes mellitus is a potential adverse effect of antipsychotic agents, but clozapine has been most frequently associated with this potential complication.[70,71,75,76] In addition to long-term diabetogenic effects of increased body weight and adiposity, clozapine seems to have unique molecular effects that increase the risk for diabetes mellitus, possibly mediated via muscarinic M3 receptor blockade decrease of cholinergic-dependent and glucose-dependent insulin secretion from pancreatic β cells.[70] However, it is sometimes difficult to determine the magnitude of the mediation effect, as most patients who develop diabetes while taking clozapine have one or more risk factors for diabetes, including a diagnosis of schizophrenia, family history of diabetes mellitus, advanced age, body mass index of ≥ 25 (calculated as kg/m^2), dyslipidemia, central obesity, gestational diabetes, or nonwhite ethnicity.[70,76–78] Since diabetes can be managed medically, diabetes mellitus development should not automatically lead to clozapine discontinuation. Rather, clinicians should identify and address other diabetogenic conditions (eg, infection, obesity, hyperthyroidism) or medication effects (eg, β-blockers, steroids) and coordinate diabetes care in collaboration with medical specialists. If fasting glucose levels are too high (ie, > 350 mg/dL) or if significant clinical symptoms develop (eg, dizziness, syncope, lethargy, confusion) that cannot be managed acutely with rehydration and lowering of blood sugar, clozapine may need to be held or discontinued until adequate glucose control has been achieved. However, clozapine should generally be reintroduced with appropriate antidiabetic management and close glucose monitoring.[79]

Diabetic ketoacidosis and diabetic hyperosmolar coma are very rare adverse effects of antipsychotics, but clozapine has been the agent most likely to be associated with this potentially life-threatening effect.[78] This side effect can either occur suddenly early in treatment or be a late sign of longer-standing diabetes that was unrecognized and untreated.[77,80] Patients present with dehydration, fruity-smelling breath, shortness of breath, lethargy, and confusion. In more severe

Table 4. Other Adverse Effects: Discontinuation Rule and Management Strategies[a]

Other Complication	Grounds for Discontinuation	Comments
Benign fever	Never	Benign phenomenon. Exclude other diagnoses, eg, agranulocytosis, neuroleptic malignant syndrome, infection, and myocarditis[81]
Neuroleptic malignant syndrome	Severe muscle rigidity, tachycardia, hypertension or hypotension, shock, leukocytosis, creatine phosphokinase elevation well above 1,000 U/L	Pause clozapine; check hydration and consider intensive care unit referral until symptoms have fully resolved; give electroconvulsive therapy in severe cases. Slower titration should be used in case of rechallenge[23]
Venous thromboembolism	Medical risk conferred by thromboembolism; repeated thromboembolism	Try exercise of lower extremities and antithrombotic treatment. Discontinue clozapine and seek treatment for underlying medical condition.[89] Rechallenge if resolved and with prophylactic treatment; if there is a recurrence, terminate clozapine therapy
Constipation	Ileus or subileus	Modify diet, try exercise, use softening laxative; if ileus or subileus occur, pause clozapine and reintroduce after addressing inadequate dietary and bowel habits.[91] A laxative with a stimulant mode of action can be used short-term
Hepatic impairment	2–3 times the upper normal limit of transaminase levels	Reducing dosage or pausing until liver enzyme levels have improved may resolve the problem[102]
Seizures	Never	Lower the dose, divide the dose, or treat with valproate sodium or other antiepileptic drug that does not affect myelopoetic cells[105]

[a]See text for detailed description.

forms, patients can develop seizures, coma, and death. Clozapine should be discontinued immediately, and the diabetic condition should be managed appropriately in an acute-care setting. Careful reintroduction of clozapine can be attempted after sustained control of diabetes and removal of potentially diabetogenic medications or treatment of diabetogenic comorbidities as listed above—and with careful glucose monitoring in place.

Other Adverse Effects (Table 4)

Benign hyperthermia. The benign fever and flu-like symptoms, or hyperthermia, encountered by up to 55% of patients during the first month of clozapine treatment[81] are explained by an increase in pyrogens and bear no relation to the long-term tolerability of clozapine.[82] While the fever may be caused by several other conditions, psychiatrists tend to focus on excluding agranulocytosis through white blood cell counts and absolute neutrophil counts, leading to a risk of missing other potentially life-threatening side effects. There are a variety of immunologic conditions, such as pancreatitis,[83] polyserositis,[84] colitis,[85] and myocarditis,[11] of which the latter in particular may produce symptoms resembling benign hyperthermia. Symptoms of any of these conditions should always lead to abrupt discontinuation of clozapine. Therefore, all patients with fever who are in their first month of clozapine treatment should be thoroughly examined; examinations should include white blood cell and absolute neutrophil counts, electrocardiogram, and troponin enzyme level measurements. Differential diagnoses for benign hyperthermia should also include neuroleptic malignant syndrome. The possibility of infection should also be considered, as patients treated with clozapine may be more prone to infections.[86]

