Treatment-Resistant Schizophrenia: Definition, Predictors, and Therapy Options

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Schizophrenia is a severe, lifelong disorder that affects cognitive, behavioral, and emotional functioning.[1] It is ranked among the 25 leading causes of disability worldwide.[2] Many individuals with schizophrenia experience numerous relapses and ongoing impairment, and less than 15% of individuals achieve functional recovery.[3] In this Academic Highlights, Drs Correll and Howes address treatment-resistant schizophrenia (TRS), including its definition, risk factors, and treatment strategies.

EARLY PREDICTORS AND IDENTIFICATION OF TREATMENT-RESISTANT SCHIZOPHRENIA

More than 20 million people—0.7%–1.0% of the world population—have schizophrenia.[4] Despite the existence of more than 60 antipsychotic treatments globally,[5] all of which currently target hyperdopaminergia in the brain via postsynaptic dopamine receptor blockade, 20%–30% of patients with schizophrenia are resistant to treatment.[6–8]

Definition of Treatment Resistance

Dr Correll explained that TRS has been defined in different ways. A literature review[9] by the Treatment Response and Resistance in Psychosis (TRRIP) Group examined 42 TRS studies and found that only half (n = 21) identified their definition for treatment resistance. However, international treatment guidelines[10–13] align on a broad definition of TRS as requiring nonresponse to at least 2 antipsychotic trials of sufficient dose and duration. The core criteria for TRS are a correct diagnosis of schizophrenia, adequate treatment, and nonresponse to that treatment.

The TRRIP Group's definition of adequate treatment[9] is a trial of two antipsychotics for ≥ 6 weeks each at a dose equivalent to ≥ 600 mg of chlorpromazine daily. Adherence must be measured by at least two sources at ≥ 80% of the prescribed doses, and, ideally, plasma drug levels should be measured at least once. Long-acting injectable treatment can also be used to insure adherence.

Response to treatment should be measured by a rating scale such as the Positive and Negative Syndrome Scale (PANSS) or the Clinical Global Impression (CGI) assessment.[9] Inadequate response is defined as ongoing symptoms and functional impairment of moderate or greater severity, such as delusions, hallucinations, conceptual disorganization, and disorganized behavior.

Although currently available antipsychotics largely have efficacy for only positive symptoms, agents with efficacy for

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The activity was chaired by **Christoph U. Correll, MD,** Zucker School of Medicine at Hofstra/Northwell, Hempstead, New York, and the faculty member was **Oliver D. Howes, MD, PhD**, Institute of Psychiatry, Psychology and Neuroscience, King's College, London, UK.

CME Objective

After studying this article, you should be able to:

- Provide evidence-based therapy for resistant schizophrenia, with appropriate monitoring

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negative and cognitive symptoms are emerging.[14] Dr Correll said that the TRIPP Group has prepared an additional definition of TRS to encompass those domains.[9]

Predictors of Treatment Resistance

Dr Correll identified several factors associated with poor response to antipsychotic treatment.

Demographic factors. Antipsychotic treatment resistance is more likely in male patients with a family history of psychosis or illness onset at an early age.[15,16]

Clinical and premorbid characteristics. Patients with TRS often have a longer duration of untreated psychosis, longer illness duration, and more severe negative symptoms.[15] A symptom combination associated with TRS is pronounced levels of conceptual disorganization, difficulty in abstract thinking, and unusual thought content.[17] The presence of extrapyramidal symptoms early in treatment is a risk factor for TRS, as is a greater number of relapses related to nonadherence and substance misuse.[15,16] Other TRS indicators may include obstetric complications, poor premorbid social adjustment, and lack of illness insight.[16,18,19]

Neurobiological markers. Dr Correll named several markers that may predict TRS: enlarged third and lateral ventricles in the brain, decreased cortical thickness, decreased brain lateralization, non-elevated dopamine levels, low cerebrospinal fluid catecholamine levels, excessive neurologic soft signs, decreased mitogen-induced lymphocyte proliferation, a low number of total T and T-helper cells, and the presence of antibrain antibodies in the serum.[20–22]

Clinical Course

According to Dr Correll, there are two types of TRS.[23,24] Primary TRS is present from the beginning of antipsychotic treatment. Secondary TRS occurs in patients who initially respond to antipsychotics but become resistant over time.

