

Epidemiology, Clinical Consequences, and Psychosocial Treatment of Nonadherence in Schizophrenia

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Partial adherence and nonadherence to medication continue to be problems in the treatment of patients with schizophrenia. Nonadherence to medication has a negative impact on the course of illness for these patients as is shown by data on relapse, rehospitalization, time to remission, and attempted suicide. Several factors that contribute to poor adherence have been identified and need to be taken into account when attempting to address the problem of nonadherence. These risk factors relate to the patient, his or her illness and social situation, and the physician. Among the measures that have the potential to improve adherence to medication are psychosocial interventions, psychoeducation in the form of professional, peer-to-peer or family-to-family interventions, and shared decision making.

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Recognizing the factors that contribute to poor adherence to antipsychotic medication and intervening are important steps to take when managing patients with schizophrenia. Partial adherence or nonadherence to medication is a problem that may lead to relapse, rehospitalization, delayed time to remission, and attempted suicide in this patient population.

EPIDEMIOLOGY OF NONADHERENCE IN SCHIZOPHRENIA

Nonadherence with medication is a persistent problem in the treatment of patients with schizophrenia. Rather than being an all-or-nothing situation, adherence falls along a spectrum of behavior (Figure 1). Some patients are fully adherent and some fully nonadherent, but the majority are only partially adherent.¹ A review² showed a mean level of adherence with antipsychotic medication of 58% among patients, and research³ has found that less than 25% of schizophrenia patients consecutively admitted to the hospital were fully adherent. Lam et al.⁴ showed that only 10 days after hospital discharge, up to 25% of patients were partially adherent, and Weiden and Zygmunt's research⁵ demonstrated that in the further course of antipsychotic treatment, 50% of patients with schizophrenia

were only partially adherent by 1 year from discharge, and by 2 years the number rose to 75%.

IMPACT OF NONADHERENCE ON COURSE OF ILLNESS

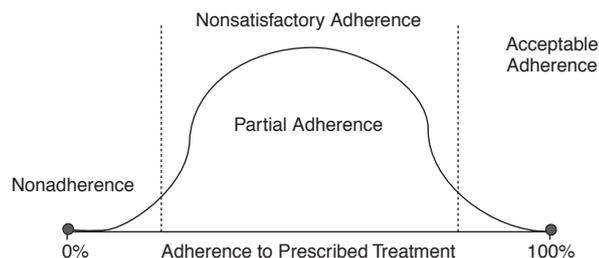
Nonadherence with medication treatment has a serious impact on the course of illness in patients with schizophrenia; nonadherence affects the risk of relapse, rehospitalization, and suicide attempts. Nonadherence to medication was found to be a major contributory factor to high relapse rates in patients with schizophrenia in a study⁶ that followed 104 patients over 5 years after treatment for a first episode of schizophrenia. Patients were treated according to a standard treatment algorithm. Responders continued taking a maintenance dose of medication, and patients who were clinically stable for 1 year were given the option of discontinuing antipsychotic medication but were monitored for symptom exacerbation. Any patient who developed signs of relapse was prescribed continuous antipsychotic medication. Researchers found that although these were first-episode patients, who generally have a better prognosis than patients who have already had multiple episodes, the relapse rates were high. At least one psychotic relapse occurred in 81.9% of patients in 5 years. The risk of relapse increased by almost 5 times when antipsychotic drug therapy was discontinued, which would equate to full nonadherence.

A systematic review and meta-analysis⁷ of randomized controlled trials comparing second-generation antipsychotics with placebo and/or conventional antipsychotics examined relapse rates and adherence to medication in patients with schizophrenia. The analysis of data from 11 studies with a total of 2032 patients showed a relapse rate of 15% in patients treated with second-generation antipsy-

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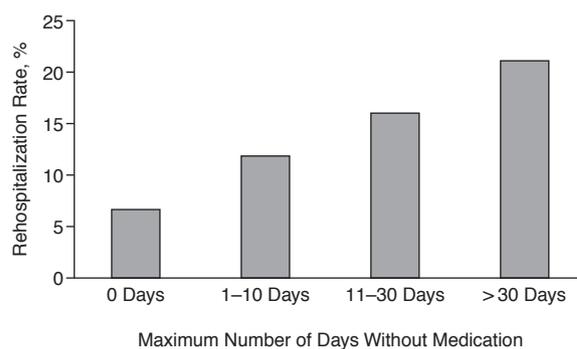
Figure 1. Spectrum of Adherence^a^aData from Valenstein et al.¹

chotics versus 23% in patients treated with the older agents. As well as demonstrating that relapse rates are low in randomized, controlled, double-blind studies comprising more adherent patients, the results showed that second-generation antipsychotics have the potential to lower the relapse rate in adherent patients.

