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This ACADEMIC HIGHLIGHTS section of *The Journal of Clinical Psychiatry* presents the highlights of the teleconference series “The Schizophrenia Remission Roller Coaster: Using Long-Acting Injectable Antipsychotics to Improve Adherence and Enhance Potential for Functional Recovery,” which was held in September and October 2019. This report was prepared and independently developed by the CME Institute of Physicians Postgraduate Press, Inc., and was supported by educational grants from Alkermes, Inc.; Otsuka America Pharmaceutical, Inc. and Lundbeck.

The teleconference was chaired by **Christoph U. Correll, MD**, Department of Psychiatry, The Zucker Hillside Hospital, Glen Oaks, and Department of Psychiatry and Molecular Medicine, Donald and Barbara Zucker School of Medicine at Hofstra/Northwell, Hempstead, New York, USA; and Department of Child and Adolescent Psychiatry, Charité Universitätsmedizin, Berlin, Germany. The faculty was **John Lauriello, MD**, Sidney Kimmel Medical College, Thomas Jefferson University, Philadelphia, Pennsylvania.

CME Objective

After studying this article, you should be able to:

- Select evidence-based treatment for patients with schizophrenia who often relapse

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Using Long-Acting Injectable Antipsychotics to Enhance the Potential for Recovery in Schizophrenia

Christoph U. Correll, MD, and John Lauriello, MD

The goals of schizophrenia treatment are to control symptoms, prevent relapse, and improve functioning and quality of life. For many patients, these goals are not being met.¹ Evidence demonstrates that long-acting injectable (LAI) antipsychotics are one of the most effective ways to prevent relapse in patients with schizophrenia, yet they remain underused.² Health care providers infrequently discuss LAI antipsychotic options with their patients with schizophrenia. Clinicians also may overestimate adherence or not even assess it.³ Patients with multiple relapses are often continued on oral medications, and few clinicians consider LAIs early in the course of illness.²

This report, based on a series of teleconferences given by Christoph U. Correll, MD, and John Lauriello, MD, will address the impact of relapse in patients with schizophrenia, patient-centered assessment, treatment options, and psychosocial interventions.

IMPACT OF RELAPSE

Schizophrenia is a complex disorder that is characterized by positive and negative symptoms.^{1,4} Positive symptoms include hallucinations and delusions. Negative symptoms consist of lack of motivation, reduction in feeling pleasure, affective blunting, alogia, avolition, and anhedonia.⁵ In addition to these symptoms, schizophrenia is associated with cognitive dysfunction, mood problems, and a high suicide rate.⁶⁻⁸

The onset of schizophrenia does not typically occur until late adolescence or early adulthood, stated Dr Lauriello.⁹ Throughout the course of the disease, patients tend to experience relapses and remissions, with each relapse potentially leading to further deterioration.³

Relapse: Definition, Impact, and Predictors

The definition of relapse in patients with schizophrenia varies among studies. In a large

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Review Process

The faculty member(s) agreed to provide a balanced and evidence-based presentation and discussed the topic(s) and CME objective(s) during the planning sessions. The faculty's submitted content was validated by CME Institute staff, and the activity was evaluated for accuracy, use of evidence, and fair balance by the Chair and a peer reviewer who is without conflict of interest.

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systematic literature review, Olivares et al¹⁰ found that hospitalization was the most widely used factor to define relapse across studies. Other factors included scores on rating scales that assess symptom severity (in particular, positive symptoms), such as the Positive and Negative Syndrome Scale (PANSS)¹¹ and the Clinical Global Impression (CGI) scale.¹² Exacerbation or re-emergence of symptoms was the next most common definition of relapse.¹⁰

Relapses are associated with long-term symptoms and disability,¹³ and with each relapse, patients have decline in brain function¹⁴ and are at a higher risk of attempting suicide.¹⁵ With multiple relapses, patients may have a less complete treatment response^{16,17} and a substantially longer time to remission.¹⁸

A representative from Schizophrenia and Related Disorders Alliance of America (SARDA) interviewed a patient with schizophrenia (oral communication, December 2019), who talked about the impact of his last relapse:

**Patient Perspectives**

"I had my relapse and they put me back in the hospital. I was working at that time, and I had the relapse while I was still working and they put me in the hospital and of course, I lost my job."