Dr Correll described a study[23] of 246 patients with first-episode schizophrenia who were followed for 5 years. In the total sample, 23% of patients (n = 56) had primary TRS. Those who experienced onset of psychosis before age 20 years were more likely to meet criteria for TRS during the study. The relationship between early age at onset and TRS was significant among Black and male patients.

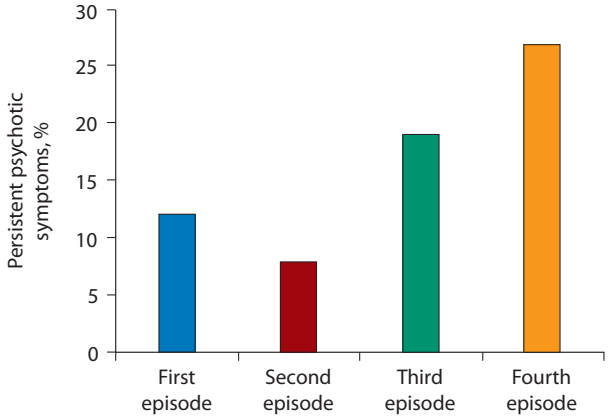
Another study[24] followed 239 patients for approximately 5 years after their first episode of schizophrenia. In this group, 56 patients (25.2%) had primary (or early) TRS, and 24 patients (12.6%) developed secondary (or late) TRS.

During the illness course, the occurrence of multiple relapses is a risk factor for secondary TRS. Dr Correll listed several studies that have demonstrated a correlation between multiple relapses and reduced response of positive symptoms to subsequent antipsychotic treatment.[25–27] In a small study (N = 82) by Wiersma and colleagues[25] over 15 years, results indicated that, on average, 1 in 6 patients (range, 8%–27%) did not remit following each episode (Figure 1).

More recent research by Takeuchi et al[27] in a larger sample (N = 130) also demonstrated a reduction in response to treatment following relapse and a longer time to response. Takeuchi noted that all patients took the same antipsychotic for their second episode as for the first episode, but at higher doses. In the sample, the proportions of patients reaching at least 50% response after 7 weeks were 49% following the first episode and 10% following the second episode.

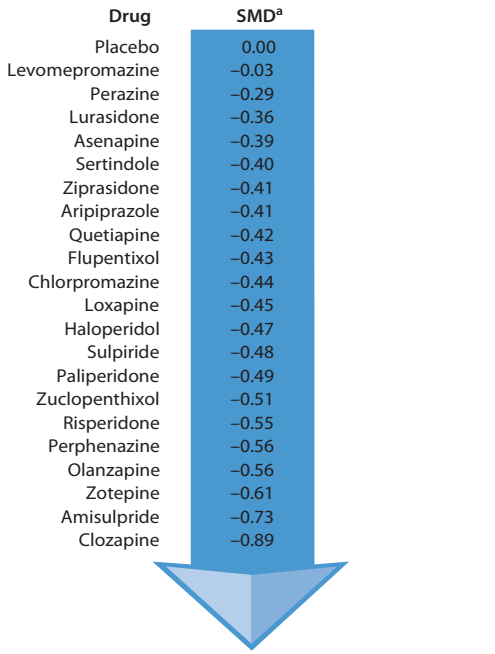
Dr Correll considered that, since the dopamine system is the primary target of all current antipsychotic

Figure 1. Rate of Lack of Remission Following Psychotic Episodes



Data from Wiersma et al.[25]

Figure 2. Overall Change in Symptoms With Antipsychotics Compared With Placebo



Data from Huhn et al.[30]
[a]Effect sizes are presented as standardized mean difference (SMD).