In the real world, however, which includes patients who do not always take medication, even with atypical oral antipsychotics the relapse rates are much higher and each successive remission takes longer to achieve. In a naturalistic study,⁸ relapse rates for 76 first-episode schizophrenia patients, discharged mainly on second-generation antipsychotics from a typical state hospital in Augsburg, Germany, were followed for up to 18 months. In this setting, 38% of the patients in the trial were rehospitalized at least once within the follow-up period. The more relapses a patient has, the more difficult it is to get him or her into remission each time.⁹ These findings emphasize the importance of minimizing nonadherence to medication because of its associated risk of relapse and cumulative adverse outcome.

Hospital stays may also be lengthened in patients who have been nonadherent to medication prior to their hospitalization. When the relapses of 27 hospitalized nonadherent (N = 16) and adherent (N = 11) patients with schizophrenia were compared,¹⁰ the nonadherent patients were found to have more psychotic features, to require involuntary commitment, and to remain in the hospital longer. The adherent patients tended to be voluntary admissions who had rapid onset of affective symptoms often associated with environmental stressors, and they recovered more quickly. The mean length of inpatient stay for nonadherent patients was 38.1 days and for adherent patients 14.3 days. Patients who adhere to their medication treatment may still relapse, but their relapse will tend to be less dramatic than the relapse of a nonadherent patient.

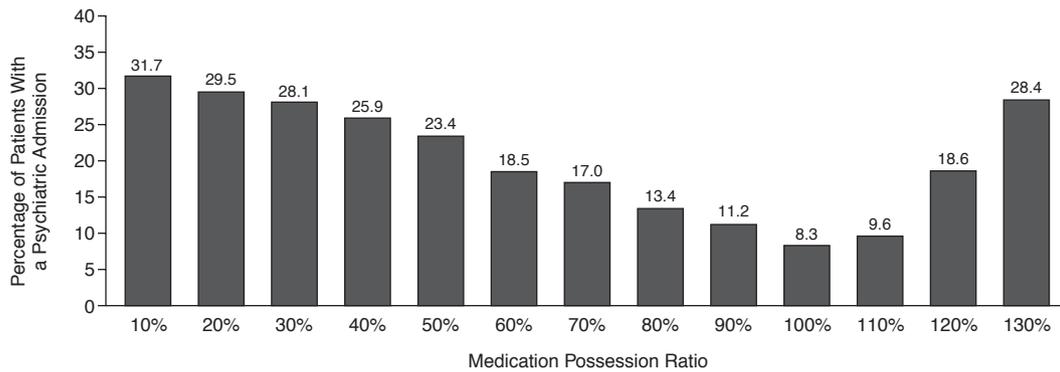
A correlation between adherence to medication and risk of hospitalization was demonstrated by 2 studies. In the first study,¹¹ a cohort of 4325 California Medicaid patients with schizophrenia were followed for 1 year. Four different measures were used to estimate adherence behavior: gaps in medication therapy, consistency of medi-

Figure 2. Role of Partial Adherence in Rehospitalization of 4325 Patients^a^aAdapted with permission from Weiden et al.¹¹

cation dose, persistence in dosing behavior, and medication possession ratio (MPR). (MPR was calculated from the number of days the patient was not hospitalized and had medication available according to pharmacy dispensing date and days' supply recorded on the prescription claim, divided by the number of ambulatory days in the study period.) The odds of hospitalization were determined using logistic regression models for each adherence estimate. The study showed a direct correlation between estimated partial adherence and hospitalization risk across a continuum of adherence behavior. For example, any gap in medication therapy was associated with increased risk of hospitalization (Figure 2). Despite the facts that medical claims data report only that the prescription was filled and not that the medication was taken and that factors such as availability of social support, substance abuse, incomplete medication efficacy, and discontinuation of care also affect hospitalization rates, the study suggests that improving a range of adherence behaviors can reduce the risk of rehospitalization among patients with schizophrenia.