Predictors of relapse in patients with schizophrenia include poor social functioning at baseline,¹⁴ male sex, and nonadherence to antipsychotic medications.¹⁹ Patients with better social functioning at baseline have a more favorable course.²⁰ Relapse is also associated with younger age and earlier onset of illness, more severe symptoms, and substance use disorder.²¹ Overall, modifiable risk factors for poor outcomes in patients with schizophrenia include longer duration of untreated illness, comorbid substance abuse, and early nonresponse to an antipsychotic, as well as the number of relapses that are related to nonadherence.²²

The Role of Nonadherence in Relapse

Dr Lauriello explained that nonadherence is a major contributor to relapse in schizophrenia, and it often starts early in the course of treatment. In a 1-year follow-up study²³ of 56 male patients with first-episode schizophrenia, 54% discontinued their medications, and 70% of these patients relapsed. A systematic review²⁴ found that 77% of nonadherent patients relapsed within the first year of treatment, while only 3% of adherent patients relapsed within the first year of treatment.

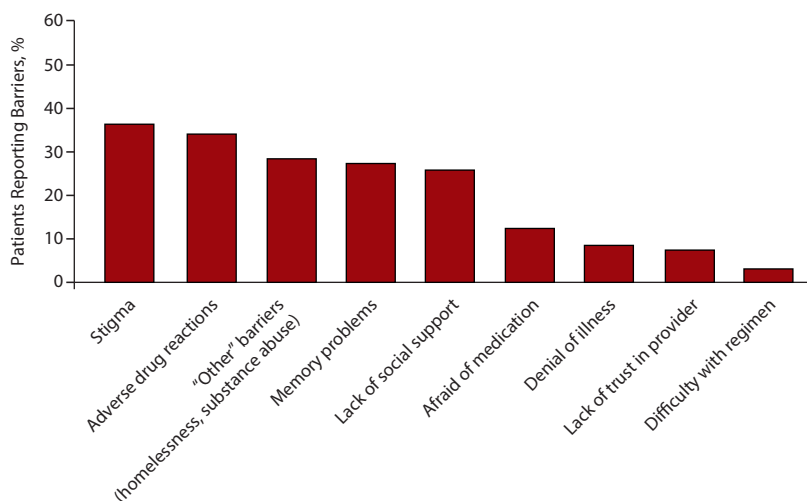
Influences on and obstacles to adherence. Several factors influence treatment adherence, including patient-related, illness-related, medication-related, clinician-related, and environmental factors.³ Illness factors that affect whether patients take their medications include positive symptoms, disorganization, and lack of insight.^{25,26} Other factors that influence adherence include the effectiveness and side effects of the treatment, the patient's relationship with the treating clinician, the treatment setting (inpatient or outpatient), and caregiver and social support.^{25,26}

Hudson et al²⁷ examined self-reported barriers to adherence in a cohort of inpatients and outpatients with schizophrenia (Figure 1). The most common barrier reported by patients was stigma related to having psychosis and having to take antipsychotic medications. In a review²⁸ of 36 articles on nonadherence, problems with illness insight (56%), substance abuse (36%), attitudes toward medications (31%), and medication side effects (28%) were the top cited reasons for antipsychotic nonadherence.

Measuring nonadherence is difficult. Asking the patient or a caregiver if the patient has taken the medications

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Figure 1. Patient-Reported Barriers to Antipsychotic Adherence^a



^aAdapted with permission from Hudson et al.²⁷

as prescribed is quite imprecise.³ Even measuring blood antipsychotic levels as part of therapeutic drug monitoring²⁹ does not adequately capture partial or intermittent nonadherence. Treating a patient with a long-acting antipsychotic, on the other hand, marks the beginning of nonadherence at the moment a person does not return for the injection visit.

A SARDAA representative interviewed the mother of a patient with schizophrenia (oral communication, December 2019), and she noted that lack of illness insight led to her son's longtime nonadherence.



Family Perspectives

"My son was diagnosed with schizophrenia at age 24. From the get-go he was resistant to medication, and he did not believe he was ill. So over the years, he must have been hospitalized at least 12 times. He started on oral medications and eventually ended up on a long-acting antipsychotic."

For more information, see the activity "Prevalence and Impact of Relapse in Patients With Schizophrenia" in this CME series.