Neuroleptic malignant syndrome. Neuroleptic malignant syndrome is a rare but potentially life-threatening condition associated with clozapine treatment and presents with autonomic instability (ie, tachycardia, hypertension or hypotension, shock), altered consciousness, fever, leukocytosis, and elevated creatine phosphokinase levels well above 1,000 U/L, as well as often-severe parkinsonism. However, parkinsonism is not always present during neuroleptic malignant syndrome that is induced by atypical antipsychotics.[87,88] Pausing clozapine and hydrating until symptoms have fully resolved is the treatment of choice; electroconvulsive therapy can also be helpful in severe and refractory cases. However, rechallenge can be attempted, with slower titration of clozapine recommended.[21]

Venous thromboembolism. Treatment with antipsychotics seems to increase the risk of venous thromboembolism, with clozapine causing the highest risk.[89] The mechanism remains largely unknown, and, because most of the studies have not been able to control for additional risk factors, such as obesity, lack of exercise, and smoking, it remains unclear whether the increased risk is a direct effect of the drug or is due to the effect of additional risk factors that are present in patients receiving antipsychotic drugs. Patients who are experiencing thromboembolism should receive traditional medical treatment and prophylactic measures, such as antithrombotic treatment. Whether clozapine should be discontinued needs to be decided by balancing the expected consequences of discontinuing or continuing clozapine treatment. Patients should be involved in this discussion. A recurrence of thromboembolism despite prophylactic treatment should always lead to clozapine discontinuation.

Constipation. Clozapine possesses extensive anticholinergic properties in combination with sedative properties, constituting a serious risk factor for constipation and, subsequently, ileus.[90] Clozapine-induced ileus may be fatal, and, in fact, more deaths are caused by clozapine-induced ileus than by agranulocytosis.[13] Patients should be asked weekly during up-titration and every month during maintenance treatment about their defecation frequency, and a frequency of less than 4 to 5 times per week should lead to intervention. A high-fiber diet, plenty of fluid, and exercise are often ineffective in clozapine-induced constipation, and often a softening laxative is warranted.[91,92] It remains controversial

whether a laxative with a stimulant mode of action can be used safely during long-term treatment because of risk of cathartic colon.[93]

Hepatic impairment. Clozapine has been associated with several types of hepatic impairment ranging from asymptomatic increases in liver function tests to fulminant liver failure with hepatic encephalopathy.[94–96] Up to 40% of clozapine patients experience alanine transaminase levels above 2 times the upper limit of normal[97]; icteric hepatitis is observed in only 0.06% of clozapine patients.[94] Abnormal liver function tends to occur during the first months of treatment but has proven to be transient in 60% of cases.[97] Hepatitis tends to occur during the same period and is reversible if clozapine is terminated in a timely manner.[41,96] Drug-induced hepatic impairment is usually a diagnosis of exclusion, the causality of which is difficult to determine.[98] Clozapine-induced hepatic impairment has received scant attention in the literature, and no clear recommendations can be given. The routine measurement of liver function enzymes has occasionally been recommended[94,99,100] but involves a risk of discontinuation based on a false indication. Clinical symptoms, such as rash, jaundice, or malaise, should always prompt the measurement of liver function. Although 2-fold and 3-fold increases in transaminase levels should not lead to discontinuation, careful monitoring is recommended. Increases in transaminase levels beyond 3 times the normal upper limit usually warrant discontinuation, but the temporary disruption of treatment while the liver function is subnormal may overcome the problem. Dose reduction may likewise be helpful, as there seems to be a dose dependency of the hepatic effects.[36,97] Cases of successful rechallenge in patients with a marked elevation of liver enzyme levels have been described.[101,102]

Seizures. Clozapine lowers the seizure threshold, and dose-dependent fluctuation in electroencephalographic activity and risk of seizure are seen.[103,104] Clozapine doses above 600 mg/d cause seizures in 4.4% of patients as compared to only 2.7% and 1.0% of patients receiving 300–600 mg/d and < 300 mg/d, respectively.[103] A careful analysis[105] of 101 clozapine-induced seizures indicated paroxysmal tonic-clonic activity in 67 patients, myoclonic seizures in 27 patients, atonic seizure in 1 patient, and partial simple or partial complex seizures in 6 patients. The mean daily dosage of clozapine at the time of the seizure ranged from 275 mg in patients with partial complex seizure to 535 mg in patients with myoclonic activity.[105] A 50% dose reduction and assessment of other causes for the decreased seizure threshold (eg, drug toxicity or withdrawal of benzodiazepines or antiepileptics, electrolyte abnormalities, diabetic ketoacidosis, organic brain disorders, or sleep deprivation) must follow the first seizure. Seizures or electroencephalographic activity indicating an epileptiform focus should not lead to discontinuation; either a reduction in dosage or a division of dosage (if administered once daily), or treatment with antiepileptic medication such as valproate sodium,[92] is recommended. Lamotrigine,[106] gabapentin,[107] and other antiepileptics have also been tried with success. Refractory epilepsy is also not an absolute contraindication to initiating clozapine.[108]

DISCUSSION

The evidence for handling the discussed side effects is sparse and is based largely on published case reports and rational deduction. Psychiatrists should be aware that discontinuing clozapine may have severe consequences, such as psychotic relapse and suicidal behavior, which underscores the importance of psychiatrists' knowledge of appropriate strategies for managing clozapine side effects and of their ability to determine when it is safe to continue clozapine. It is noteworthy that the discontinuation cases described in many of the studies have since been shown to be prompted by unwarranted alarm over relatively harmless side effects.

