Addressing Patients' Unmet Needs to Improve Outcomes in Schizophrenia

Philip D. Harvey, PhD, and John M. Kane, MD

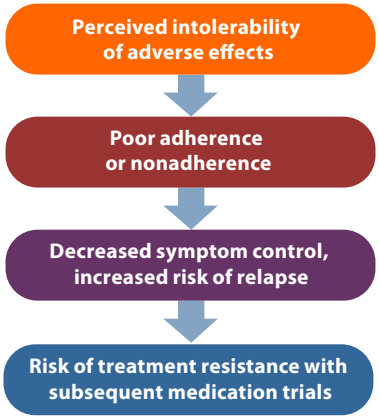
Schizophrenia is a severe, lifelong disorder that affects cognitive, behavioral, and emotional functioning.[1] It is ranked among the top 25 leading causes of disability worldwide.[2] Many individuals with schizophrenia experience numerous relapses and ongoing impairment, and less than 15% of individuals achieve functional recovery.[3] Over the last 70 years, recovery rates and associated disability following a first psychotic episode in patients with schizophrenia have not improved despite regular clinical care.[4]

In this Academic Highlights, Drs Harvey and Kane will address best practices for improving adherence and outcomes for people living with schizophrenia, including lessening the side effect burden and providing comprehensive, patient-centric care.

LESSENING THE SIDE EFFECT BURDEN TO IMPROVE ADHERENCE AMONG INDIVIDUALS WITH SCHIZOPHRENIA

According to Dr Kane, clinicians tend to put great emphasis on symptom resolution and functioning as treatment goals, whereas patients put greater value on well-being and quality of life.[5] Many patients may experience more difficulty with adverse effects (AEs) than clinicians realize, he explained. AEs are a frequent reason for nonadherence to antipsychotic treatment among patients with schizophrenia.[6] Dr Kane stated that poor adherence is associated with an increased risk of relapse, which may be associated with treatment resistance when medication is resumed (Figure 1).[7]

Figure 1. Risks Associated With Intolerable Adverse Effects in Patients Living With Schizophrenia



Based on Kane and Correll.[7]

CME Background
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To obtain credit, read the article, correctly answer the questions in the Posttest, and complete the Evaluation.

This ACADEMIC HIGHLIGHTS section of *The Journal of Clinical Psychiatry* presents the highlights of the teleconference series "Overcoming Adherence Issues and Providing Patient-Centered Care for People Living With Schizophrenia," which was held in October and November 2020. This report was prepared and independently developed by the CME Institute of Physicians Postgraduate Press, Inc., and was supported by an educational grant from Intra-Cellular Therapies, Inc.

The teleconference was chaired by **Philip D. Harvey, PhD**, University of Miami Miller School of Medicine, Florida. The faculty was **John M. Kane, MD**, Zucker School of Medicine at Hofstra/Northwell, Hempstead, New York.

CME Objective
After studying this article, you should be able to:

- Address adverse events that affect adherence in patients with schizophrenia
- Adopt a patient-centered approach to treatment for patients with schizophrenia

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Review Process
The faculty members agreed to provide a balanced and evidence-based presentation and discussed the topics and CME objectives 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.

The opinions expressed herein are those of the faculty and do not necessarily reflect the opinions of the CME provider and publisher or the commercial supporter.

Patient Perspectives

Here, patients living with schizophrenia describe adverse effects with their prescribed antipsychotics, and some consider whether they are balanced by efficacy:

"All antipsychotics cause me an anxiety which isn't there if I am not on meds. It's the kind of anxiety that makes me scared of driving/other people's driving and law and parents' death. I have this fear that something bad will happen that will get me in trouble."[8]

"I can function better I suppose, meaning that what I experience daily with hallucinations are [sic] more easy to ignore (still there though). Delusions and paranoia are almost not there. Sometimes they will come flowing out but it doesn't last long while on the meds. As far as side effects go with the meds, I have almost zero energy every day. I have insomnia and hardly sleep and almost no appetite at all. Due to hardly ever getting hungry, I at times just forget to even eat. The meds has [sic] helped but they are no miracle cure. They cause many other new problems that you have to deal with, and at times the 'cure' is worse then [sic] the illness."[9]

"I struggle with insomnia or sometimes sleep too much to the point it's super hard to get up—no in-between. This is gonna cause a lot of trouble when I do get a job."[9]

"I have gained massive weight . . . and become diabetic. My delusions are improved however."[8]

"All of these medications unfortunately have the potential for negative side effects. I notice a couple side effects like grogginess and more hunger, but the benefits outweigh the negatives for me."[9]