PATIENT-CENTERED ASSESSMENT

Dr Correll addressed proposed definitions for response, remission, and recovery; the need for assessing patient-reported outcomes in the clinical setting; and the treatment challenges posed by negative, cognitive, and affective symptoms and adverse effects.

Definitions of Clinical Outcomes

Treatment outcomes in schizophrenia can be divided into categories, including response, remission, and

recovery. *Response* is generally defined as a certain percentage decrease in symptoms compared to baseline, usually measured with the Brief Psychiatric Rating Scale (BPRS)³⁰ or the PANSS.^{31,32} Using any of the appropriate scales, *remission* is defined as a rating of mild or less on 4 positive and 4 negative symptom items, sustained for at least 6 months.³³ Recovery is the most desired treatment outcome. Liberman et al³⁴ defined *recovery* as a period of at least 2 years in which the patient has maintained symptom remission, vocational functioning, independent living, and peer relationships (at least 1 interaction with someone outside the family per week).

Patient-Centered Outcomes and Decision-Making

A comprehensive assessment of the efficacy and impact of care in schizophrenia requires a patient-centered approach to treatment evaluation. In addition to clinical outcomes, clinicians should consider patient-centered treatment aims, including quality of life, health-related quality of life, and functioning.

A patient-centered framework, constructed by Kikkert and Dekker²⁶ and based on the Health Belief Model, provides a first-person perspective on key factors related to patient decision-making. This model suggests that, for patients, taking their medication—or not taking it—is a means to achieving the best possible outcome.²⁶

Positive treatment decisions are tied to patient-defined goals.^{35,36} To help patients make positive treatment decisions, using a combined shared decision-making and motivational interviewing technique is recommended.^{35,37}

Patient-Reported Outcomes

Self-reporting can enhance a patient's feeling of involvement in the treatment process, thereby improving

self-esteem while also providing the clinician with knowledge of the patient's insight into the illness.³¹ A patient-reported outcome (PRO) is a measurement that is directly reported by the patient about his or her health, quality of life, or functional status that is not amended or interpreted by the clinician or anyone else.

Patient-reported outcome measures (PROMs) are the tools or instruments used to measure PROs.³⁸ PROMS can be general in nature or disease-specific and are usually self-completed questionnaires. Multiple PROMS can be used for patients to report on domains relevant to schizophrenia.³¹ (For more information on PROM scales, see the activity "Using Patient-Centered Assessment in Schizophrenia Care: Defining Recovery and Discussing Concerns and Preferences" in this CME series.)



Case Practice Question

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

Case 1. Karl is a 24-year-old patient with schizophrenia since he was 19 years old; he lives with his parents. Karl had been stable on oral risperidone 3 mg/d. He stopped this medication unbeknownst to his psychiatrist and parents. He has started to hear voices again and has become very suspicious of two neighbors. Karl's parents bring him to your psychiatric office seeking help to avoid a full relapse and rehospitalization. You discover that he stopped the medication due to sexual side effects and "brain fog." Which is NOT an evidence-based argument that you could offer Karl and his parents that he should consider trying a long-acting injectable (LAI) antipsychotic as his next treatment step?

- LAI significantly reduce the risk for relapse.
- LAI are helpful for treatment-resistant patients.
- LAI reduce the risk of premature death.
- LAI reduce nonadherence rates.

Challenges in Relapse Prevention

Dr Correll stated that relapse prevention and recovery require treatment that (ideally) successfully targets all of the clinical domains of schizophrenia and minimizes adverse effects.⁵ Unfortunately, most pharmacotherapeutic options with demonstrated efficacy address mainly the positive symptoms of the disease and produce adverse events that might contribute to nonadherence.