As the mechanisms behind many of these side effects are largely unknown, it is difficult to determine the best time to discontinue clozapine treatment. Many of the side effects, eg, abnormal liver function and neutropenia, are often transient and benign in nature, whereas, in other cases, the effects can progress to life-threatening conditions, such as liver failure or agranulocytosis. Unfortunately, the course of these side effects is unpredictable, leaving the psychiatrist with no other option than to discontinue clozapine treatment and then reinitiate clozapine when parameters have stabilized. Other side effects are more clearly handled because discontinuation is the only option (eg, agranulocytosis, myocarditis, cardiomyopathy) or because the effects are harmless and should not lead to discontinuation (eg, benign hyperthermia, benign leukocytosis or neutrophilia, eosinophilia, idiopathic sinus tachycardia, seizures).

Many of the side effects are idiosyncratic, with no dose dependency, such as agranulocytosis and myocarditis, whereas some dose dependency exists for others, such as tachycardia and seizure. For the latter, it is important to remember that clozapine is susceptible to several pharmacokinetic interactions that may change plasma levels and contribute to toxic clozapine levels. Smoking cessation is the most important one because of the high prevalence of smoking among patients with schizophrenia. Plasma clozapine levels may in extreme cases increase by 80% and have in some cases caused seizures.[109] Infection and inflammation can also cause extreme plasma levels.[110,111] In these conditions, dose reduction will solve the problem. Furthermore, the addition of medications that are strong cytochrome P450 inhibitors, such as fluvoxamine or ketoconazole, can also significantly increase clozapine levels.

When discontinuation of clozapine has been decided, the dosage should be tapered off over a period of weeks to months, depending on variables such as size of the dosage, psychotic symptoms, and the duration of treatment. Only in cases of agranulocytosis, myocarditis, or other severe medical conditions should treatment be terminated abruptly, as abrupt discontinuation increases the risk of rebound psychosis and anticholinergic withdrawal symptoms. The latter can be avoided by adding an anticholinergic drug as a temporary substitution, followed by a gradual tapering of the

clozapine dose.[15] Guidance on the best antipsychotic drug replacement is more difficult, as clozapine patients have typically failed to respond to several other antipsychotic drugs. Some case reports[112] of agranulocytosis and neutropenia have raised concern that replacement with olanzapine could prolong the neutropenia period due to olanzapine's chemical similarity with clozapine, while other case reports[113] have demonstrated that olanzapine could be used safely during clozapine-induced agranulocytosis. In conclusion, olanzapine currently seems to have the best evidence for preventing rebound psychosis or withdrawal psychosis.

This review has several limitations. Foremost, high-quality data on specific side effects, risk factors, and the most effective management strategies are scarce. Most of the cited evidence is based on small samples, uncontrolled observations, and clinical guidelines rather than randomized controlled trials or population-based register studies. Furthermore, this overview is selective, as it was intended to cover only the most common pitfalls of clozapine therapy. Therefore, it should be stressed that additional conditions not covered in this review may occur, in which case psychiatrists are recommended to seek assistance from colleagues who have greater experience with clozapine, from the published literature, or from physicians in the corresponding medical specialties.

Clearly, since clozapine is such a valuable resource for a substantial subgroup of treatment-refractory patients with psychotic disorders, further study of the development, trajectory, and best management of serious clozapine-related side effects and of appropriate grounds for clozapine discontinuation is warranted.

Drug names: aripiprazole (Abilify), bupropion (Wellbutrin, Aplenzin, and others), clozapine (Clozaril, FazaClo, and others), fluvoxamine (Luvox and others), gabapentin (Neurontin, Gralise, and others), ketoconazole (Ketozole, Nizoral, and others), lamotrigine (Lamictal and others), lithium (Lithobid and others), lorcaserin (Belviq), metformin (Glucophage, Fortamet, and others), naltrexone (Vivitrol, ReVia, and others), olanzapine (Zyprexa and others), phentermine (Adipex-P, Suprenza, and others), topiramate (Topamax and others), valproate sodium (Depacon and others), ziprasidone (Geodon and others).

Disclosure of off-label usage: The authors have determined that, to the best of their knowledge, aripiprazole, bupropion, and topiramate are not approved by the US Food and Drug Administration for minimizing clozapine-induced weight gain, and lithium is not approved for increasing absolute neutrophil count.

Author affiliations: Centre for Schizophrenia, Aalborg Psychiatric Hospital, Aalborg University Hospital, Aalborg, Denmark (Dr Nielsen); Division of Psychiatry Research (Dr Correll), Department of Medical Services (Dr Manu), and Department of Psychiatry (Dr Kane), The Zucker Hillside Hospital, Glen Oaks, New York; Departments of Psychiatry and Molecular Medicine (Drs Correll and Kane) and Department of Medicine (Dr Manu), Hofstra North Shore–Long Island Jewish School of Medicine, Hempstead, New York; and Universitatea Transilvania, Brasov, Romania (Dr Manu).