treatments, primary TRS may be related to dysfunction in neurotransmitters other than dopamine. Secondary TRS may be associated with inherent disease processes or relapse.[22]

Patient Perspectives

An individual living with schizophrenia discusses her relapses and recovery:

"I had my first psychosis when I was 19. … A year later I stopped my meds and had another psychosis and month-long hospital stay. Both my hospitalizations were involuntary.…

"Thankfully I found a medication I could tolerate. I fought with hallucinations for years. At my first job I didn't talk to anyone for 6 months. I had to relearn how to commutate [communicate]. People didn't react well when I told them I had schizophrenia, so I learned to hide it. …

"The last time I had a relapse, I was told by the doctor, every time I have one, the harder it is to come back. My mom forced me to take my medication. She would watch me take it. Over the years I gained enough insight to know I need meds. Psychosis is my biggest fear. I never want to end up in that state of mind again."[28]

Clinical Points

- Up to 30% of patients with schizophrenia are resistant to treatment. Primary TRS is present from the beginning of treatment, while patients with secondary TRS initially respond to antipsychotics but become resistant over time.
- Treatment response rates decrease following each relapse.
- Although definitions of TRS vary among studies, national and international guidelines align on a broad definition that requires inadequate response to at least two antipsychotic trials of sufficient dose and duration.
- Response to treatment should be measured by a rating scale such as the PANSS or CGI assessment; inadequate response is the presence of ongoing symptoms and functional impairment of moderate or greater severity.

THERAPEUTIC OPTIONS FOR TREATMENT-RESISTANT SCHIZOPHRENIA

Dr Howes began his presentation by noting that multiple national and international guidelines recommend clozapine for treating TRS after adequate trials of two other antipsychotic treatments have been unsuccessful.[9] Several recommend that at least 1 of the antipsychotic trials be an atypical or second-generation agent (other than clozapine).[9]

Clozapine Efficacy and Clinical Outcomes

Dr Howes discussed a seminal study[29] that established clozapine's importance in treating TRS. Patients who had not responded to at least 4 antipsychotics were randomly assigned to receive clozapine or chlorpromazine for 6 weeks. Among those receiving clozapine, 30% of patients responded, and among those receiving chlorpromazine, 4% responded.

A 2019 network meta-analysis[30] of placebo-controlled and head-to-head randomized controlled trials compared 32 oral antipsychotics (Figure 2). Among 402 studies, effect size estimates suggested that all antipsychotics reduced overall symptoms more than placebo (although not statistically significantly so for 6 drugs). The standardized mean differences ranged from −0.89 (95% CI, −1.08 to −0.71) for clozapine to −0.03 (−0.59 to 0.52) for levomepromazine (40,815 participants). Another meta-analysis examined trials that compared clozapine to other antipsychotics in patients with and without TRS. Clozapine

was superior to other antipsychotics in improving total and positive (but not negative) symptoms for both TRS and nonresistant schizophrenia.[31] In studies that defined TRS more rigorously, clozapine was superior for positive, but not total or negative, symptoms. Furthermore, in a meta-analysis[32] of 63 cohort studies (N = 109,341), clozapine was also superior to other second-generation antipsychotics in the prevention of hospitalization and all-cause discontinuation, despite the fact that patients started on clozapine had greater illness severity.

Epidemiologic studies show that clozapine reduces the risk of suicide in patients with schizophrenia. In one recent study, clozapine was the only antipsychotic (among 10) that significantly reduced the risks of attempted or completed suicide.[33] A recent meta-analysis of studies lasting 1 to 12 years showed that the mortality rate with clozapine is about 44% lower than that with other antipsychotics when used continuously.[34]

Alternatives to Clozapine

Dr Howes stated that alternative strategies to clozapine for TRS are not strongly supported by evidence.[35,36] He noted that some clinicians augment the first antipsychotic with a second antipsychotic or with a mood stabilizer such as sodium valproate.