Adverse Effects and Nonadherence

Dr Kane explained that meta-analyses of acute antipsychotic treatment[10] and maintenance antipsychotic treatment[11,12] indicate that, although some agents have symptom efficacy advantages over others, greater differences are found in their clinically relevant side effect profiles. When atypical antipsychotics were first introduced, it was hoped that because they had fewer neurologic side effects than older antipsychotics, they would significantly increase the adherence rate. Yet, Dr Kane stated, nonadherence continues to be an enormous problem.[13,14]

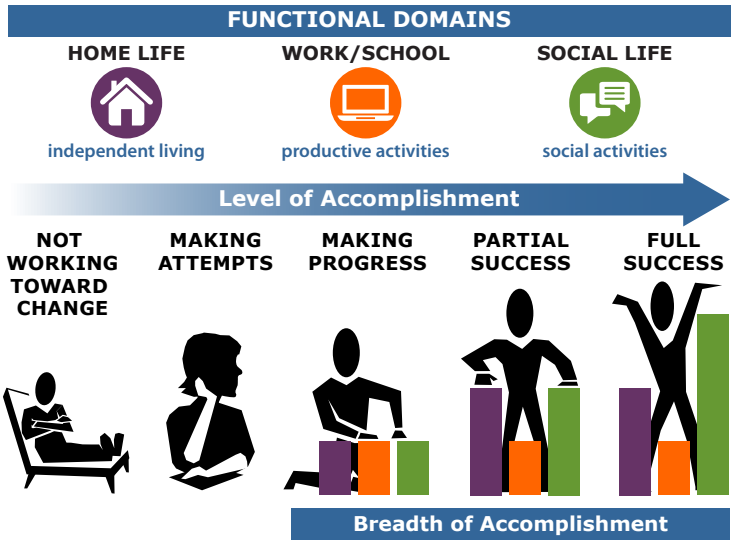
According to data from the CATIE study,[15] which examined the comparative effectiveness of second-generation antipsychotics for 1,493 individuals with schizophrenia, hypersomnia/sleepiness was the most commonly reported AE among patients receiving olanzapine, quetiapine, risperidone, and perphenazine. The rates of treatment discontinuation due to intolerable side effects before the study was completed were 18% with olanzapine, 10% with risperidone, and 15% each with quetiapine, perphenazine, and ziprasidone.

Certain antipsychotic-related AEs are especially problematic for patients. Dr Kane noted that the AE that patients describe as having the most negative impact on their quality of life is weight gain,[16] which is often associated with some antipsychotics, particularly olanzapine. One recent patient survey[17] (N = 200) reported that, while 92% of patients said that their oral antipsychotic treatment improved symptoms and 67% indicated that they needed medication, only half of the patients thought that the antipsychotic did more good than harm. The 3 most commonly reported side effects were anxiety (88%), feeling drowsy or tired (86%), and trouble concentrating (85%).[17] More respondents rated weight gain and sexual dysfunction as extremely or very bothersome than they did other AEs.[17] Dr Kane mentioned that another patient survey,[18] in which only 43% of respondents reported complete adherence, found reduced adherence with the following types of AEs: agitation, extrapyramidal symptoms (EPS), sedation and cognition problems, prolactin and endocrine effects, and metabolic effects.

Adverse Effects and Health Risks

Dr Kane explained that patients with schizophrenia may have health risks related to genetics and lifestyle, meaning that AEs not only can be bothersome to patients but also can exacerbate existing morbidity and mortality risks.[19] Many patients are overweight and smoke, he noted.[20] The Recovery After an Initial Schizophrenia Episode (RAISE) study,[20] which assessed first-episode patients (aged 15 to 40 years) who were treated with antipsychotic drugs for less than 6 months, showed that the patients had a myriad of health concerns. Of the 404 patients, 57% had

Figure 2. Functional Remission Model for Patients With Schizophrenia



Based on Harvey and Bellack.[37]

dyslipidemia, 10% experienced high blood pressure, and 13% had metabolic syndrome. Based on hemoglobin A_{1c} results, 15% were prediabetic, and 3% had diabetes.[20] Because of the short duration of antipsychotic use, these data illustrate that exposure to antipsychotics is not the only factor increasing the risk of health problems.

