Review of Treatments That Can Ameliorate Nonadherence in Patients With Schizophrenia

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Nonadherence to medication is one of the major problems in treating patients with schizophrenia. Clinicians can use a variety of assessment strategies to identify patients who are nonadherent, although none of these is completely reliable. Interventions to improve adherence include psychosocial strategies, second-generation oral antipsychotics, and long-acting injectable antipsychotics. Because of the potential for reduced relapse and rehospitalization rates and the availability of second–generation antipsychotics in injectable form, a case is made for using long-acting injectable second-generation antipsychotics, when appropriate, to treat patients with schizophrenia.

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Adherence to medication treatment has long been acknowledged as playing a crucial role in successfully treating schizophrenia, but achieving a high level of adherence to medication is difficult with many patients. Long-acting injectable antipsychotic drugs can help improve adherence and reduce relapse and hospitalization rates. Since the introduction of second-generation antipsychotics in oral form, long-acting injectable agents have declined in use. Recently available second-generation antipsychotics in injectable form present an opportunity for clinicians and patients to enhance adherence and improve the treatment of schizophrenia.

THE CHALLENGES OF NONADHERENCE OR PARTIAL ADHERENCE

Psychiatrists view nonadherence to medication as one of the major problems in treating patients with schizophrenia.[1] Research[2] has shown that schizophrenia is second only to weight reduction in terms of difficulty in producing adherence to treatment sufficient for optimum therapeutic effect (Figure 1).

A study[3] by my colleagues at The Zucker Hillside Hospital showed that nonadherence plays a tremendous role in increasing the risk of psychotic relapse. The study focused on 104 individuals in late adolescence or early adulthood who had experienced their first psychotic episode. The data showed the cumulative rate of relapse over the 5 years that the patients were followed: 81.9% of them had at least one psychotic relapse, and 78.0% of them had a second relapse. Patients who discontinued medication were almost 5 times more likely to relapse than patients who continued taking medication, whether it was the first or the second relapse.

Some people may assume that in order for nonadherence to lead to relapse or rehospitalization, the patient has to miss medication for many weeks. A study[4] of California Medicaid outpatients (N = 4325) demonstrated that even short medication gaps, from 1 to 10 days, were associated with an increase in the risk of hospitalization. The data show a linear increase in the risk of hospitalization as the medication gap increases (Figure 2).

Detecting medication gaps and intervening in time to prevent a relapse is difficult. I reviewed relapse rates after 1 year of continuous or intermittent maintenance therapy with conventional antipsychotics.[5] With intermittent treatments, patients received a placebo until they showed early signs of relapse, and then the clinical team would reintroduce an antipsychotic medication. Despite that intervention, intermittent treatment was associated with significantly higher rates of relapse than continuous treatment. So, preventing relapse is challenging even when clinicians monitor for it carefully, but it can be more challenging if clinicians think patients are more adherent than they really are.

MEASURING ADHERENCE

Measuring adherence is not easy, but clinicians can use a variety of assessment strategies to identify patients who