A meta-analysis[37] compared studies of antipsychotic monotherapy versus polypharmacy. Although the investigators found evidence of a significant reduction in symptoms when a second antipsychotic was added, these findings were from open-label and low-quality studies. Double-blind and high-quality studies showed no significant benefit from augmentation with a second antipsychotic.

Meta-analyses[38,39] have also examined augmentation of antipsychotic treatment with sodium valproate. Again, the investigators found significantly greater improvement for the augmentation strategy only in low-quality, open-label trials and not in randomized, controlled trials.

Timing of Clozapine Use

According to Dr Howes, patients who initiate clozapine after longer illness duration are less likely to respond.[40] In a nationwide Danish database study[41] of 633 patients with schizophrenia initiating clozapine treatment, independent predictors of shorter time to hospitalization included increasing numbers of different antipsychotics and admissions prior to first clozapine prescription, earlier onset of schizophrenia, and lower clozapine dose. Additionally, a chart review examined response rates of 90 patients with TRS who had taken clozapine for at least 3 months.[42] The researchers analyzed outcomes by time to clozapine initiation and found a predictive cutoff of 2.8 years. Patients who began taking clozapine earlier than 2.8 years from TRS onset had an 82% response rate, but patients with initiation after 2.8 years had a 31% response rate.

In 2003, a study reported that the average time between identification of TRS and initiation of clozapine was 5 years.[43] This study was repeated in 2012 and found a delay of 4 years.[44] Both studies found that, despite guideline recommendations, polypharmacy or high-dose antipsychotic monotherapy strategies were commonly attempted prior to clozapine use, a finding that was replicated in a survey[7] of 204 US psychiatrists. A review of studies in multiple countries showed delays averaging between 1 and 14 years prior to clozapine initiation.[45]

A study[46] of patients with first-episode schizophrenia demonstrated benefit from initiating clozapine early in the illness course, ie, after 24 weeks of nonresponse to first-line treatment. Initial treatment was either olanzapine or risperidone.[46] Patients who did not respond by 12 weeks were offered the other first-line antipsychotic, and those who did not respond after 12 more weeks were offered clozapine. After the first 12 weeks, 75% of patients had responded to olanzapine or risperidone. Of those who did not, 17% of patients who initiated the other first-line therapy responded. Of those who still had nonresponse and began taking clozapine at week 24, 75% responded.

Clinical Barriers

Evidence and guidelines support earlier initiation of clozapine for TRS than typically occurs in clinical practice. Dr Howes said that this incongruity indicates the presence of barriers to clozapine initiation.

Failure to recognize TRS. A systematic review[47] of barriers to clozapine use found concern about identifying suitable candidates. Clinicians should routinely, actively assess patients with schizophrenia for inadequate response to treatment.

Lack of experience or confidence. Clozapine requires gradual titration and is associated with serious potential side effects requiring active management.[48] According to Dr Howes, clinicians who are inexperienced in managing patients on clozapine treatment might hesitate to recommend it for these reasons.[49]

Lack of resources. During initiation of clozapine, patients must be seen often to adjust dosing and monitor for side effects.[50] Resources are required for blood sampling, which may inhibit some clinicians from initiating clozapine. Surveys[51,52] of practitioners indicate a need for staffing and clear processes.

Removing Clinical Barriers

Dr Howes recommends a model[53] in which a dedicated team assesses patients for treatment resistance and manages initiation, titration, and ongoing use of clozapine treatment. This dedicated team becomes a repository of experience in clozapine treatment, which diminishes or eliminates barriers related to recognition, experience, confidence, and resources.

Patient-Related Barriers and Solutions

Blood monitoring. Dr Howes noted that some patients decline clozapine initiation because of the blood testing required.[54] To alleviate these concerns, he suggested

several approaches including a numbing agent, fingerstick or butterfly sampling, low-dose benzodiazepine, minimizing the number of blood tests, or behavioral approaches to help desensitize patients with fear of needles.