Positive and negative symptoms. Antipsychotic medications indicated for the treatment of schizophrenia are generally effective at controlling positive symptoms but have limited efficacy against the remaining clinical domains.⁷ Negative symptoms are relatively common and impair functionality.⁵ In an analysis of 1,447 antipsychotic-treated outpatients, approximately 1 in 5 had predominant negative symptoms.³⁹

Patients who exhibit negative symptoms in their first episode of psychosis have lower rates of response, higher

rates of delayed response, higher rates of nonresponse, and higher rates of relapse compared with patients exhibiting positive symptoms.⁴⁰

Cognition. Cognitive dysfunction in schizophrenia affects all cognitive domains⁶ and has an impact on real-world functioning.⁴¹⁻⁴³ Although currently no medications are approved for the treatment of cognitive deficits in schizophrenia, clinicians can address secondary cognitive symptoms to improve patients' functioning and quality of life.⁵

Affective symptoms. Patients with schizophrenia commonly experience affective symptoms, including depression, anxiety, and suicidality, but it can be difficult for clinicians to differentiate negative symptoms from depressive symptoms. An analysis⁴⁴ of patients presenting with symptoms that could be categorized as depressive or negative found that certain symptoms indicated the likelihood of either depression or negative symptoms. Depression in people with schizophrenia is relevant because low mood is a strong predictor of low quality of life⁴⁵ and suicidality.^{26,35}

Adverse events. Side effects of antipsychotics⁴⁶ impact adherence levels,⁴⁷ poor adherence is associated with increased rates of relapse,^{24,48} and relapse prevents recovery.²² Therefore, medication tolerability is the link between effective symptom control, recovery, quality of life, and functional capacity.⁴⁹ The clinician's objective assessment and the patient's subjective perspective are both important when assessing side effects. In a large, nationwide study⁴⁷ of adults with a self-reported diagnosis of schizophrenia, approximately 86% of participants reported experiencing at least 1 side effect.

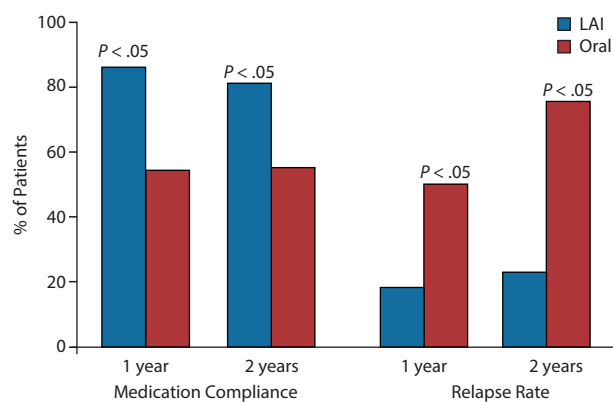
TREATMENT OPTIONS

Dr Correll reviewed existing antipsychotic treatments. (For information on emerging agents, see the activity "Current Treatment Options and Emerging Agents for Schizophrenia" in this CME series.)

A recent network meta-analysis by Huhn et al⁵⁰ analyzed data from 402 randomized, placebo-controlled trials including 53,463 participants to make direct and indirect efficacy and safety comparisons among 32 oral antipsychotics in acute schizophrenia. Seventeen outcomes—8 efficacy and 9 major adverse effect outcomes—were included. Results indicated that clozapine, amisulpride, zotepine, olanzapine, and risperidone may have slightly better total symptom and positive symptom efficacy than others, but these differences were relatively small.⁵⁰ On the other hand, side effect differences were much larger and considered clinically relevant.⁵⁰

Similarly, a meta-analysis⁵¹ of maintenance oral antipsychotic treatment indicated that some antipsychotics have slight symptom advantages compared with others, but the same antipsychotics have clinically relevant side effect burdens. Side effects can impact adherence levels,⁴⁷ and poor adherence is associated with increased rates of

Figure 2. Impact of LAI or Oral Antipsychotic Use on Medication Compliance and Relapse Rate at 1 and 2 Years^a



^aData from Kim et al⁶⁶ and adapted with permission from Stevens et al.⁶⁷
Abbreviation: LAI = long-acting injectable.

relapse.⁴⁸ Novel agents, therefore, are needed to provide broader symptom improvement with fewer tolerability issues.

An example of a novel agent is lumateperone, which is approved by the US Food and Drug Administration (FDA) for the treatment of schizophrenia; it is a partial D₂ agonist presynaptically and a full D₂ antagonist postsynaptically.⁵² Other antipsychotics are either partial agonists or full antagonists on the dopamine receptors both pre- and postsynaptically. Additionally, lumateperone has selective serotonin reuptake inhibition and D₁ receptor modulation-related, proglutamatergic activity.⁵² In 2 controlled studies, lumateperone was superior to placebo as measured by the PANSS total score.^{53,54} One study found similar efficacy for lumateperone and risperidone in total symptom reduction.⁵⁴ However, in a third study with a high placebo response, lumateperone was not superior to placebo on the PANSS total score, while risperidone was.⁵⁵ Risperidone was associated with more adverse effects, which could have partially uncovered treatment assignment. Risperidone also had the highest dropout rate, calling into question whether more poorly responsive patients dropped out early on risperidone.⁵⁶ Across the 3 trials, lumateperone had minimal adverse effects, with sedation/somnolence and dry mouth being present in at least 5% and at twice the rate as with placebo.