Financial disclosure: **Dr Nielsen** has received research support from Pfizer and has received speakers or advisory board honoraria from AstraZeneca, Bristol-Myers Squibb, HemoCue, and Lundbeck. **Dr Correll** has received grant/research support from Bristol-Myers Squibb, Ortho-McNeil/Janssen/Johnson & Johnson, and Otsuka; has been a consultant to Alexza, AstraZeneca, Bristol-Myers Squibb, Eli Lilly, Genentech, Gerson Lehrman Group, Intra-Cellular Therapies, Lundbeck, MedAvante, Pfizer, Otsuka, Roche, Takeda, Teva, and Vanda; has been a member of the speakers or advisory boards for Actelion, Alexza, AstraZeneca, Bristol-Myers Squibb, Intra-Cellular Therapies, MedAvante, Merck, Novartis, Otsuka, Pfizer, and Sunovion; and has received honoraria from Bristol-Myers Squibb, Cephalon, Ortho-McNeil/Janssen/Johnson & Johnson, Medscape, Otsuka, ProPhase, Takeda, Teva, and Vanda. **Dr Kane** has received grant support from the National Institute of Mental Health; has been a consultant to Alkermes, Amgen, Bristol-Myers Squibb, Eli Lilly, Intra-Cellular Therapies, Janssen, Johnson & Johnson, Lundbeck, Merck, Novartis, Otsuka, Pfizer, Pierre Fabre, Proteus, Roche, and Sunovion; and is a stock shareholder of and has received honoraria from MedAvante. **Dr Manu** has no personal affiliations or financial relationships with any commercial interest to disclose relative to the article.
Funding/support: None reported.

REFERENCES

1. Nielsen J, Nielsen RE, Correll CU. Predictors of clozapine response in patients with treatment-refractory schizophrenia: results from a Danish Register Study. *J Clin Psychopharmacol*. 2012;32(5):678–683.
2. Kane J, Honigfeld G, Singer J, et al. Clozapine for the treatment-resistant schizophrenic. a double-blind comparison with chlorpromazine. *Arch Gen Psychiatry*. 1988;45(9):789–796.
3. Azorin JM, Spiegel R, Remington G, et al. A double-blind comparative study of clozapine and risperidone in the management of severe chronic schizophrenia. *Am J Psychiatry*. 2001;158(8):1305–1313.
4. Conley RR, Kelly DL, Richardson CM, et al. The efficacy of high-dose olanzapine versus clozapine in treatment-resistant schizophrenia: a double-blind crossover study. *J Clin Psychopharmacol*. 2003;23(6):668–671.
5. Leucht S, Corves C, Arbter D, et al. Second-generation versus first-generation antipsychotic drugs for schizophrenia: a meta-analysis. *Lancet*. 2009; 373(9657):31–41.
6. Meltzer HY, Alphs L, Green AI, et al; International Suicide Prevention Trial Study Group. Clozapine treatment for suicidality in schizophrenia: International Suicide Prevention Trial (InterSePT). *Arch Gen Psychiatry*. 2003;60(1):82–91.
7. Chengappa KN, Vasile J, Levine J, et al. Clozapine: its impact on aggressive behavior among patients in a state psychiatric hospital. *Schizophr Res*. 2002; 53(1–2):1–6.

8a. Ciapparelli A, Dell'Osso L, Bandettini di Poggio A, et al. Clozapine in treatment-resistant patients with schizophrenia, schizoaffective disorder, or psychotic bipolar disorder: a naturalistic 48-month follow-up study. *J Clin Psychiatry*. 2003;64(4):451–458.

8b. Nielsen J, Kane JM, Correll CU. Real-world effectiveness of clozapine in patients with bipolar disorder: results from a 2-year mirror-image study. *Bipolar Disord*. 2012;14(8):863–869.

