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CME Article

Strategies for optimizing medication adherence in schizophrenia

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Abstract

Medication nonadherence is a common problem in the treatment of schizophrenia. The consequences of nonadherence are numerous and can be quite serious, including increased risk of rehospitalization and suicide. There are numerous factors that affect a patient's decision and ability to take medication, including medication efficacy and tolerability, treatment regimen, cognitive deficits, and the patient's relationship with the treatment team. Fortunately, there are several strategies that may increase treatment adherence, including individualization of medication selection and dosing strategy to maximize efficacy and minimize adverse side effects, utilization of long-acting injectable depot formulations that eliminate the need for the patient to remember daily oral medication, and psychosocial approaches that emphasize the benefits of staying well.

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Target Audience

This activity is designed to meet the educational needs of psychiatrists and others who treat patients with psychiatric conditions.

Needs Assessment

Medication nonadherence is a common problem in the treatment of schizophrenia. The consequences of nonadherence are numerous and can be quite serious, including increased risk of rehospitalization and suicide. There are numerous factors that affect a patient's decision and ability to take medication, including medication tolerability, cognitive deficits, and the patient's relationship with the treatment team. Fortunately, there are several strategies that may increase treatment adherence, including pharmacological options for decreasing adverse side effects, utilization of long-acting injectable depot formulations that eliminate the need for the patient to remember daily oral medication, and psychosocial approaches that emphasize the benefits of staying well.

Learning Objectives

After completing this activity, participants should be better able to:

- Recognize the importance of cognitive factors in schizophrenia, including evolving new diagnostic criteria and methods for assessing cognition in clinical practice
- Differentiate antipsychotic drug treatments from each other on the basis of pharmacologic mechanisms and evidence-based clinical trial results
- Implement evidence-based treatment strategies that maximize adherence and patient outcomes
- Combine practical experience with evolving new evidence in order to integrate new and soon-to-be introduced treatments into clinical practice

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This CME activity is in the form of a printed supplement and incorporates instructional design to enhance your retention of the information and pharmacologic concepts that are being presented. You are advised to review this activity from beginning to end, and then complete the posttest and activity evaluation. The estimated time for completion of this activity is 1.5 hours.

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CME ARTICLE

Strategies for optimizing medication adherence in schizophrenia

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Introduction

Schizophrenia is the most common psychotic illness with nearly 1% lifetime prevalence in the population worldwide. There are numerous antipsychotic treatment options available, with various associated side effects and individual efficacy. However, one common issue in the treatment of schizophrenia is the high rate of nonadherence to medication. In fact, although definitions vary, some studies have estimated total or partial nonadherence to be as high as 74%.[1,2] Treatment nonadherence is associated with symptom worsening and increased rehospitalization and relapse, as well as the accompanying financial burdens.[3,4] Even partial nonadherence to medication is correlated with risk of relapse, such that a 20% reduction in treatment adherence may result in as much as a 3.1 point increase in PANSS total score.[5] Even small gaps in therapy of 1–10 days raise the likelihood of hospitalization 2-fold.[6] Nonadherence has also been linked with increased alcohol-related problems, arrests, violence, suicide, and reduced satisfaction with life.[7,8] In addition to these negative consequences of nonadherence on functional outcomes for those with schizophrenia, medication nonadherence makes it nearly impossible to accurately evaluate the efficacy of antipsychotic agents. Nonadherence can lead to suboptimal response and, if it is assumed that the medication is being taken as prescribed, the clinician may be prompted to increase the medication dose. Such a dose increase may lead to adverse side effects that otherwise would be absent, and may even increase the risk of treatment resistance. Clinicians might also abandon a potentially effective medication or mistakenly label a patient as "treatment resistant."

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Measuring Treatment Adherence

There are several ways that medication adherence can be measured; each has its positive and negative features (Figure 1). For instance, although patient self-reporting (e.g., When do you take your medications? In the last week, how many doses do you think you have missed?) may be the least invasive method for assessing adherence, it is also the least accurate. On the other hand, physiological monitoring of drug plasma levels, while perhaps the most accurate measurement of adherence, is expensive and the most invasive.[9] Electronic monitoring using medication caps that record each time a pill container is opened also provides a reliable measure; however, such devices are costly and not typically used outside of clinical trials.[4] In addition to the negative consequences of medication nonadherence, it has also been shown that nonadherence as defined by missed outpatient and follow-up appointments is highly correlated with increased risk of relapse, and may also be predicted by such factors as previous nonadherence.[10–12] Thus, although it seems prudent to suggest that nonadherence has adverse effects on medication efficacy and patient outcomes, it is difficult to fully assess the extent of those effects.