Maintenance treatment is strongly suggested in the management of schizophrenia,^{57,58} but a considerable proportion of patients have suboptimal outcomes despite continued treatment.²² However, what appears to be treatment resistance in some patients may actually be the result of poor adherence with the medication regimen. The Treatment Response and Resistance in Psychosis (TRRIP) consensus guidelines⁵⁹ suggest the use of LAI antipsychotics to help ensure adherence and differentiate pseudo-resistance

from true antipsychotic treatment resistance. Although some LAIs must be initiated with a few weeks of oral cotreatment to establish therapeutic plasma levels,² several new LAIs reduce or remove this requirement.⁶⁰

Certain adverse effects are especially problematic for patients. For example, weight gain is often associated with some antipsychotics, particularly olanzapine.⁴⁶ Tardive dyskinesia (TD) is a potentially persistent side effect that can impair function and quality of life.⁶¹ Incidence rates with SGAs are much lower compared with first-generation antipsychotics,⁶¹ but TD can still occur. Two novel vesicular monoamine transporter-2 (VMAT-2) inhibitors—deutetrabenazine and valbenazine—have demonstrated efficacy in (and have received FDA approval for) reducing TD.⁶²



Case Practice Question

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

Case 2. Joseph is a 28-year-old single man who was diagnosed with schizophrenia at the end of his senior year in college. His symptoms were mainly delusions and intermittent hallucinations, which appeared not to respond well to a number of different oral antipsychotics. It was unclear if Joseph took his medications consistently. Prior to his illness, he had been doing well and had been accepted to law school. In the first year of law school, he continued to have symptoms and was unable to complete the year. He has now brought to a new psychiatrist for a second opinion. Which intervention would be the *best* next step?

- Prescribe Joseph clozapine because he is clearly treatment resistant.
- Consider that the diagnosis might not be schizophrenia because the symptoms have not responded well to antipsychotics.
- Give Joseph an LAI antipsychotic to determine if he is truly resistant or if the lack of response is due to nonadherence.
- Consider transcranial magnetic stimulation (TMS).

PATIENT-CENTERED INTERVENTIONS

Dr Lauriello described how clinicians can greatly reduce the risk of relapse in patients with schizophrenia and keep them on the course to recovery using patient-centered care.⁶¹ The collaborative model of care comprises a team-based approach to improve patient care via a partnership between the clinician and the patient.⁶² The clinician's expertise is recognized and valued, but patients ultimately decide which treatment course is best for them.⁶³

Pharmacologic Interventions

Although adherence rates are commonly thought to be higher with atypical than typical antipsychotics, patients are still nonadherent to atypical medications. Dolder and colleagues⁷² used pharmacy refill records to compare medication adherence rates in veterans

receiving typical versus atypical antipsychotics over a 12-month period. Cumulative mean gap ratios were 23.2% for typical and 14.1% for atypical antipsychotics at 12 months. Patients who received typical antipsychotics did not have medication for an average of 7 days per month, and patients who received atypical antipsychotics did not have medication for an average of 4 days per month. Interventions are needed to improve adherence in patients who are receiving atypical antipsychotics.

Long-acting injectable antipsychotics. Guidelines^{63,64} recommend that LAIs should be considered as an alternative to oral formulations of antipsychotics because they provide more reliable drug delivery, reduce peak-trough level differences, and offer greater dosing precision.⁶⁵ Researchers have reported significantly higher medication adherence rates and lower relapse rates with LAIs compared to oral antipsychotics (Figure 2).^{66–69} Additionally, LAIs have been shown to reduce the risk of mortality more than oral antipsychotics compared to no antipsychotic use at all in people with schizophrenia.⁷⁰

Barriers to using LAIs. Unfortunately, despite the many benefits of LAIs, clinicians rarely discuss this option with their patients. One reason for this is that clinicians believe that patients will not be open to treatment with LAIs. Jaeger and Rossler⁷¹ examined the attitudes to LAIs of psychiatrists, patients, and their relatives using a semistructured questionnaire. They found that 67% of patients in the study did not receive information about LAIs from their psychiatrist. Thus, patients' negative attitudes toward LAIs might, at least in part, be related to the low level of information that clinicians provide them.