9. Pollack S, Woerner MG, Howard A, et al. Clozapine reduces rehospitalization among schizophrenia patients. *Psychopharmacol Bull*. 1998;34(1):89–92.
10. Angermeyer MC, Löffler W, Müller P, et al. Patients' and relatives' assessment of clozapine treatment. *Psychol Med*. 2001;31(3):509–517.
11. Merrill DB, Ahmari SE, Bradford JM, et al. Myocarditis during clozapine treatment. *Am J Psychiatry*. 2006;163(2):204–208.
12. Taylor DM, Douglas-Hall P, Olofinjana B, et al. Reasons for discontinuing clozapine: matched, case-control comparison with risperidone long-acting injection. *Br J Psychiatry*. 2009;194(2):165–167.
13. Nielsen J, Meyer JM. Risk factors for ileus in patients with schizophrenia. *Schizophr Bull*. 2012;38(3):592–598.
14. Fontaine KR, Heo M, Harrigan EP, et al. Estimating the consequences of anti-psychotic induced weight gain on health and mortality rate. *Psychiatry Res*. 2001;101(3):277–288.
15. Seppälä N, Kovio C, Leinonen E. Effect of anticholinergics in preventing acute deterioration in patients undergoing abrupt clozapine withdrawal. *CNS Drugs*. 2005;19(12):1049–1055.
16. Krivoy A, Malka L, Fischel T, et al. Predictors of clozapine discontinuation in patients with schizophrenia. *Int Clin Psychopharmacol*. 2011;26(6):311–315.
17. Pai NB, Vella SC. Reason for clozapine cessation. *Acta Psychiatr Scand*. 2012; 125(1):39–44.
18. Whiskey E, Wykes T, Duncan-McConnell D, et al. Continuation of clozapine treatment: practice makes perfect. *Psychiatr Bull*. 2003;27(6):211–213.
19. Munro J, O'Sullivan D, Andrews C, et al. Active monitoring of 12,760 clozapine recipients in the UK and Ireland: beyond pharmacovigilance. *Br J Psychiatry*. 1999;175(6):576–580.
20. Moeller FG, Chen YW, Steinberg JL, et al. Risk factors for clozapine discontinuation among 805 patients in the VA hospital system. *Ann Clin Psychiatry*. 1995;7(4):167–173.
21. Nielsen J, Damkier P, Lublin H, et al. Optimizing clozapine treatment. *Acta Psychiatr Scand*. 2011;123(6):411–422.
22. Nielsen J, Dahm M, Lublin H, et al. Psychiatrists' attitude towards and knowledge of clozapine treatment. *J Psychopharmacol*. 2010;24(7):965–971.
23. Manu P, Sarpal D, Muir O, et al. When can patients with potentially life-threatening adverse effects be rechallenged with clozapine? a systematic review of the published literature. *Schizophr Res*. 2012;134(2–3):180–186.
24. Lindström LH. The effect of long-term treatment with clozapine in schizophrenia: a retrospective study in 96 patients treated with clozapine for