Techniques for Reducing Adverse Effects

Dr Kane shared that, in his clinical experience, he has found that prescribing the lowest effective dose of antipsychotics may minimize AEs. Both efficacy and AEs may increase as dosage increases.[21] The increase in efficacy diminishes considerably above twice the minimum effective dose.[21,22] In maintenance treatment, he explained that it is important to try using the lowest effective dosage to reduce the risk of AEs and increase the likelihood that patients will adhere to treatment. Dr Kane stated that often in his clinical practice he has seen patients who are receiving higher than necessary doses, which are not associated with greater efficacy but are associated with greater AEs. Additionally, once-daily administration of antipsychotic treatment is not inferior in efficacy to divided doses, and some AEs, such as anxiety and sleepiness, are reduced by using once-daily dosing.[23] Dr Kane also noted that because the newer antipsychotic agents have lower rates of motor, metabolic, cardiovascular, and endocrinal AEs than the older agents,[24,25] patients may find them more tolerable.

Guidelines[26–28] recommend that, in making treatment decisions, clinicians consider medication side effect profiles and patient preferences. With a patient-centered approach, noted Dr Kane, clinicians assess not only patients' degree of adherence but also their reasons for nonadherence. By evaluating patients' concerns about particular AEs, clinicians can make an effort to match treatment regimens to patients' preferences as much as possible so that adherence problems related to AEs might be resolved.

PATIENT-CENTERED TREATMENT STRATEGIES TO IMPROVE OUTCOMES IN SCHIZOPHRENIA

In his presentation, Dr Harvey discussed factors that are associated with successful clinical and functional outcomes in patients with schizophrenia. These factors include a short duration of untreated psychosis,[29] an early response to antipsychotic treatment,[30] a collaborative therapeutic alliance,[31] a supportive family or caregiver,[32] and opportunities to engage in functional activities and specialized interventions.[33]

Defining Remission and Recovery

The Remission in Schizophrenia Working Group (RSWG) developed the first consensus-based criteria[34] for symptom remission as applied to schizophrenia. The RSWG employed the Positive and Negative Syndrome Scale (PANSS),[35] which defines remission as symptom ratings of mild or lower severity (PANSS score ≤ 3) for at least 6 months.[34]

Criteria for functional recovery[36] typically require patients to experience symptom remission, vocational function, independent living, and peer relationships for more than 2 years. According to Dr Harvey, however, in his clinical experience, he finds it critical to view recovery more as a process than an outcome.[37,38] Dr Harvey and his colleague Alan S. Bellack, PhD, created a model for functional remission[37] that delineates domains of functioning as well as levels and breadth of accomplishment across the functional domains (Figure 2). The 3 domains of functioning are independent living,

productive activities, and social life. In these domains, patients may make no attempt at progress or may attempt achievements without success, but they may also reach various levels of accomplishment, including making progress with little success, achieving partial success, and achieving full success. Their breadth of accomplishment describes how many domains in which they are achieving progress or success. When patients are striving to make accomplishments, whether in 1 domain or more, clinicians should view their efforts as important steps in the process toward recovery.

Patient Perspectives

Patients shared their experiences taking steps toward recovery:

"I've seen a steady improvement in my life since starting antipsychotics about a year ago. I started [a medication] last February or so. It worked really well for me overall but around the end of October I had a major episode that lasted for about 2–3 weeks. I didn't think I was ever going to get out of it. My psychiatrist then switched [to another antipsychotic]. I've snapped out of that episode and now I feel like I'm starting to get my life on track. I've been able to hold down a part time job because of it, which has in return been a positive thing for me instead of sitting at home in my head all day."[9]

"I have been working for a year at my job and am doing well. I still have symptoms but weather the storm and am doing fairly well. I don't work full-time though but am able to pay my bills and for my food. I am doing ok and am grateful for the medication. . . . Without medication, I was homeless and severely symptomatic. I learned from my experience of homelessness that I need to be on medication at all costs. I also realized I would rather work than do nothing. So, since I want to work, I need to take my medication. . . . I know that being compliant is key for my survival and independence."[9]

Nonadherence and Relapse

Relapses of psychotic symptoms impede recovery.[39] With each successive relapse, Dr Harvey explained, the next remission becomes harder to achieve.[40] The single biggest risk factor for relapse is medication nonadherence.[41] A 2020 analysis of studies that reported medication nonadherence found that, among 2,643 patients with schizophrenia, the rate of nonadherence was 56%.[42] In a naturalistic study[43] that followed 876 patients with schizophrenia for 1 year after hospital discharge, the relapse rates were 21% among adherent patients and 55% among nonadherent patients.

Patient Perspectives

Here, a patient describes maintaining his adherence, despite friends telling him not to, because he does not want to relapse:

"I've got this longstanding women [sic] friend . . ., she keeps on pushing me to come off meds. Usually with friends I explain, [and] then if they don't drop it, I question their motives and whether they really are friends. We have a lot of arguments as she watches these questionable you tube videos. Today she watched one about mental health; when I said I don't want to hear more, we had an argument.