Lack of patient/caregiver knowledge. Patients and their care partners may have concerns about potential adverse effects and may not know if clozapine would be helpful to them.[54] When patients decline clozapine, Dr Howes recommends educating them about the evidence supporting clozapine, including alleviation of symptoms and reduced risk of mortality, to help them make an informed decision.[11] Dr Howes recommends informing patients and caregivers about the possible side effects and reassuring them that many clozapine side effects subside after the first few weeks of treatment.

Incapacity. Some patients are incapable of making an informed decision due to psychosis. In these cases, Dr Howes suggested initiation with intramuscular clozapine, which is not a long-term solution because it requires daily injections. However, it enables patients to experience therapeutic benefits and then make an informed decision regarding clozapine continuation. Dr Howes cited a recent retrospective study[55] of 39 patients who were given intramuscular clozapine after initial nonadherence to oral medication; 92% of these patients were successfully transferred to oral clozapine.

Principles for Initiating Clozapine

Start low and go slow. When initiating clozapine, Dr Howes advises starting with a low dose and increasing gradually because clozapine affects many neurologic receptors that cause side effects.[50] By increasing the dosage slowly, the clinician can monitor for side effects and the patient can adjust more easily to the medication.[11] Therapeutic dose monitoring personalizes the treatment and is cost-effective.[50]

Use the lowest effective dose. Monitor symptoms carefully during the gradual increase in clozapine dosage. Response is usually seen with doses from 150 to 900 mg/d.[35] When an effective level is reached, maintain that level to avoid the side effects that may occur at higher doses.

Monitor for and manage side effects. Because the titration phase takes time, patients might experience side effects sooner than they perceive therapeutic benefit.[11] Patients may experience side effects that cause them to discontinue medication without discussing it with their clinician. Therefore, it is important to frequently ask the patient about side effects using a tool such as the Glasgow Antipsychotic Side Effect Scale.[56] Proactive side-effect management helps make clozapine treatment as tolerable to the patient as possible and as safe as possible.[48,50]

Plasma Clozapine Level Monitoring

To measure the clozapine level in a patient's plasma, perform the test at trough levels, either just before the patient's next dose is due or after omitting a dose.[11]

In most patients, efficacy is greatest when plasma clozapine levels exceed 350 µg/L, although this level is not universal.[11,35] Doses at which the target plasma level is reached may vary between 250 mg/d for a female nonsmoker to 550 mg/d for a male smoker.[35]

The relationship between clozapine dose and subsequent plasma levels varies widely between patients and is influenced by several factors. Because smoking affects enzymes in the liver that metabolize clozapine, smokers may require higher doses of clozapine than nonsmokers.[11] Plasma clozapine levels are generally greater at lower doses in patients with heavy caffeine consumption than in nonusers, in women than in men, in obese vs non-obese people, in those with inflammation (including COVID-19 infection) vs without inflammation, and in older individuals than young patients.[11,50] Patients taking certain enzyme inhibitors also require lower doses of clozapine.[35]

Patient Perspectives

A patient who struggled to achieve relief from persistent hallucinations describes how clozapine changed her life:

"I tried paliperidone, aripiprazole, ziprasidone, and olanzapine, but with little symptom relief. The voices broke through. . . . It seemed as though nothing would take them away. . . .

"After 12 months of failed medication trials, my new psychiatrist introduced me to an older medication called clozapine. . . . He cautioned that the drug could cause me to gain 50 or even 100 pounds. But despite that risk, I knew I had to try it.

"Over the next few weeks . . . the residual voices became quieter. Once again, I was able to read, study, and retain the information I read. My mind became clearer than it had been in years. . . .

"At 6 months, I was going out into the community and making friends. At one year, I made plans to return to college. After 18 months, I enrolled in a university class . . . , earned an A grade, and went on to graduate. . . .