up to 13 years. *Acta Psychiatr Scand*. 1988;77(5):524–529.
25. Nielsen J, Graff C, Kanters JK, et al. Assessing QT interval prolongation and its associated risks with antipsychotics. *CNS Drugs*. 2011;25(6):473–490.
26. Nielsen J, Andersen MP, Graff C, et al. The effect of sertindole on QTD and TPTE. *Acta Psychiatr Scand*. 2010;121(5):385–388.
27. Kang UG, Kwon JS, Ahn YM, et al. Electrocardiographic abnormalities in patients treated with clozapine. *J Clin Psychiatry*. 2000;61(6):441–446.
28. Merrill DB, Dec GW, Goff DC. Adverse cardiac effects associated with clozapine. *J Clin Psychopharmacol*. 2005;25(1):32–41.
29. Ronaldson KJ, Fitzgerald PB, Taylor AJ, et al. A new monitoring protocol for clozapine-induced myocarditis based on an analysis of 75 cases and 94 controls. *Aust N Z J Psychiatry*. 2011;45(6):458–465.
30. Ronaldson KJ, Fitzgerald PB, Taylor AJ, et al. Clinical course and analysis of ten fatal cases of clozapine-induced myocarditis and comparison with 66 surviving cases. *Schizophr Res*. 2011;128(1–3):161–165.
31. Bray A, Reid R. Successful clozapine rechallenge after acute myocarditis. *Aust N Z J Psychiatry*. 2011;45(1):90.
32. Ronaldson KJ, Fitzgerald PB, Taylor AJ, et al. Observations from 8 cases of clozapine rechallenge after development of myocarditis. *J Clin Psychiatry*. 2012;73(2):252–254.
33. Testani M Jr. Clozapine-induced orthostatic hypotension treated with fludrocortisone. *J Clin Psychiatry*. 1994;55(11):497–498.
34. Low PA, Singer W. Management of neurogenic orthostatic hypotension: an update. *Lancet Neurol*. 2008;7(5):451–458.
35. Stryjer R, Timinsky I, Reznik I, et al. Beta-adrenergic antagonists for the treatment of clozapine-induced sinus tachycardia: a retrospective study. *Clin Neuropharmacol*. 2009;32(5):290–292.
36. Marinkovic D, Timotijevic I, Babinski T, et al. The side-effects of clozapine: a four year follow-up study. *Prog Neuropsychopharmacol Biol Psychiatry*. 1994;18(3):537–544.
37. Rakovec P. Treatment of inappropriate sinus tachycardia with ivabradine. *Wien Klin Wochenschr*. 2009;121(21–22):715–718.
38. Ketch J, Herd A, Ludwig L. ST segment elevations without myocardial infarction in a patient on clozapine. *Am J Emerg Med*. 1996;14(1):111–112.
39. Low RA Jr, Fuller MA, Popli A. Clozapine induced atrial fibrillation. *J Clin Psychopharmacol*. 1998;18(2):170.
40. Amital D, Gross R, Amital H, et al. Coexistence of eosinophilia and agranulocytosis in a clozapine-treated patient. *Br J Psychiatry*. 1997;170:194.
41. Fong SY, Au Yeung KL, Tosh JM, et al. Clozapine-induced toxic hepatitis with skin rash. *J Psychopharmacol*. 2005;19(1):107.
42. Ames D, Wirshing WC, Baker RW, et al. Predictive value of eosinophilia for neutropenia during clozapine treatment. *J Clin Psychiatry*. 1996;57(12):579–581.
43. Lucht MJ, Rietschel M. Clozapine-induced eosinophilia: subsequent neutropenia and corresponding allergic mechanisms. *J Clin Psychiatry*. 1998;59(4):195–197.
44. Duggal HS, Singh I. Psychotropic drug–induced neutropenia. *Drugs Today (Barc)*. 2005;41(8):517–526.
45. Duggal HS, Singh I. Re: late-onset neutropenia with clozapine [letter]. *Can J Psychiatry*. 2006;51(2):125. Author reply: 125–126.
46. Small JG, Weber MC, Klapper MH, et al. Rechallenge of late-onset neutropenia with clozapine. *J Clin Psychopharmacol*. 2005;25(2):185–186.
47. Thompson A, Girishchandra B, Castle D, et al. Late onset neutropenia with clozapine. *Can J Psychiatry*. 2004;49(9):647–648.
48. Tamam L, Kulan E, Ozpoyraz N. Late onset neutropenia during clozapine treatment. *Psychiatry Clin Neurosci*. 2001;55(5):547–548.
49. Hummer M, Kurz M, Barnas C, et al. Transient neutropenia induced by clozapine. *Psychopharmacol Bull*. 1992;28(3):287–290.
50. McKee JR, Wall T, Owensby J. Impact of complete blood count sampling time change on white blood cell and absolute neutrophil count values in clozapine recipients. *Clin Schizophr Relat Psychoses*. 2011;5(1):26–32.
51. Esposito D, Chouinard G, Hardy P, et al. Successful initiation of clozapine treatment despite morning pseudoneutropenia. *Int J Neuropsychopharmacol*. 2006;9(4):489–491.
52. Rajagopal S. Clozapine, agranulocytosis, and benign ethnic neutropenia. *Postgrad Med J*. 2005;81(959):545–546.
53. Spencer BW, Williams HR, Gee SH, et al. Granulocyte colony stimulating factor (G-CSF) can allow treatment with clozapine in a patient with severe benign ethnic neutropaenia (BEN): a case report. *J Psychopharmacol*. 2012;26(9):1280–1282.
54. Whiskey E, Taylor D. Restarting clozapine after neutropenia: evaluating the possibilities and practicalities. *CNS Drugs*. 2007;21(1):25–35.
55. Flanagan RJ, Dunk L. Haematological toxicity of drugs used in psychiatry. *Hum Psychopharmacol*. 2008;23(suppl 1):27–41.
56. Brunoni AR, Kobuti Ferreira LR, Gallucci-Neto J, et al. Lithium as a treatment of clozapine-induced neutropenia: a case report. *Prog Neuropsychopharmacol Biol Psychiatry*. 2008;32(8):2006–2007.
57. Kutscher EC, Robbins GP, Kennedy WK, et al. Clozapine-induced leukopenia successfully treated with lithium. *Am J Health Syst Pharm*. 2007;64(19):2027–2031.
58. Hägg S, Rosenius S, Spigset O. Long-term combination treatment with clozapine and filgrastim in patients with clozapine-induced agranulocytosis. *Int Clin Psychopharmacol*. 2003;18(3):173–174.
59. Schulte PF. Risk of clozapine-associated agranulocytosis and mandatory white blood cell monitoring. *Ann Pharmacother*. 2006;40(4):683–688.
60. Nielsen J, Thode D, Stenager E, et al. Hematological clozapine monitoring with a point-of-care device: a randomized cross-over trial. *Eur Neuropsychopharmacol*. 2012;22(6):401–405.
61. Tharyan P. Is monitoring of platelets necessary during clozapine therapy? *Indian J Psychiatry*. 1999;41(3):263–264.
62. Mahendran R. Leukopenia and thrombocytopenia induced by clozapine. *Hong Kong J Psychiatry*. 2002;12(3):19–20.
63. Lambertenghi Deliliers G. Blood dyscrasias in clozapine-treated patients in Italy. *Haematologica*. 2000;85(3):233–237.
64. Focosi D, Azzarà A, Kast RE, et al. Lithium and hematology: established and proposed uses. *J Leukoc Biol*. 2009;85(1):20–28.
65. Hampson ME. Clozapine-induced thrombocytosis. *Br J Psychiatry*. 2000;176(4):400.
66. Sopko MA, Caley CF. Chronic leukocytosis associated with clozapine treatment. *Clin Schizophr Relat Psychoses*. 2010;4(2):141–144.
67. Madhusoodanan S, Cuni L, Brenner R, et al. Chronic leukocytosis associated with clozapine: a case series. *J Clin Psychiatry*. 2007;68(3):484–488.
68. Popli A, Pies R. Clozapine and leukocytosis. *J Clin Psychopharmacol*. 1995;15(4):286–287.
69. Nielsen J, Boysen A. Clozapine treatment associated with increased risk of acute myeloid leukemia (AML). *Schizophr Res*. 2010;123(2–3):270–272.
70. De Hert M, Detraux J, van Winkel R, et al. Metabolic and cardiovascular adverse effects associated with antipsychotic drugs. *Nat Rev Endocrinol*. 2012;8(2):114–126.
71. Correll CU, Lencz T, Malhotra AK. Antipsychotic drugs and obesity. *Trends Mol Med*. 2011;17(2):97–107.
72. Caemmerer J, Correll CU, Maayan L. Acute and maintenance effects of non-pharmacologic interventions for antipsychotic associated weight gain and metabolic abnormalities: a meta-analytic comparison of randomized controlled trials. *Schizophr Res*. 2012;140(1–3):159–168.
73. Maayan L, Vakhrusheva J, Correll CU. Effectiveness of medications used to attenuate antipsychotic-related weight gain and metabolic abnormalities: a systematic review and meta-analysis. *Neuropsychopharmacology*. 2010;35(7):1520–1530.
74. Gallego JA, Nielsen J, De Hert M, et al. Safety and tolerability of antipsychotic polypharmacy. *Expert Opin Drug Saf*. 2012;11(4):527–542.
75. Nielsen J, Skadhede S, Correll CU. Antipsychotics associated with the development of type 2 diabetes in antipsychotic-naïve schizophrenia patients. *Neuropsychopharmacology*. 2010;35(9):1997–2004.
76. Henderson DC, Nguyen DD, Copeland PM, et al. Clozapine, diabetes mellitus, hyperlipidemia, and cardiovascular risks and mortality: results of a 10-year naturalistic study. *J Clin Psychiatry*. 2005;66(9):1116–1121.
77. Cohen D. Atypical antipsychotics and new onset diabetes mellitus: an overview of the literature. *Pharmacopsychiatry*. 2004;37(1):1–11.
78. Cohen D, Correll CU. Second-generation antipsychotic-associated diabetes mellitus and diabetic ketoacidosis: mechanisms, predictors, and screening need. *J Clin Psychiatry*. 2009;70(5):765–766.
79. Raja M. Clozapine safety, 35 years later. *Curr Drug Saf*. 2011;6(3):164–184.
80. Henderson DC, Cagliero E, Copeland PM, et al. Elevated hemoglobin A1c as a possible indicator of diabetes mellitus and diabetic ketoacidosis in schizophrenia patients receiving atypical antipsychotics. *J Clin Psychiatry*. 2007;68(4):533–541.
81. Lowe CM, Grube RR, Scates AC. Characterization and clinical management of clozapine-induced fever. *Ann Pharmacother*. 2007;41(10):1700–1704.
82. Tham JC, Dickson RA. Clozapine-induced fevers and 1-year clozapine discontinuation rate. *J Clin Psychiatry*. 2002;63(10):880–884.
83. Martin A. Acute pancreatitis associated with clozapine use. *Am J Psychiatry*. 1992;149(5):714.
84. Catalano G, Catalano MC, Frankel Wetter RL. Clozapine induced polyserositis. *Clin Neuropharmacol*. 1997;20(4):352–356.
85. Friedberg JW, Frankenburg FR, Burk J, et al. Clozapine-caused eosinophilic colitis. *Ann Clin Psychiatry*. 1995;7(2):97–98.
86. Nielsen J, Foldager L, Meyer JM. Increased use of antibiotics in patients treated with clozapine. *Eur Neuropsychopharmacol*. 2009;19(7):483–486.
87. Nielsen J, Bruhn AM. Atypical neuroleptic malignant syndrome caused by olanzapine. *Acta Psychiatr Scand*. 2005;112(3):238–240. Discussion: 240.
88. Baciewicz AM, Chandra R, Whelan P. Clozapine-associated neuroleptic malignant syndrome. *Ann Intern Med*. 2002;137(5 pt 1):374.
89. Jönsson AK, Spigset O, Hägg S. Venous thromboembolism in recipients of antipsychotics: incidence, mechanisms and management. *CNS Drugs*. 2012;26(8):649–662.