A second study¹ showing that different rates of partial adherence to medication have a proportional effect on rehospitalization rates and length of hospital stay used national pharmacy data to calculate the MPR of patients with schizophrenia treated in the Department of Veterans Affairs. The MPR was calculated by dividing the number of days' supply of oral antipsychotic medication the patient had received by the number of days' supply needed to take medication continuously. Among patients (N = 49,003) on one antipsychotic, those with MPRs closest to 100% had the lowest rates of admission (Figure 3). While 23% of poorly adherent patients were admitted, only 10% of adherent patients were admitted. The poorly adherent patients, once admitted, also had more inpatient days during the year (mean of 33 days) than did patients with good adherence (mean of 24 days).

Partial adherence to antipsychotic medication has cost implications as a consequence of its negative effect on the

Figure 3. Role of Medication Possession in Rehospitalization^a

^aAdapted with permission from Valenstein et al.¹

course of the illness. A study¹² of 7864 patients receiving antipsychotic agents in a Medicaid program found that patients whose adherence was less than 80%, about one third of the sample, were 49.0% more likely than adherent patients to have an inpatient hospitalization for an episode of schizophrenia or bipolar disorder. Partially adherent patients incurred 54.5% higher inpatient charges, although the overall costs were comparable.

Another adverse outcome due to poor adherence to antipsychotic medication in patients with schizophrenia is an increased risk for suicide attempts. Research¹³ has shown that nonadherence to schizophrenia medication increases this risk 4-fold. Investigators analyzed the pharmacy records of 603 patients, aged 15–45 years, suspected to have schizophrenia, discharged from the hospital, and prescribed atypical antipsychotic medication. Nonadherence to medication for at least 30 days was found in 33% of the patients, and these patients had a 4.2 greater risk of suicide attempt compared to those patients who adhered to their medication treatment.

REASONS FOR NONADHERENCE AND PARTIAL ADHERENCE

Nonadherence and partial adherence to medication among patients with schizophrenia have a wide range of causes.¹⁴ Some of these causes can be classified¹⁵ as deriving from the patient or the illness, and others can be said to derive from the physician. Distinguishing between factors related to the patient, patient's environment, underlying illness, treating clinician, or the treatment itself may help clinicians to assess risk and prevent and manage adherence problems.¹⁶

Patient Factors

Reviews^{15,16} have identified several patient factors that contribute to the risk of nonadherence or partial adherence with medication treatment. Adherence can be af-

ected by the patient's age, gender, and financial situation. The nature of the illness may make patients afraid to take medication, reluctant to give up pleasant symptoms like grandiose delusions, or have motivational difficulties. Patients may not have a clear understanding of the causes and severity of the illness, or may have a stigmatized perception of the illness that leads them to avoid treatment. Schizophrenia may affect patients' insight or judgment, making it difficult for them to understand their need for medication. Cognitive impairment can make patients unable to take their medication or forgetful, and they may have difficulty making a distinction between intention and actual performance. A study¹⁷ of 20 inpatients and outpatients showed that people with schizophrenia have particular difficulty remembering something that has to be done in the future, without explicit prompting. A study¹⁸ of 110 outpatients (45 years of age and older) with schizophrenia showed cognitive function, especially conceptualization and memory, to be the strongest patient-related predictor of ability to manage medication.

Comorbid substance abuse can be a crucial factor that together with nonadherence may lead to frequent hospital admissions. A study¹⁹ of 99 patients followed for 4 years after a relapse of schizophrenia showed that the median length of community survival time to first readmission achievable with antipsychotic medication (37 months) is reduced by substance abuse to 10 months and further reduced to 5 months when combined with nonadherence to medication. Compliant patients with comorbid substance abuse also remained in the hospital longer (mean = 32 days) compared with adherent patients who did not abuse substances (mean = 18 days).

Environmental factors, such as supportive caregivers with positive attitudes to treatment, can improve adherence to medication, while unsupportive, overly emotional, and demanding family members and significant others may have a negative effect on adherence to medication.¹⁶ Medical and nonmedical professionals and other patients

can either help or hinder positive attitudes to treatment, as can the patient's perception of the clinician's interest in him or her.¹⁵ Factors relating to the medication itself such as delayed onset of action, tolerability, and multiple dosage times can all contribute to poor adherence to antipsychotic medication.¹⁵

Physician Factors

Nonadherence to medication is usually seen as a problem deriving from patients' difficulties, but some studies have suggested that physicians' attitudes and behavior can inadvertently be a contributing factor to nonadherence.