"Today, I have been in full recovery without relapse for over 10 years, thanks to clozapine. . . . I feel slightly sedated at times, and I sleep a few more hours every night, but I have left the symptoms of schizophrenia in my past."[57]

Side Effect Mitigation

Many of the side effects associated with clozapine are caused by its effects on various neurologic receptors.[58] Although many side effects can subside over time, others sometimes persist. Risk evaluation and mitigation strategies have been developed and should be used according to different countries' recommendations.[50,59]

Sedation. Because clozapine has a high affinity for histamine receptors, sedation is common during the first 3 months.[60] If it is problematic, Dr Howes advises either slowing the titration until the sedation subsides or prescribing a single daily dosage in the evening.[11] If the patient takes other sedative medications such as benzodiazepines or antihistamines, they might be discontinued.

Hypersalivation. Another common adverse effect of clozapine is hypersalivation, which often subsides after a few months but may persist in some patients.[35] Hypersalivation can cause embarrassment, discomfort, and an increased risk of aspiration pneumonia. Solutions include chewing sugarless gum during the day and elevating the head of the bed or pillows at night.[11,35]

Hypotension or hypertension. During the first few weeks of clozapine therapy, patients may experience hypotension and should be advised to stand up slowly and increase fluid intake.[35] Similarly, hypertension is common and may require hypotensive therapy. With either condition, the rate of titration should be as slow as possible, or dose reduction may be necessary.[11,35]

Tachycardia and other cardiac complications. Tachycardia usually subsides after a few weeks of treatment but persists in some patients.[11,35] The clinician should check for other cardiac symptoms—particularly myocarditis, which is a rare but potentially fatal complication of clozapine treatment.[50] Dr Howes stressed the importance of stopping clozapine and referring the patient for urgent assessment by a cardiologist if myocarditis is suspected.[35]

Sustained tachycardia increases the risk of cardiomyopathy.[35] If tachycardia persists, Dr Howes advised 24-hour heart rate monitoring, even if the patient is asymptomatic, while reducing the clozapine dose and slowly titrating again.[11,35] Patients can be encouraged to decrease other drugs that might affect heart rate (eg, nicotine, caffeine). If tachycardia continues, a β-blocker can be used, but treatment is typically not indicated unless symptoms are present or heart rate is substantially higher than 120 bpm because other side effects such as orthostatic hypotension may occur.[11]

Seizure. Clozapine doses exceeding 500 mg/d, high plasma levels (exceeding 500 µg/L), and rapid dose escalation are associated with a risk of seizure.[11,35] For patients taking high doses or with a high plasma level, a prophylactic anticonvulsant agent can be prescribed.[35] If the patient has experienced myoclonus, the threshold for seizure may be lowered. In this case, the clinician should either lower the clozapine dose or prescribe a prophylactic anticonvulsant.[61]

If seizure occurs, check the patient's plasma clozapine levels, stop clozapine for 24 hours, and restart it at a lower dose (approximately 50% of the previously prescribed dose) with a supplementary antiepileptic, typically valproic acid.[35]

Constipation. Clozapine's antimuscarinic effect reduces gastrointestinal motility. Constipation usually subsides after the first few weeks of treatment but may persist in some patients. Because it can become severe, causing bowel obstruction, perforation, or toxic megacolon,[62] Dr Howes advised asking the patient about this side effect weekly during initiation of clozapine and regularly thereafter.

Dr Howes recommended advising the patient to increase intake of dietary fiber and water, increase exercise, and use an osmotic or stimulant laxative, stool softener, and/or bulk-forming agent.[11,35]

Case Practice Questions

Discussion of the best responses can be found at the end of the activity.

Case: Renee is a 19-year-old female smoker. At age 16 years, she had an episode of depression, was successfully treated, and has not experienced any subsequent mood episodes. At age 18 years, Renee had a 3-month decline in functioning: she developed delusions that teachers were instructing her to travel to Africa as part of a spiritual mission and that she would be in danger if she remained at home; she also began hearing voices of teachers talking about her and began to believe they could control her thoughts. Renee was found acting bizarrely at the airport trying to get a flight to Nigeria with no ticket or money and was subsequently admitted to the hospital.

She was treated with oral olanzapine up to 20 mg/d, which was well tolerated, and she was discharged to her parents' home. Although her delusions are now held less tenaciously, Renee continues to be distressed by auditory hallucinations and passivity phenomena.