90. Rondla S, Crane S. A case of clozapine-induced paralytic ileus. *Emerg Med J*. 2007;24(2):e12.
91. Palmer SE, McLean RM, Ellis PM, et al. Life-threatening clozapine-induced gastrointestinal hypomotility: an analysis of 102 cases. *J Clin Psychiatry*. 2008;69(5):759–768.
92. Fitzsimons J, Berk M, Lambert T, et al. A review of clozapine safety. *Expert Opin Drug Saf*. 2005;4(4):731–744.
93. Flanagan RJ, Ball RY. Gastrointestinal hypomotility: an under-recognised life-threatening adverse effect of clozapine. *Forensic Sci Int*. 2011;206(1–3):e31–e36.
94. Macfarlane B, Davies S, Mannan K, et al. Fatal acute fulminant liver failure due to clozapine: a case report and review of clozapine-induced hepatotoxicity. *Gastroenterology*. 1997;112(5):1707–1709.
95. Thatcher GW, Cates M, Bair B. Clozapine-induced toxic hepatitis. *Am J Psychiatry*. 1995;152(2):296–297.
96. Luo D, McColl P, Walmsley R. Acute onset of ascites with clozapine-induced hepatitis. *Intern Med J*. 2007;37(3):204–205.
97. Hummer M, Kurz M, Kurzthaler I, et al. Hepatotoxicity of clozapine. *J Clin Psychopharmacol*. 1997;17(4):314–317.
98. Stine JG, Lewis JH. Drug-induced liver injury: a summary of recent advances. *Expert Opin Drug Metab Toxicol*. 2011;7(7):875–890.
99. Berk M, Fitzsimons J, Lambert T, et al. Monitoring the safe use of clozapine: a consensus view from Victoria, Australia. *CNS Drugs*. 2007;21(2):117–127.
100. Markowitz JS, Grinberg R, Jackson C. Marked liver enzyme elevations with clozapine. *J Clin Psychopharmacol*. 1997;17(1):70–71.
101. Eggert AE, Crismon ML, Dorson PG, et al. Clozapine rechallenge after marked liver enzyme elevation. *J Clin Psychopharmacol*. 1994;14(6):425–426.
102. Erdogan A, Kocabasoglu N, Yalug I, et al. Management of marked liver enzyme increase during clozapine treatment: a case report and review of the literature. *Int J Psychiatry Med*. 2004;34(1):83–89.
103. Devinsky O, Honigfeld G, Patin J. Clozapine-related seizures. *Neurology*. 1991;41(3):369–371.
104. Freudenreich O, Weiner RD, McEvoy JP. Clozapine-induced electroencephalogram changes as a function of clozapine serum levels. *Biol Psychiatry*. 1997;42(2):132–137.
105. Wong J, Delva N. Clozapine-induced seizures: recognition and treatment. *Can J Psychiatry*. 2007;52(7):457–463.
106. Muzyk A, Gala G, Kahn DA. Use of lamotrigine in a patient with a clozapine-related seizure. *J Psychiatr Pract*. 2010;16(2):125–128.
107. Usiskin SI, Nicolson R, Lenane M, et al. Gabapentin prophylaxis of clozapine-induced seizures. *Am J Psychiatry*. 2000;157(3):482–483.
108. Jarbin H, Johansson BA, Lundgren J. Clozapine and therapy-refractory epileptic seizures. *Eur Child Adolesc Psychiatry*. 2001;10(3):209–210.
109. Meyer JM. Individual changes in clozapine levels after smoking cessation: results and a predictive model. *J Clin Psychopharmacol*. 2001;21(6):569–574.
110. Haack MJ, Bak ML, Beurskens R, et al. Toxic rise of clozapine plasma concentrations in relation to inflammation. *Eur Neuropsychopharmacol*. 2003;13(5):381–385.
111. Jecel J, Michel TM, Gutknecht L, et al. Toxic clozapine serum levels during acute urinary tract infection: a case report. *Eur J Clin Pharmacol*. 2005; 60(12):909–910.
112. Sayin A, Cosar B. Prolongation of clozapine-induced leukopenia with olanzapine treatment. *Prog Neuropsychopharmacol Biol Psychiatry*. 2006; 30(5):958–959.
113. Tollefson GD, Birkett MA, Kiesler GM, et al; The Lilly Resistant Schizophrenia Study Group. Double-blind comparison of olanzapine versus clozapine in schizophrenic patients clinically eligible for treatment with clozapine. *Biol Psychiatry*. 2001;49(1):52–63.