Physicians tend to overestimate the adherence to medication of their own patients. A recent consensus survey²⁰ showed that although only 28% of schizophrenia patients were shown by the literature to be adherent, i.e., miss less than 20% of prescribed medication, physicians estimated the adherence of their own patients as 43%. Byerly et al.²¹ studied 21 patients over 3 months, defining nonadherence as $\leq 70\%$ using the Medication Event Monitoring System (MEMS) or $\leq 4\%$ on the Clinician Rating Scale. The MEMS uses a bottle cap that records when the bottle is opened. The trial showed 61.9% of patients to be nonadherent according to the MEMS compared with only 5.3% according to the Clinician Rating Scale. It is difficult for clinicians to address the problem of adherence to medication if they do not take into account their patients' potential nonadherence to the prescribed treatment.

In addition to overestimating patients' adherence to antipsychotic medication, physicians do not necessarily share consensus on treatment recommendations. More than 10 years ago, Kissling's study²² of the treatment recommendations of 213 German psychiatrists showed there was no consensus on treatment recommendations or on duration of maintenance treatment. Treatment recommended for patients who had a history of multiple episodes varied between the 5 hospitals involved in the study, and even within individual hospitals, there was no uniform recommendation. This lack of consensus led Kissling to postulate that improving physicians' treatment standards should reduce relapse rates of patients with schizophrenia because receiving uniform recommendations might decrease patient confusion about treatment and encourage them to adhere to their medication. He coined the term *doctors' noncompliance* to describe this problem.

Hamann and colleagues²³ tried recently to replicate Kissling's²² finding. Their study involved 50 physicians in state hospitals and 100 patients about to be discharged. Their findings showed that physicians' knowledge of scientific treatment guidelines had improved since the Kissling study. Physicians knew about the duration of maintenance therapy according to the guidelines for 75% of the patients. However, physicians communicated the recommendations according to the guidelines to only 33% of their patients. Only 11% of patients had an accurate

knowledge of the optimal duration of maintenance therapy. Clear communication with the patient can be a key to adherence.

Factors relating to both patient and physician contribute to poor adherence to antipsychotic medication. As both physicians and patients tend to overestimate adherence, measuring it is not straightforward.²⁴ But measuring treatment efficacy and dose response is difficult without accurate information on adherence to medication.²⁵ In order to improve adherence to medication, it is necessary to take into account the multiple factors contributing to patient nonadherence. Several strategies may be required to address a combination of factors.¹⁴ A pharmacologic strategy to make identification of noncompliance easier is the use of a long-acting injectable antipsychotic, but this topic is addressed elsewhere in this supplement.²⁶

PSYCHOSOCIAL INTERVENTIONS TO IMPROVE ADHERENCE

A strategy sometimes available to improve adherence to antipsychotic medication in patients with schizophrenia is psychosocial intervention. Psychosocial interventions offered to patients and families by either health professionals or experienced patients and families, or involving patients more in the treatment decision-making process, can be effective in improving adherence to medication.

Results of Psychosocial Interventions

Family interventions such as group sessions delivered by health professionals can effectively improve adherence to medication in patients with schizophrenia. A meta-analysis²⁷ analyzed 25 studies of family and patient interventions designed to inform patients and relatives and help them to cope with the schizophrenia. The results, measured by patient relapse rate, showed that family intervention can reduce relapse rates by approximately 20%. Interventions that continued for more than 3 months were particularly effective. The results were similar for different types of family intervention. Treatment that provided psychosocial support to relatives and schizophrenia patients along with medical treatment was clearly more effective than medication treatment only.

Psychoeducation for patients was shown by a Cochrane Review²⁸ to be effective in reducing relapse and readmission rates. This review of 10 studies showed that any kind of psychoeducational intervention significantly decreased relapse or readmission rates at 9 to 18 months' follow-up compared with standard care.

Despite the effectiveness of psychoeducation, the number of family members and patients taking part in this approach was shown to be low in a survey²⁹ of all psychiatric hospitals in Germany, Austria, and Switzerland. Data from the 54% of hospitals that replied to the survey showed that in 2003 only 2% of family members and only 21% of

patients with schizophrenia took part in psychoeducation about schizophrenia.

Resources

Lack of resources may be one of the reasons for such low numbers of people taking part in psychoeducation about schizophrenia. An example of a solution to this problem is Germany's Alliance Psychoeducation Program,³⁰ which provides educational materials for use by therapeutic teams. The program provides all the psychoeducation materials: manuals describing the educational modules, videos, flip charts, and documentation sheets. Although preparing psychoeducation materials is not difficult, it is time-consuming. A scheme like this means that therapists do not have to go through the process of developing the program themselves. One training workshop was presented, after which colleagues at these hospitals could deliver the material themselves.