Question 1: After 2 months of olanzapine treatment, Renee's symptoms persist. What would you do?

a. Augment olanzapine treatment with sodium valproate.

b. Discontinue olanzapine and switch to paliperidone.

c. Initiate clozapine treatment.

Question 2: Renee's olanzapine was switched to oral paliperidone, and then injectable paliperidone, titrated to 150 mg/mo. She tolerates this treatment but continues to experience symptoms over the next 4 months. What treatment is the most reasonable choice for Renee at this stage?

a. Increase the injectable paliperidone dose to 200 mg/mo

b. Switch to chlorpromazine

c. Initiate clozapine treatment

Question 3: Clozapine is initiated and slowly titrated. At 300 mg/d, Renee is tolerating clozapine well, but she remains symptomatic. What would you do next, based on evidence?

a. Increase clozapine to 600 mg/d.

b. Augment with valproate.

c. Check plasma clozapine levels weekly, titrate clozapine until plasma levels exceed 350 µg/L, and then reassess.

d. Check plasma clozapine levels weekly, titrate clozapine until plasma levels exceed 500 µg/L, and then reassess.

Nocturnal enuresis. Dr Howes advises asking patients about nocturnal enuresis because they may be too embarrassed to mention it themselves. Strategies for managing nocturnal enuresis include reducing the evening dose of clozapine, restricting fluid intake in the evening, scheduled nighttime toileting, and voiding the bladder twice before bed.[35] If these strategies fail, Dr Howes recommended desmopressin nasal spray, but the patient's sodium levels must be monitored.[35]

Weight gain. According to a recent meta-analysis, patients initiating clozapine gain an average of about 3 kg after a median duration of 6 weeks (range, 2–13 weeks).[63] Weight gain is associated with decreased self-esteem, reduced quality of life, and increased morbidity and mortality, and it is among the most common causes of patient nonadherence.[64] Because of these serious issues, Dr Howes stressed the importance of measuring patients' weight weekly when initiating clozapine.[35] Prevention is easier than reversing weight gain, and patients should be counseled about exercise and healthy dietary habits.[11]

Some off-label strategies may also help mitigate weight gain, including adding the lowest effective dose of aripiprazole (5–15 mg/d) or metformin (500–2,000 mg/d).[35,65,66] Patients taking metformin must have their vitamin B_{12} levels checked yearly due to its association with vitamin B_{12} deficiency.[35]

Agranulocytosis. The risk of fatal agranulocytosis was initially overestimated, and clinicians may remain hesitant to use clozapine due to concern about this adverse effect.[11] However, with monitoring of white blood cell (or neutrophil) count, the risk is manageable.[50] Agranulocytosis occurs in 0.8% of patients taking clozapine, and 80% of cases occur within 18 weeks of clozapine initiation.[35,67] A recent meta-analysis[68] found an overall prevalence of death by agranulocytosis in clozapine patients of 0.05%. Although rare, this side effect's mortality risk requires weekly blood monitoring during the first 18–26 weeks of clozapine treatment followed by biweekly or monthly blood monitoring, each based on different, country-level recommendations[69]; clinicians should advise patients to seek medical help promptly if infection symptoms such as cough or fever occur.[35] Some individuals have benign ethnic neutropenia.[11]

CONCLUSION

Schizophrenia is a severe, lifelong disorder that affects cognitive, behavioral, and emotional functioning. Unfortunately, many patients experience primary or secondary treatment resistance, and relapses increase the risk of future treatment resistance. When a patient fails to respond after two antipsychotic treatments of sufficient dosage and duration, guidelines worldwide identify clozapine as the best treatment option. Although side effects are common, many subside weeks or months after initiation of clozapine treatment, and those that persist can generally be managed. By starting with a low dosage, titrating gradually, and monitoring plasma clozapine levels, the lowest effective dose can be identified while minimizing side effects.