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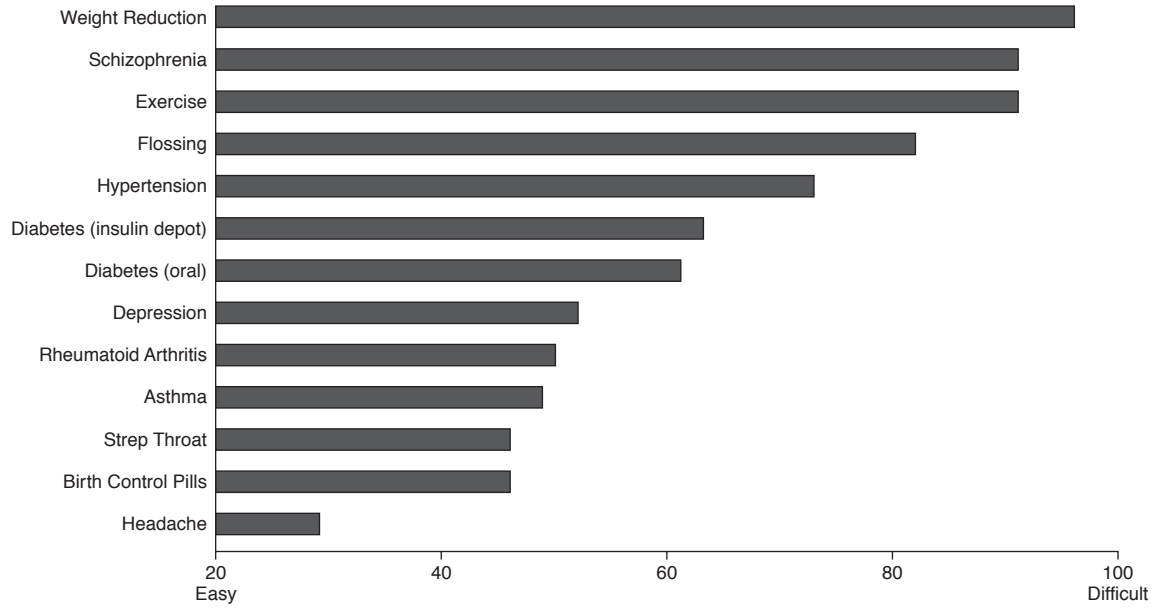
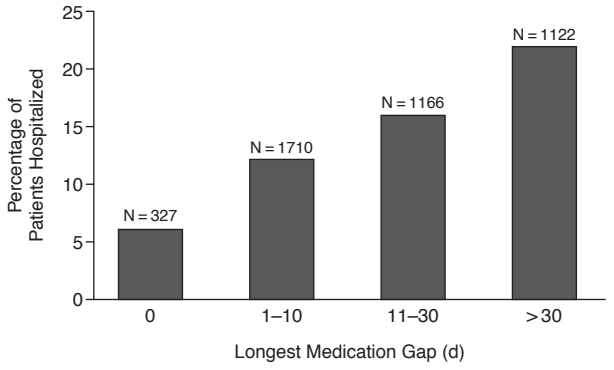
Figure 1. Degree of Difficulty to Produce Adherence Sufficient for Therapeutic Effect[a]



[a]Adapted with permission from Keith and Kane.[2]

Figure 2. Partial Adherence and Hospitalization[a]



[a]Adapted with permission from Weiden et al.[4]

Table 1. Strategies to Measure Adherence to Medication

Strategy	Method
Self-report	Patients fill out a questionnaire. From their responses, clinicians measure their level of adherence. Patients may be more honest if they complete the questionnaire anonymously
Caregiver report	A significant other or a caregiver reports whether patients are taking medication
Clinician assessment	The clinician uses his or her best judgment to assess adherence
Pill counts	Clinicians count the number of pills left in a bottle. The pills not being there does not mean that the patient took them, particularly if the patient knows that the medicine will be counted
MEMS cap	Microelectronic monitoring system (MEMS) records the date and time the pill bottle is opened. It cannot record that the pill was taken
Blood levels	An objective method for assessing adherence. Patients may have a detectable amount of a drug in their system at the time of the test, but that does not tell how much of the medicine has been taken on a consistent basis. Testing blood levels is expensive and invasive

are nonadherent (Table 1). None of these assessment techniques is completely reliable, but one of the more reliable is the microelectronic monitoring system (MEMS) cap, which records the date and time that the pill bottle is opened.

In a study[6] done in an outpatient clinic, clinicians were asked to assess patients (N = 21) in terms of their level of adherence. Any patient whom the clinician determined to be missing more than 30% of his or her medication was considered to be nonadherent. The researchers found that 5.3% of the patients were judged by the clinician to be nonadherent. At the same time, the patients were given their medication in a bottle that had the MEMS cap. According to the MEMS cap measurement, 61.9% of the patients were nonadherent. This research showed a tremendous discrepancy between the proportion of patients identified as nonadherent by the clinician and the proportion of patients identified by the computer chip in the bottle cap as nonadherent.