"I'm the first to say in an ideal world I wouldn't need meds but this isn't an ideal world. In what I consider the real world, I've seen schitzoprenics [sic] get into some terrible situations by coming off meds . . . What goes with it [is] alienating what few people I know, losing what I've gained over the years.

"I asked my GP what would happen, she said we don't know but without any guarentees [sic], [it's] playing with fire."[44]

Reasons for Nonadherence

Patients may fail to fill medication prescriptions or may fail to take medication they have. Dr Harvey discussed 3 factors that are empirically associated with adherence failure: cognitive challenges, unawareness of illness, and problems with organization.[41,45]

Cognitive challenges. Impairments in memory, executive function, and cognitive performance are associated with nonadherence.[46] These impairments correlate directly with performance-based assessments of the ability to manage medication: patients are not able to remember to fill their medication, are unable to remember how to take their medication, or are not organized enough to manage to properly take their medication.

Unawareness of illness. Functional insight is often impaired due to a patient's deficit of awareness of their illness.[47] This lack of insight may leave patients with schizophrenia unable to index how likely they are to succeed in certain tasks, what training they might need, and what tasks they are capable of performing. Dr Harvey shared that, in his clinical experience, if a patient is not aware that they have an illness, and they do not appreciate the fact that their medication has a specific purpose, they may not adhere simply because they cannot piece together the reasons for taking the medication.

Organizational challenges. According to Dr Harvey, organizational challenges, which lie on the boundary between cognitive challenges and lack of illness insight, affect patients in various ways. For example, he mentioned that some patients typically fill their prescriptions but do not store the medication adequately, and other patients generally fill their prescriptions only when they are reminded by someone else.

Dr Harvey pointed out that many patients lack the functional capacity necessary to navigate the refill system.[48] In our current health care system, prescriptions are sent to the pharmacy electronically, and if the patient has the right device, they receive a message that their medication is ready to be picked up. If the refill system is not automated via text messages, refills have to be ordered using the telephone or internet, and internet access is still inaccessible for many populations, such as US veterans.[49,50]

Other organizational challenges identified by Dr Harvey include the following: some antipsychotics (eg, ziprasidone[51]) have food requirements; patients may have to meet laboratory requirements to get their medication refill[52]; and lack of attendance at mental health clinic appointments may result in a patient being terminated from the clinic.[53,54,55]

Improving Outcomes With Patient-Centered Treatment Strategies

Shared decision-making. Samalin and colleagues[56] found that psychiatrists cited personal experience as the factor that most influenced their decision-making about treatment for patients with schizophrenia. Too often, clinicians do not recognize that patients want to be involved in clinical decisions. One study[57] found that antipsychotic treatment decisions were made without input from patients or caregivers 67% of the time. The use of shared decision-making strategies could reduce perceived coercion by patients with schizophrenia in regard to prescribed treatments.[58] Active involvement in treatment decisions may alleviate the patient's fears and disperse negative thoughts about previous experiences. Patients who have been allowed to take a more active role in clinical decisions have been found to report greater satisfaction with treatment.[59]

Simplification of treatment. Simplification of treatment regimens[60] can increase medication adherence, reduce relapses, and aid recovery. For example, research indicates that certain medications, particularly anticonvulsants and antidepressants, show little efficacy in schizophrenia.[61–64] Dr Harvey noted that data are particularly poor for antidepressants prescribed to treat negative symptoms.[65] If the clinician adds an anticonvulsant or an antidepressant to a patient's treatment regimen for schizophrenia, that regimen may have little efficacy and yet may be very challenging for the patient to keep up with.[66,67]

People with schizophrenia are also commonly treated with more than 1 antipsychotic, but data suggest that treating a patient with 2 antipsychotics does not have benefit compared to monotherapy.[68,69] Additionally, Dr Harvey shared that in his clinical experience, once-per-day dosing is an effective way to prescribe medication. Dosing frequency is diminished further with the use of long-acting injectable (LAI) antipsychotics, which can be given once per month or less often. A 12-month study[70] comparing the use of oral medication versus LAIs reported that patients receiving LAIs had lower discontinuation rates and fewer inpatient admissions and hospital days.

Psychosocial interventions. Dr Harvey said that offering psychosocial intervention programs is another way to support individuals with schizophrenia.[71] Nonpharmacologic therapies not only complement medication, they may also ensure that patients remain adherent to their medications.[72] Psychotherapies, such as cognitive-behavioral therapy (CBT), supportive therapy, and compliance therapy, educate patients about the importance of taking their medications. One recent study[73] found a 57% recovery rate in patients with schizophrenia who received psychosocial interventions.