Factors That May Influence Treatment Adherence

Numerous factors may affect whether or not a patient with schizophrenia takes medication as prescribed. In addition to logistical and financial barriers, there are factors inherent to the disease state or its treatment that may influence a patient's adherence to medication. In some cases, the patient may feel compelled to try and "solve the problem" on his or her own.[13] Interestingly, the factors that affect adherence may change over the course of the illness as the patient's experience with the illness and its treatment change.[14]

Positive symptoms

Not surprisingly, more severe positive symptoms and poor illness insight can dramatically affect medication

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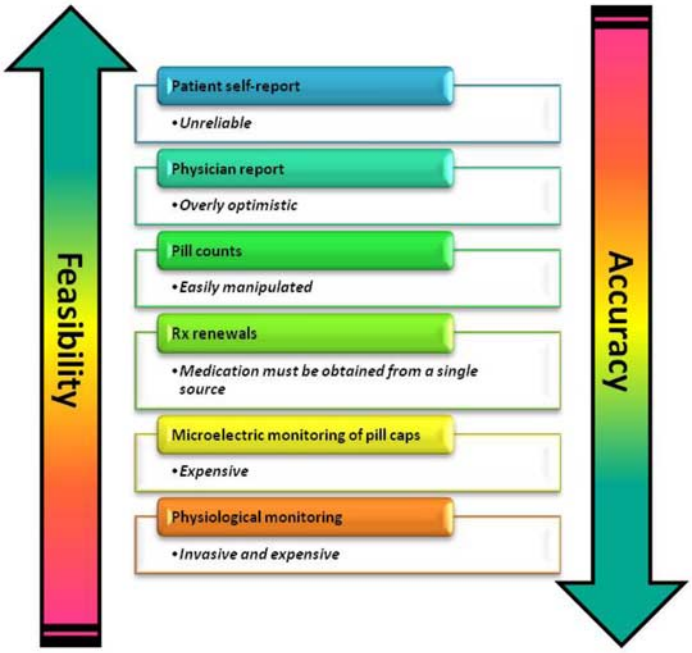


Figure 1. Pros and cons of various measures of adherence.

adherence; those who do not see themselves as ill will likely not feel a need to take medication.[15] Unfortunately, decreased symptoms can also lead to poor medication adherence because patients may neglect taking medication once there are no symptomatic reminders.[4] In fact, a patient may feel temporarily *better* after discontinuing medication due to relief from side effects.

Medication efficacy and tolerability

The "first generation" or conventional antipsychotics are effective in many patients for alleviating positive symptoms of schizophrenia such as hallucinations and delusions. However, the conventional antipsychotics have a high risk of extrapyramidal side effects (EPS) associated with them due to antagonism of dopamine (D2) receptors. The "second generation" or atypical antipsychotics are also effective for treatment of positive symptoms in many individuals with schizophrenia, and may possibly improve negative and cognitive symptoms as well due to more diverse receptor pharmacologic profiles. However, the actions of atypical antipsychotics at a wide range of receptors also increase the risk of a variety of adverse side effects including sedation and cardiometabolic issues. Not only may poor treatment response affect adherence, but adverse side effects associated with both conventional and atypical antipsychotics may also impact nonadherence, especially if the perceived efficacy of the antipsychotic is less than optimal.[16] In fact, the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) study indicated that one of the most common reasons for discontinuing antipsychotic medication was intolerability of side effects.[1] EPS, weight gain, sedation, and sexual dysfunction have all been linked to nonadherence. The receptor functional groups responsible for some of these adverse side effects are outlined in Figure 2. Unfortunately, there may often be a "don't ask, don't tell" scenario in which there is an under-reporting of adverse side effects by patients and an under-recognition of side effects by clinicians.[17,18] Given the apparent connection between side effects and medication nonadherence, it is important for both patient and clinician to investigate, recognize, and adequately address any adverse effects.

Treatment regimen

While there appear to be similar high discontinuation rates for both conventional and atypical antipsychotics, some studies have indicated that adherence may be better for some atypical antipsychotics in comparison to others.[1,19] For instance, both olanzapine and clozapine may have slightly higher adherence rates compared to risperidone.[20] The complexity of the treatment regimen is also important for adherence; data have shown that number of doses per day is inversely related to adherence.[21,22] More complex regimens may disrupt a patient's daily routine and further compound problems with adherence that are due to memory deficits. For this reason, long-acting depot formulations may be especially advantageous to those with cognitive impairments.