Although clinicians use their best judgment to evaluate nonadherence, it is difficult to achieve an accurate assessment. Patients may not provide reliable data, wanting to

Table 2. Psychosocial Interventions to Improve Adherence to Medication in Patients With Schizophrenia

Intervention	Description
Family and individual psychoeducation	Involves explaining to the patient and his or her family the nature of the illness and why the patient needs to take medicine
Community-based intervention	Employs strategies like assertive community treatment or intensive case management
Motivational interviewing	Uses the patient's own desires, wishes, and goals to help motivate him or her to take medicine
Cognitive behavior therapy	Helps patients change their way of thinking and develop new behaviors
Mixed modality intervention	Includes a number of the above strategies

avoid hurting the doctor's feelings or making the doctor angry. Patients with schizophrenia may have cognitive disturbances and may not realize how much medication they have missed. In addition, human nature makes it hard for people to remember and track whether they have taken every dose of medication.

INTERVENTIONS TO IMPROVE ADHERENCE

Psychosocial Interventions

Several psychosocial strategies have been used to improve medication adherence in schizophrenia patients (Table 2).

A review[7] examined 39 studies of psychosocial interventions aimed at improving antipsychotic medication adherence. One third of the studies demonstrated superior efficacy for the adherence intervention over control treatments. The successful programs were most likely to use concrete problem-solving or motivational techniques. Interventions that were targeted specifically at problems of nonadherence were more likely to be effective than were the more broadly based treatment interventions. In this review, no one specific modality demonstrated overwhelming success in improving adherence.

One study[8] examined the effectiveness of adherence therapy in 74 inpatients who were randomly assigned to 4 to 6 sessions (mean = 4.7) of either adherence therapy (motivational interviewing and cognitive approaches to psychotic symptoms) or a control. The control group received an equal number (mean = 4.5) of sessions of supportive counseling. All of the patients in the study were receiving antipsychotic drugs. Over an 18-month follow-up period, the results showed a significantly longer time to readmission among patients receiving adherence therapy. A Cox regression analysis on survival time to readmission produced a regression coefficient of 0.79 for the compliance treatment (SE = 0.32, z = 2.52). The hazard function for risk of readmission of a person in the control group was 2.2 times that of a person in the adherence therapy group. However, when the investigators looked at overall relapse rates or time spent in hospital, no significant differences between the 2 groups were found.

Various psychosocial methods for enhancing adherence to medication in patients with schizophrenia exist, but they are not always available to patients, and some methods may require an unrealistic amount of time and effort from patients' families, clinicians, and others. More research is needed on adherence therapy. The critical question remains whether these methods can provide the optimal level of adherence to medication treatment among patients with schizophrenia.

Second-Generation Oral Antipsychotics

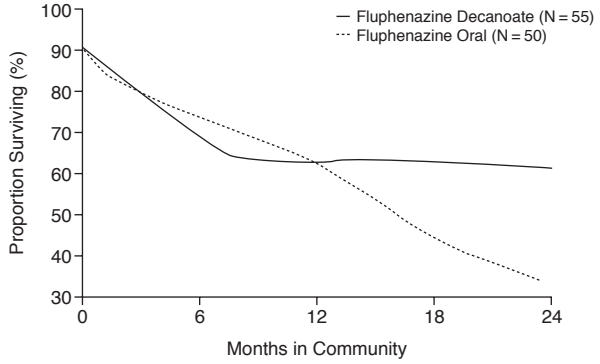
It has been postulated that adherence to medication would improve in patients taking newer second-generation antipsychotics, which were only available in oral form until recently, because these medications are generally better tolerated than conventional antipsychotics. A 1-year naturalistic study[9] of patients with schizophrenia examined whether adherence improved if patients were taking second-generation antipsychotics rather than conventional antipsychotics; the study used prescription refill data to evaluate whether or not patients received their antipsychotic medicine. Results showed that patients taking conventional antipsychotics were without their medicine a mean of 125 days out of the year, whereas patients taking second-generation antipsychotics were without their medicine a mean of 110 days out of the year. Although adherence was better in patients treated with atypical versus conventional agents, patients treated with atypical antipsychotics were still missing their medication for about a third of the year. Even though there are many advantages to second-generation antipsychotic drugs, in oral form they have not solved the problem of nonadherence.