Another barrier to the use of LAIs is clinicians' misconception that LAIs are only for chronically ill patients. To the contrary, studies suggest that LAI formulations are effective early in the course of treatment or for a first episode of schizophrenia.⁶⁷

Patient-related barriers to using LAIs include fear of injection site pain and a general dislike of receiving injections.⁷¹ Patients may also be concerned that using LAIs will mean that they lose control over taking their medications.

Psychosocial Interventions

When working with patients with schizophrenia, clinicians need to be nonjudgmental, empathic, and proactive in taking a therapeutic stance. Clinicians may be able to change patients' attitudes toward adherence with psychosocial strategies and counseling.

Psychosocial strategies that may improve adherence can be divided into 3 major categories—educational, behavioral, and affective.⁷² Psychoeducation is the education of an individual with mental illness in areas that serve the goals of treatment and rehabilitation. Behavioral strategies address unfavorable patient attitudes toward taking or staying on medications through routine assessment, emphasis on the patient-clinician alliance, and the use of a patient-centered approach to care.

Behavioral strategies that have been proven to be effective in improving adherence include motivational interviewing, cognitive-behavioral therapy, and compliance therapy. Affective strategies address factors such as family support. For more information on psychosocial strategies that may improve adherence, see the activity “Patient-Centered Psychopharmacology and Psychosocial Interventions: Treatment Selection and Shared Decision-Making to Enhance Chances for Recovery” in this CME series.



Clinical Points

- Adopt a patient-centered approach that incorporates the use of patient-reported outcome measures.
- Select medications based on a balanced risk-benefit assessment including the focus on addressing symptoms for which the agents were superior to placebo and/or active controls.
- Consider LAI antipsychotics as an alternative to oral medications, as they offer benefits such as reliable drug delivery, uncovering nonadherence and pseudoresistance, and reduced risk of relapse and mortality.
- Implement psychosocial interventions that have been proven to be effective in improving adherence and overall outcomes.



Discussion of Case Practice Questions

Case 1. Preferred response is b. LAIs are helpful for treatment-resistant patients.

In meta-analyses, LAIs have been shown to reduce the risk of relapse, nonadherence, and mortality in people with schizophrenia compared with placebo and oral antipsychotic treatment. However, while an LAI treatment trial has been suggested by the TRRIP consensus group to rule out pseudoresistance (lack of response due to insufficient medication adherence), the evidence base is lacking that in patients with established treatment resistance, LAIs are the treatment of choice (here, clozapine has the best evidence). Moreover, Karl has not yet failed two adequate trials with an antipsychotic, which would define treatment resistance. He is in the process of relapsing after having stopped his oral antipsychotic medication.

Case 2. Preferred response is c. Give Joseph an LAI antipsychotic to determine if he is truly resistant or if the lack of response is due to nonadherence.

Not responding to antipsychotics does not eliminate the diagnosis; many patients do not respond to specific antipsychotics. Starting Joseph on clozapine is a reasonable option if you are sure he has taken his previous oral antipsychotics. His questionable adherence raises the question of whether he has had adequate trials of any medications. Clozapine is the only proven antipsychotic for treatment resistance, but it has a number of serious side effects and requires blood monitoring. While TMS is an approved treatment for refractory depression and OCD, it is only used off-label for schizophrenia and has mixed results. A trial of an LAI antipsychotic is a good option here because it assures that Joseph is receiving medication, and then you can evaluate whether the medication has any effect.

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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 (Keyword: August CME) to complete the Posttest and Evaluation.

1. You are treating a 47-year-old woman with schizophrenia who has had several relapses in the few years that she has been your patient. Which approach to assessing her medication adherence should you use to achieve the greatest precision?
 - a. Ask the patient if she has taken all of her medications
 - b. Ask the caregiver if the patient has taken all of her medications
 - c. Measure her blood antipsychotic levels
 - d. Try treating her with a long-acting antipsychotic

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