Posttest

To obtain credit, go to PSYCHIATRIST.COM (Keyword: June) to take this Posttest and complete the Evaluation online.

1. You prescribed clozapine a few months ago for Mr A because of his treatment resistance and aggression. He has developed flu-like symptoms, fatigue, and dyspnea. An electrocardiogram shows ST-segment elevation, and you diagnose myocarditis. What is the *best* management strategy, according to available evidence and expert opinion?

a. Lower the dose of clozapine and monitor troponin levels
b. Discontinue clozapine and rechallenge later, while monitoring troponin levels
c. Discontinue clozapine and do not rechallenge
d. Continue clozapine at the same dose

2. You prescribed clozapine 3 years ago for Ms B because of her treatment resistance and suicidal ideation. Both her schizophrenia and her suicidality improved. Blood monitoring shows that she has suddenly developed an absolute neutrophil count of 1,200/μL. You rule out morning pseudoneutropenia and benign ethnic neutropenia. What is the *best* management strategy for Ms B's neutropenia, according to available evidence and expert opinion?

a. Interrupt clozapine treatment until the absolute neutrophil count is normal, and then resume clozapine with increased monitoring
b. Lower the dose of clozapine and add lithium and granulocyte colony–stimulating factor
c. Keep the clozapine regimen the same unless agranulocytosis develops
d. Discontinue clozapine and do not rechallenge

3. Mr C began taking clozapine 6 years ago. Although his schizophrenia has been controlled better than with any other antipsychotic he took previously, his waistline has increased and he has developed hypertriglyceridemia. You consult with Mr C's medical specialist about the options. Among the following management strategies, which one should be avoided if possible, according to available evidence and expert opinion?

a. Be sure that Mr C is taking the lowest dose of clozapine that is effective for his symptoms
b. Encourage him to walk more and replace processed foods with fresh foods when possible
c. Try adjunctive treatment with metformin, topiramate, or aripiprazole
d. Discontinue clozapine

4. Which of the following statements about clozapine and hepatic impairment is *false*?

a. Abnormal liver function tends to occur during the first months of clozapine treatment and is transient in the majority of cases
b. Up to 40% of patients taking clozapine experience icteric hepatitis
c. Symptoms such as rash, malaise, or jaundice should always prompt liver function measurement
d. Increases in transaminase levels to 2 to 3 times the upper limit of normal usually warrant clozapine discontinuation, but dose reduction or temporary disruption of treatment may resolve the problem