Long-Acting Injectable Antipsychotics

Schooler[10] reviewed 6 randomized clinical trials of oral and depot antipsychotic medications. When the data were weighted by the number of participants, the rate of relapse at 1 year was 42% for oral medication and 27% for depot medication. Although the author notes some methodological limitations in some of the studies, this review suggests that one of the potentially most useful strategies for enhancing adherence and thus preventing relapse and hospitalization is the use of long-acting injectable antipsychotics.

The improvement in hospitalization rates of patients with schizophrenia treated with depot medication was reviewed by Davis et al.[11] in 1994. Examination of 6 mirror-image studies comparing the number of hospital days of outpatients treated with depot versus oral medication showed a statistically significant reduction in time in hospital among patients treated with depot antipsychotics.

Figure 3. Long-Term Efficacy of Depot and Oral Antipsychotics[a]



[a]Adapted with permission from Hogarty et al.[12]

It is particularly important to have a long-term perspective on the efficacy of depot medication in reducing relapse rates in schizophrenia patients. The long-term efficacy of depot medication was indicated in a double-blind study[12] of 105 patients that extended over a 2-year period (Figure 3). In the first 6 to 12 months, there was no apparent difference in relapse rates between patients receiving depot (35.1%) and oral (39.5%) medication. Between 12 and 24 months, however, the relapse rates for these treatments began to separate dramatically. Over the total 2-year period, the relapse rates were 40.3% for patients receiving the depot antipsychotic and 64.7% for patients receiving the oral medication. These data suggest that it might take more than 12 months to realize the full advantages of long-acting medication in preventing relapse. An extended period of time may be necessary in randomized clinical trials where adherent patients are probably overrepresented and patients are seen more frequently and monitored more carefully than in routine clinical practice.

Reasons why injectable antipsychotics are not used. Despite their potential to reduce relapse, long-acting injectable antipsychotics are not used to treat schizophrenia as often as they should be. A number of factors could account for this. Until recently, clinicians had the difficult choice of either an oral second-generation antipsychotic or a long-acting injectable first-generation antipsychotic. No atypical long-acting medications were available. This was a dilemma that led to a decline in use of long-acting drugs.

Other reasons why long-acting antipsychotics have not been more widely prescribed by physicians included physicians' and patients' fears of causing patient discomfort, the patient's perception of loss of control over the amount of medication in the patient's system, and fear of difficulty managing adverse effects due to inability to withdraw the medication.[13] Patients and physicians also do not consider injectable medication because they tend to associate these drugs with the most refractory or uncooperative patients. Other factors include clinicians' beliefs that (1) their patients are more adherent to medication than the data would suggest, (2) they will be able to tell if adherence is becoming a problem, and (3) patients need to "learn" from relapses due to nonadherence.

Advantages of long-acting injectable antipsychotics. Long-acting injectable antipsychotics have several advantages over oral medication in the treatment of schizophrenia.[13] Very importantly, injectable agents improve adherence by assuring medication delivery. When patients take oral medication, clinicians may not be aware of nonadherence until the patient has an exacerbation of symptoms or a relapse. However, if a patient misses an injection, the clinical team is immediately aware that the patient is nonadherent, and the team has an opportunity to intervene. Another advantage is that long-acting injectable drugs encourage regular contact between the patient and the management team, which is especially helpful for first-time patients.

The delivery method has several other advantages. Injectable medication avoids the first-pass metabolism, substantially reducing the variability in absorption and bioavailability associated with the use of oral medication. Because of this, long-acting injectable antipsychotics produce predictable and stable plasma levels, which provide consistency of treatment to patients with schizophrenia and enable a lower effective dose to be used. Long-acting injectable drugs have provided the best evidence of minimum dosage required to prevent relapse in schizophrenia; lower doses have the advantage of being associated with fewer adverse effects. Other advantages are that injections can be administered every few weeks so the patient is freed from having to take daily medication, and there is also no abrupt discontinuation of treatment if an injection is missed, because some of the medication will still be present in the patient's body.