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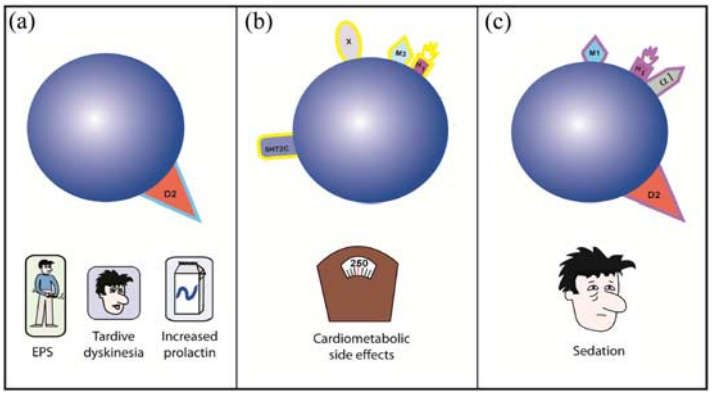


Figure 2. Receptor functional groups responsible for side effects linked to nonadherence. (A) Extrapyramidal side effects (EPS), tardive dyskinesia, and hyperprolactemia are attributable to the action of antipsychotics at dopamine (D2) receptors. (B) Serotonin (5HT 2C) and histamine (H1) antagonism have been linked to weight gain and muscarinic (M3) receptor antagonism can alter insulin regulation. The "X" functional group is a yet-unidentified mediator of insulin resistance. (C) D2, M1, H1, and alpha 1 adrenergic antagonism are all associated with sedation.

Therapeutic alliance

The relationship between patient and treatment team has also been found to greatly affect treatment adherence.[23] One study determined that over half of all patients who were nonadherent with medication had a poor therapeutic relationship with their clinician (compared to only 29% of patients who did adhere to their medication).[24] These data underline the value of the patient–clinician relationship and highlight the need for patients to be actively engaged in their own treatment. The patient needs to sense that there is an alliance with the treatment team and to feel respected and empowered, rather than feeling as though the relationship is one of control by the treatment team over the patient.

Cognitive and negative symptoms

In addition to the positive symptoms present in schizophrenia, both cognitive and negative symptoms are also prominent; however, cognitive dysfunction is not currently part of the diagnostic requirements. Both cognitive deficits (such as memory issues) and negative symptoms (such as apathy) have been linked to nonadherence.[2,16] Cognitive deficits not only affect a patient's ability to remember to take medication, but also may limit the ability of the patient to budget finances to pay for medications or to be educated about incorrect perceptions regarding illness and treatment.[14,25] Perhaps due to the correlation with adherence, baseline cognition actually predicts later functional outcome, and verbal memory, working memory, and executive functioning have been specifically linked to functional outcome.[26] In fact, while both cognitive and negative symptoms are associated with functional outcome, positive symptoms do not have that same correlation with functional outcomes.[27] Unfortunately, cognitive and negative symptom domains represent the two major unmet therapeutic areas in schizophrenia because they are less responsive, in general, to antipsychotic treatment compared to positive symptoms. Given their predictive power regarding both medication adherence and functional outcome, it has been suggested that improvement in cognitive or negative symptoms alone should warrant FDA approval of a therapeutic agent for treatment in schizophrenia.[27] It should be noted that it is difficult to separate how much each symptom domain uniquely affects functional outcome, as there is much overlap between the effects of cognitive and negative symptoms and, in fact, negative symptoms often predict deficits in neurocognition.[28]

Strategies to Maximize Treatment Adherence and Improve Functional Outcome

Minimizing side effects and increasing drug efficacy

Given the correlation between adverse side effects and medication nonadherence, it is essential that the clinician be aware of any side effects experienced by the patient and seek to minimize those effects that the patient finds intolerable.[29] Although individual response will differ, data from the CATIE study indicate that the atypical antipsychotic olanzapine has the longest time to discontinuation but is associated with the most discontinuation due to weight gain, whereas the conventional antipsychotic perphenazine is associated with the most discontinuation for EPS relative to second-generation atypical antipsychotics.[1]

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Table 1. *Characteristics of various atypical antipsychotics that may affect adherence*

		Alternative formulations		Side effects*			
Atypical antipsychotic	Dosing schedule of oral formulation	Long-acting depot	Other	Sedating	Weight gain	EPS	Additional caveats
Aripiprazole	1× day	4 wk in trials	10 and 15 mg oral disintegrating tablets; 9.75 mg/1.3 injection	unusual	unusual	not unusual	May be activating rather than sedating
Asenapine	2× day		Only available in 5 and 10 mg sublingual tablets	common	not unusual	not unusual	Patient should not eat or drink immediately after drug administration
Iloperidone	2× day	4 wk in trials		common	not unusual	unusual	Gradual titration to minimize orthostatic hypotension
Olanzapine	1× day	2 wk 4 wk	Oral disintegrating tablet	common	problematic	unusual	No titration needed. Oral supplementation of depot may be needed
Paliperidone	1× day	4 wk 12 wk in trials	Only available in extended release formulation	common	common	common	No titration needed
Quetiapine	2× day			problematic	common	unusual	Minimum titration required for XR
Quetiapine XR	1× day						
Risperidone	1× day	2 wk 4 wk in early trials	0.5, 1, and 2 mg oral disintegrating tablets; 1 mg/mL liquid	common	common	common	Titration needed
Ziprasidone	2× day		10–20 mg IM formulation available	not unusual	unusual	not unusual	Should be taken with food
Lurasidone	1× day			common	unusual	common	No titration needed; should be taken with food

*Side effects scale: Unusual = reported in few patients; Not unusual = occurs in a significant minority; Common = many experience or can be in significant amount; Problematic = occurs frequently, can be in a significant amount, and may be a health problem in some patients.