Rehabilitative programs targeting social cognition may further facilitate the recovery progress and re-engagement with work, school, and life. Studies[74–77] indicate that cognitive remediation, social cognition training, and functional skills training lead to improvements in employment, cognition, and negative symptoms. Functional skills can be assessed using computer-based simulations of everyday activities, such as banking, refilling prescriptions, and completing forms.[48] Studies have found reductions in both clinical symptom severity and rehospitalization when patients work for pay.[78] Participation in paid work is also associated with increased quality of life.[79]

Patient Perspectives

An individual living with schizophrenia discusses her recovery with the support of her mother and health care provider:

"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. I just want to give hope to those out there suffering from this illness that with the right meds and dedication you can overcome this illness enough to where you can find peace in life."[80]

Case Practice Question

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

DeShawn is 23 years old and has had schizophrenia for 2 years. When he began treatment, he had trouble concentrating and started gaining weight, so he was reluctant to keep taking medication. After a period of nonadherence, DeShawn relapsed and was rehospitalized. After his discharge on a different antipsychotic that is less associated with weight gain, his mother decided DeShawn needed different outpatient care, so she brought him to your office. As you discuss the road to recovery with them, which of the following statements would you *avoid*, based on evidence?

a. You will monitor his antipsychotic adherence, response, and side effects to find the minimum effective dose so that DeShawn's adverse effects might be reduced.

b. If antipsychotic monotherapy does not adequately manage symptoms, you can prescribe DeShawn 2 different medications.

c. If DeShawn is interested in not taking daily medication, he could try a long-acting injectable antipsychotic.

d. Finding paid work, which DeShawn says he wants to do, is a suitable goal.

CONCLUSION

Schizophrenia is a severe, lifelong disorder that affects cognitive, behavioral, and emotional functioning. Many individuals living with schizophrenia experience numerous relapses and ongoing impairment. Adverse effects are a frequent reason for medication nonadherence among patients with schizophrenia, and nonadherence is a major risk factor for relapse. Strategies that may contribute to better outcomes include addressing patients' side effect burden, simplifying the medication regimen, using shared decision-making, and offering psychosocial interventions. Clinicians should view recovery as a process and applaud patients' steps toward progress in various functional domains even when patients do not fully succeed in all domains.

Clinical Points

- Use a patient-centric approach that focuses on alleviating problems that inhibit treatment adherence, such as adverse effects (AEs).
- A lower dose of antipsychotic agents may minimize AEs without impairing efficacy, thereby increasing the likelihood of treatment adherence.
- Evaluating patients' concerns about particular AEs can help in matching treatment regimens to patients' preferences as much as possible.
- Simplify dosing frequency and eliminate unnecessary medications to encourage adherence.
- Long-acting injectables are preferred over oral medications for many patients who have problems with adherence but who are responsive to treatment.
- Psychosocial interventions may improve patients' medication adherence and thereby aid recovery.

Discussion of Case Practice Question

The preferred response is b.

Both efficacy and AEs may increase as antipsychotic dosage increases.[21] Guidelines[28] recommend monitoring adherence, response, and AEs. Data suggest that treating a patient with 2 antipsychotics does not have benefit compared to monotherapy.[68,69] Less frequent dosing can improve patients' adherence,[70,81] and some patients prefer LAI antipsychotics.[82] Person-centered care involves understanding patients' goals,[28] such as obtaining paid work, which is associated with improved quality of life[79] and greater clinical stability.[78]

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Disclosure of off-label usage: Dr Harvey 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. **According to a recent survey, the antipsychotic side effects that are most bothersome to patients are:**
   a. Extrapyramidal symptoms (EPS) and anxiety
   b. Daytime sleepiness and trouble concentrating
   c. Weight gain and sexual dysfunction
   d. Dry mouth and prolactin-related effects
2. **Gerard has been stabilized after experiencing acute psychosis. He was diagnosed with schizophrenia 3 years ago, and you were surprised by his relapse because he has insight into his illness and had been making progress toward recovery. A few months ago, Gerard began a part-time job. When Gerard tells you that he stopped taking his medication, which of the following strategies should you avoid?**
   a. Tell Gerard that he knows he should take the antipsychotic as prescribed and that you will be monitoring his adherence more closely.
   b. Ask Gerard about his reasons for discontinuation, such as dealing with stigma from his new coworkers or adverse effects.
   c. Reassure Gerard that recovery can be viewed as a process, not an outcome.
   d. Talk about his goals and describe psychosocial interventions that could help Gerard progress toward the goals.