An important factor in favor of trying long-acting antipsychotic medication is the opinion of patients. A review[14] showed that when patients have had the experience of receiving long-acting injectable antipsychotic drugs, the majority of them voiced a preference for the long-acting drug in comparison to the oral drug. Patients found it more convenient to have an injection every few weeks than to take oral medication daily, and they liked the timing and dosage of treatment that injections offered, the social contact with other patients receiving injections, and the access to health care professionals that injections provided. If reluctant patients try at least 1 injection to see what it is like, often they find that their fear far exceeds the reality. As patients have more experience with injections, they tend to relax and thus any pain associated with injections diminishes.

Long-Acting Injectable Atypical Antipsychotic

The U.S. Food and Drug Administration approved the first long-acting injectable atypical antipsychotic, risperidone, for the long-term treatment of schizophrenia in October 2003. The availability of a second-generation long-acting injectable antipsychotic provides an opportunity to reexamine the use of long-acting injectable antipsychotics because it combines the advantages of both the newer type of medication and the long-acting formulation. A 2003 review[14] concluded that long-acting injectable risperidone is efficacious, safe, and well tolerated.

Guidelines[15] for the use of long-acting injectable atypical antipsychotics recommend that every patient should be evaluated for suitability for treatment with long-acting injectable atypical antipsychotic medication. Treatment with long-acting injectable atypical antipsychotics can be initiated once acute or severe symptoms are under control. Stable patients and recently diagnosed patients should be considered for this medication, but it would not be appropriate as monotherapy for patients who are suffering from acute symptoms, due to a 3-week period after the first injection before therapeutic effects occur. In addition to partially adherent patients, patients with comorbid substance abuse disorders or patients exhibiting aggressive or violent behavior might be particularly helped by the availability of continuous treatment. Patients may experience fewer side effects from injectable risperidone than the oral version because injectable long-acting risperidone has lower peak plasma concentrations and smaller variations in peak and trough plasma concentrations.[16,17]

One perceived barrier to using injectable antipsychotics, the pain associated with the injection, has been shown to be based on unfounded fears. In a trial by Lasser et al.,[18] long-acting risperidone injections were shown to be associated with a low incidence of pain at the injection site. This evidence is corroborated by a 12-week, multisite, randomized, double-blind, parallel group study[16] in which 400 patients with schizophrenia received intramuscular injections of long-acting risperidone (25 mg, 50 mg, or 75 mg) or placebo injections that were identical in appearance every 2 weeks. At the beginning of the trial, pain and swelling experienced after injections were low, and most patients reported to investigators that they had no pain or swelling at the site of the injection after the sixth injection.

CONCLUSION

Long-acting injectable antipsychotics can play a major role in facilitating medication adherence and improving outcomes for schizophrenia patients. Since the introduction of second-generation oral medication, the use of injectable medication declined because the second-generation antipsychotic was preferred but was not available in injectable form. Research has shown that patients who have experienced both oral and injectable medication often prefer long-acting injectable medication. With the introduction of an injectable form of a second-generation antipsychotic, there is an opportunity to offer patients the second-generation medication in a long-acting form. Clinicians can encourage patients for whom a long-acting drug is indicated to try second-generation antipsychotic injectable medication and see what it is like. Clinicians must emphasize that we are controlling the illness, not controlling the patient. Clinicians need to educate patients and families regarding the frequency and consequences of nonadherence in a nonaccusatory, nonjudgmental fashion and explain the potential advantages of long-acting injectable medication. This effort can go a long way toward improving outcomes in this illness.

Drug names: fluphenazine (Prolixin and others), risperidone (Risperdal, Risperdal Consta).

Disclosure of off-label usage: The author has determined that, to the best of his knowledge, no investigational information about pharmaceutical agents that is outside U.S. Food and Drug Administration–approved labeling has been presented in this article.

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