In patients experiencing tardive dyskinesia, it is recommended that a switch to clozapine or quetiapine be made.[18] For any given patient, it may be necessary to attempt several different monotherapies, and even antipsychotic combinations, prior to finding the most efficacious treatment offering the least adverse effects in order to maximize adherence. Although this practice remains questionable, when switching from one treatment to another, there are specific strategies recommended in order to minimize residual symptoms and adverse responses.[30,31]

Long-acting depot formulations

Long-acting formulations of antipsychotics offer many benefits over their oral counterparts.[25,29,32] Assured

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medication delivery and continuous antipsychotic coverage certainly increase medication adherence and have been shown to decrease the risk of psychotic relapse.[33–36] There is no need for the patient to remember to take medication every day, and a decision to adhere to the treatment regimen need only be made a few times a month rather than every day or even several times a day. These factors may be especially important for patients with concomitant cognitive deficits or poor illness insight. The more frequent contact between the patient and treatment team required for administration of depot formulations offers possible strengthening of the patient–clinician alliance that is instrumental to adherence. Also, if a dose is missed, the clinician may be notified prior to the drug concentration dropping to ineffective levels and further increasing the chance of nonadherence. Also with depot formulations, there is avoidance of first-pass metabolism and thus a better relationship between dose and level of drugs available to the system. Depot formulations may also offer lower peak plasma levels and decreased peak-to-trough variability compared to oral formulations, and therefore may lead to better tolerability and safety. There are now several conventional and atypical antipsychotics available as depot formulations, and more are currently in development (Table 1).

Psychosocial interventions

In addition to pharmaceutical-based interventions for improving adherence, there are several psychosocial measures that have been shown to enhance adherence. In terms of the patient–clinician alliance, it is important to clearly communicate with the patient regarding benefits and hazards of all treatment options and to take into account the patient's preferences in terms of the treatment regimen.[23] Refill reminders and organized packaging of daily medications have been shown to significantly improve adherence.[37] Compliance therapy involving the evaluation of patient illness insight and attitude toward medication followed by discussion with the patient emphasizing the importance of staying well and consequences of nonadherence have also been shown to be effective.[38] Assertive community treatment (ACT) has also been associated with increased medication adherence in schizophrenia.[39] ACT involves use of a multidisciplinary treatment team that reaches out with a high frequency of contact to patients in the community.

Addressing cognitive deficits

The National Institute of Mental Health (NIMH)-sponsored Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) study was designed to standardize the evaluation of therapeutic agents intended to improve cognitive deficits in schizophrenia. The MATRICS group developed a consensus battery to test 7 cognitive domains in schizophrenia.[40] However, there are inconsistent data regarding the relative benefits of individual antipsychotics for specific cognitive domains.[41] Cognitive adaptation training, which uses checklists, alarms, and organization of medications into daily use containers to cue adaptive behavior, and cognitive remediation therapy have also both been shown to improve adherence and prevent relapse in schizophrenia.[9,31,42,43]

Conclusion

Given the profound impact of medication nonadherence on functional outcomes for the patient, it is of great importance that factors affecting treatment adherence be recognized and the necessary pharmaceutical and psychosocial measures be taken to minimize nonadherence.

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1. Factors that may affect a patient's adherence to antipsychotic treatment include:

   a. Therapeutic alliance with the clinician
   b. Cognitive deficits
   c. Medication efficacy
   d. Treatment regimen complexity
   e. All of the above

2. Extrapyramidal side effects associated with some antipsychotics is most likely due to:

   a. Serotonin (5HT7) receptor antagonism
   b. Histamine (H1) receptor antagonism
   c. Muscarinic (M3) receptor antagonism
   d. Dopamine (D2) receptor antagonism
   e. Alpha 1 adrenergic receptor antagonism

3. The following strategies may improve treatment adherence in schizophrenia:

   a. Minimizing adverse side effects associated with medication
   b. Use of a long-acting depot formulation
   c. Cognitive Remediation Therapy
   d. Refill reminders
   e. All of the above

4. Which of the following antipsychotic treatments is currently available as a long-acting depot formulation?

   a. Asenapine
   b. Ziprasidone
   c. Quetiapine
   d. Paliperidone
   e. All of the above

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