Clinical Points

- Guidelines worldwide recognize clozapine as the most effective treatment for TRS. Limited evidence from poor quality studies supports alternatives like augmentation with a second antipsychotic or sodium valproate.
- Clozapine response rates are higher when it is initiated earlier in the course of illness.
- Side effects are common, particularly in the first few weeks, and require proactive assessment, intervention, and reassurance to patients.
- Plasma leukocyte and granulocyte levels must be monitored weekly during the first 18–26 weeks of treatment, the time of greatest risk for agranulocytosis, and regularly thereafter according to country regulations.
- Plasma clozapine levels can be helpful in identifying the adequate target dose, and levels are higher relative to the dose in women, nonsmokers, and those with heavy caffeine use.

Discussion of Case Practice Questions

Question 1: Preferred response is b. Discontinue olanzapine and switch to paliperidone.

Augmentation with sodium valproate is a strategy for TRS that is not well supported by research, and it is possible that Renee does not have TRS. The patient has been treated with only one antipsychotic medication, but guidelines require two sequential antipsychotic treatments to fail before clozapine is initiated. Therefore, olanzapine should be discontinued and paliperidone or another first-line antipsychotic should be prescribed before clozapine is considered.

Question 2: Preferred response is c. Initiate clozapine treatment.

Two antipsychotic trials have been attempted for a sufficient duration, and the most recent was a long-acting injectable, which allows the treatment team to rule out covert nonadherence as a contributor to insufficient response. Since Renee continues to experience symptoms, according to guidelines, she meets criteria for having TRS and should initiate clozapine treatment. Rather than waiting to start clozapine treatment until other antipsychotic trials have been conducted, the chance of efficacy with clozapine is greater the sooner it is started.

Question 3: Preferred response is c. Check plasma clozapine levels weekly, titrate clozapine until plasma levels exceed 350 µg/L, and then reassess.

Although Renee is a woman, which might mean a lower dose of clozapine would offer a therapeutic benefit, she is also a smoker, and smokers generally require higher doses of clozapine than nonsmokers. Guidelines state that clozapine efficacy is typically greater when plasma levels exceed 350 µg/L.[11,35] Continue to titrate gradually if the patient continues to experience symptoms, but to reduce the risk of seizures and other side effects, the plasma clozapine level should remain below 500 µg/L.

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Disclosure of off-label usage: Dr Correll has determined that, to the best of his knowledge, no investigational information about pharmaceutical agents or device therapies that is outside US Food and Drug Administration–approved labeling has been presented in this activity.

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Posttest

To obtain credit, go to PSYCHIATRIST.COM to complete the Posttest and Evaluation.

1. Raoul is a 25-year-old man. Almost 2 years ago, he developed persecutory delusions that his girlfriend was an imposter sent to harm him, and he experienced auditory hallucinations. He was diagnosed with schizophrenia. Medication trials included aripiprazole, risperidone, and ziprasidone, but symptoms persisted despite adequate doses and assured adherence. After transitioning to clozapine 3 months ago, Raoul's symptoms have improved substantially. He is now able to attend a day care program and he often helps with the family shop. You regularly monitor symptoms and side effects. His mother reports that Raoul experiences auditory hallucinations only at night when he is alone in his room; he is often heard talking to himself but is no longer concerned with his ex-girlfriend. Raoul is taking 425 mg/d of clozapine and complains of being tired during the day, and he has experienced 2 kg weight gain. He has not moved his bowels for 4 days. You note that his pulse is 120 bpm, and he has no cardiac symptoms. What do you do first?

a. Address the constipation first because it can progress rapidly and result in bowel obstruction, which can be fatal.

b. Because weight gain is a common reason for people stopping clozapine, refer Raoul to a dietician and an exercise program, if available; add metformin 500 mg/day and titrate to 1000 mg twice daily.

c. For asymptomatic tachycardia, Raoul should receive 24-hour heart rate monitoring and treatment with a β-blocker.

d. Because full response to clozapine can take 6 months or more, talk with Raoul and his mother about continued symptom monitoring for auditory hallucinations while he is taking a therapeutic dose.