Peer-to-Peer

Even if the psychoeducational materials are available, clinicians may not have time to deliver the program. Some other interventions involve patients and families who have a lot of experience with the illness in the provision of psychoeducation to other patients and families. This peer-to-peer psychoeducation has been studied by Rummel and colleagues,³¹ who developed a 5-step curriculum to train peer moderators. Recovered patients were trained to offer 8 group sessions, each 60 minutes long, for 6 to 10 patients at a time. A physician was present at the sessions and provided assistance if asked to do so by the moderators. The patients (N = 49) who participated in the groups were evaluated over a 6-month period for change in knowledge and concept of illness from baseline to endpoint. Participants' knowledge of illness improved significantly (N = 44, $p < .001$), and their concept of illness changed significantly in 3 subscales: trust in physician (N = 40, $p = .002$) and trust in medication (N = 40, $p = .001$) increased, while negative treatment expectations decreased (N = 40, $p = .001$). Patients' subjective assessments of peer moderators were positive, likely due to the credibility of having personally dealt with the illness.

Family-to-Family

Research³² into family-to-family psychoeducational groups has also been carried out. Interested and capable family members were trained as group moderators in psychoeducation for family members of patients with schizophrenia. A 5-step curriculum was developed and evaluated. Trainee moderators participated in a psychoeducation group and in training workshops, conducted psychoeducational group sessions with professional comoderation, independently conducted group sessions, and recruited future group moderators. Among families taking part, an increase from 70% to 80% occurred in knowledge

about schizophrenia and concept of the illness changed. There was high acceptance of family moderators by participating family members. This kind of intervention has limitations; for example, the family and peer moderators, although trained, cannot have the medical knowledge of a fully trained psychiatrist, and there is a need for a system of substitute moderators in case of absence.^{31,32} Although results on both peer-to-peer and family-to-family psychoeducation are preliminary, they deserve further evaluation.

Compliance Therapy

Another technique aiming at improvement of adherence is compliance therapy. This is a brief pragmatic intervention, based on motivational interviewing and recent cognitive approaches to psychosis, that targets treatment adherence in psychotic disorders. Focusing on insight and attitude toward the treatment, 4 to 6 sessions are administered. So far, only inconclusive data about the positive effect of the intervention are available.³³⁻³⁵

Shared Decision Making

Shared decision making is another approach that has the potential to improve adherence to medication. Although new to the treatment of patients with schizophrenia, this method has been applied for some time in other medical fields.³⁶ Unlike the "paternalistic" system in which the physician takes the major role in deciding on treatment, in shared decision making the physician communicates information about the illness, treatment options, and recommendations to the patient. The patient and the physician then jointly choose the treatment. Shared decision making also differs from the informed-choice model, in which the physician presents the patient with the information and the patient alone decides on treatment, such as getting vaccines for tropical trips. It is hoped that shared decision making will improve adherence to medication in schizophrenia treatment because the patient will feel more involved in the decision to take antipsychotic maintenance medication.

The German Ministry of Health is currently sponsoring a number of randomized, controlled studies on shared decision making in different medical areas. In the first trial³⁷ in schizophrenia, 107 acutely ill patients have been randomly assigned to either shared decision making or routine care and will be followed up at 6 weeks and 18 months. A 16-page booklet containing aids to help choose between oral or injectable medication has been produced to inform patients and prepare them for shared decision making. After consulting the booklet with a nurse, the patient and physician discuss treatment options and then make a joint decision on treatment. Research³⁸ involving 122 inpatients with schizophrenia using the Autonomy Preference Index and the Drug Attitude Inventory showed that patients with schizophrenia wanted to share the deci-

sion making with their physicians as much as patients from other medical fields and that this desire was particularly strong in younger patients, patients involuntarily admitted to the hospital, and those who reported negative attitudes toward antipsychotic medication.

CONCLUSION

Partial adherence is still an underrecognized problem in schizophrenia treatment. The underlying illness itself as well as patient and physician factors contribute to the risk of poor adherence to medication treatment. Poor adherence has a negative effect on treatment outcomes as demonstrated by relapse, rehospitalization, and attempted suicide rates. Nonadherence to medication prevents patients from gaining maximum benefit from medication. Psychosocial interventions have the potential to improve adherence to medication in patients with schizophrenia.

Disclosure of off-label usage: The authors have determined that, to the best of their 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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