Overview of Partial Compliance

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A substantial proportion of patients with psychiatric and nonpsychiatric chronic illnesses fail to take their medications as prescribed. A number of studies suggest that 50% or more of individuals with schizophrenia are noncompliant with medications at some time during their illness. In most cases, patients are partially compliant, taking only a portion of their prescribed medications. Noncompliance is probably the most important element contributing to relapse in schizophrenia. Factors contributing to the rate of noncompliance include medication side effects, the severity of psychotic symptoms, impaired cognition, and an inadequate understanding of the role of medication for preventing relapse. In addition, both patients and clinicians overestimate patients' compliance. Strategies for managing partial compliance include the treatment of medication side effects, the education of patients about their illness, and the use of long-acting antipsychotic formulations.

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Research carried out during the 1970s and 1980s established a number of principles of antipsychotic treatment for long-term maintenance therapy. The first principle is that antipsychotics are highly effective in preventing relapse in stable patients. A number of studies have managed stabilized patients with schizophrenia with either an antipsychotic or a placebo. Approximately 75% of individuals relapse with placebo, whereas only about 25% relapse with active drug.[1] The second principle is that patients derive greater benefit from antipsychotic treatment that is continuous rather than sporadic. Studies that have compared intermittent or targeted antipsychotic treatment with continuous treatment have almost always found that relapse rates were lower on continuous treatment.[2] The third principle is that patients who receive guaranteed drug delivery through a long-acting depot route have lower relapse rates than patients who receive oral medications.[3]

These principles provide a context for looking at the prevalence and impact of noncompliance in individuals who are receiving antipsychotic medications for schizophrenia and other disorders. Definitions of compliance differ, but it can be considered to be the degree to which a patient's behavior is consistent with medical advice.[4] The term *adherence* has been proposed as an alternative to *compliance* since it emphasizes the role of the patient as a collaborator in decisions regarding treatment. This article uses the terms interchangeably since both are commonly used.

PREVALENCE OF NONCOMPLIANCE AND PARTIAL COMPLIANCE

The prevalence of noncompliance in schizophrenia should be evaluated in the context of noncompliance in other medical conditions. A study by Cramer and Rosenheck[5] reviewed studies of medication compliance for both psychiatric and medical illnesses. Compliance in these studies was estimated using a number of methods from the least reliable method, which is questioning patients, to more reliable methods, such as urine testing and microelectric monitoring. Unfortunately, studies of antipsychotics tended to use the least reliable methods for monitoring compliance. The mean levels of compliance were 58% for antipsychotics and a slightly better 65% for antidepressants. The mean rate was 76% for medications for nonpsychiatric conditions. Other studies in arthritis and seizure disorders (reviewed by Fenton et al.[6]) have found somewhat higher rates of noncompliance. The study of nonpsychiatric patients is informative, since noncompliance in these individuals cannot be related to psychiatric symptoms such as suspiciousness, lack of insight, or depression. In other words, nonadherence is prominent in nearly every condition in which a patient is told to take a medication.

Other studies in schizophrenia have found similar rates of noncompliance. Young and coworkers[7,8] reviewed a number of studies that assessed rates of compliance. They

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reported a median noncompliance rate of 41% for oral medication and 25% for depot. Outpatients with schizophrenia who were followed for 2 years after hospital discharge had noncompliance rates of over 50%.[6,9]

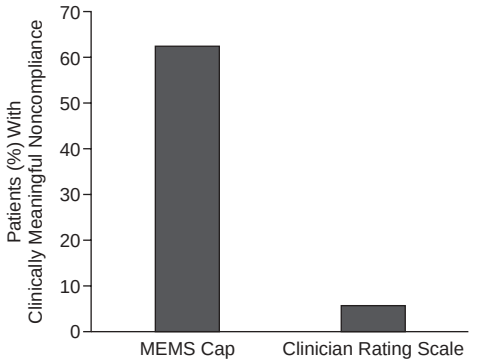
The high rates of noncompliance in nonpsychiatric conditions demonstrate the important point that a substantial amount of irregular pill-taking is not attributable to the psychiatric condition. Rather, nearly every individual who is asked to take a pill every day for a prolonged period of time will fail at one time or another to take his or her medication. Poor compliance is more common when patients are taking medication for an illness that is not experienced in active symptoms such as pain. That is, patients are more likely to neglect taking medications for illnesses such as hypertension, for which there may be no symptomatic reminders. The situation is similar for the prevention of relapse in stabilized patients with schizophrenia. That is, it is particularly difficult for patients to remember to take medication for an illness that they do not physically experience. In fact, these patients often initially feel better when they neglect to take their medications—whether antihypertensives or antipsychotics—since they are relieved of side effects. Relapse in schizophrenia may occur months after drug discontinuation, and the patient may fail to appreciate that the 2 events are linked.

PARTIAL COMPLIANCE IN SCHIZOPHRENIA

An important contribution of the Cramer and Rosenheck study[5] is that patients are not simply categorized as compliant or noncompliant. Rather, rates are expressed in terms such as the percentage of the recommended dose that is taken. This approach emphasizes that the typical behavior being studied is one in which patients take a portion of their prescribed medication rather than all or none of it. This behavior is referred to as "partial compliance." This practice is demonstrated in a review by Oehl and colleagues,[10] who reported that a third of patients reduce the dose of medication prescribed or take less than is actually prescribed. The concept of partial compliance is useful, since it permits patients to be classified on a continuum from those who refuse to take any medication to those who take all of their medication.

The level of partial adherence varies over time. Following a hospitalization or a recent exacerbation, patients are likely to take their medications relatively consistently. As time passes, the likelihood of noncompliance increases.[11] This increase is probably related to Barry Blackwell's[12] observation that compliance is associated with the patient's perceived need for medications, which decreases as time elapses following an episode in which the patient was symptomatic. This viewpoint is supported by a study by Weiden et al.,[9] who found that compliance with depot medication treatment tended to deteriorate over time. These observations indicate that a large proportion of patients—perhaps the great majority—will stop taking their medication if the clinician waits long enough. A history of reliable pill-taking should not be considered as evidence that the individual will not become partially compliant in the future, which suggests that clinicians should inquire about medication adherence on a regular basis.

Figure 1. Clinically Meaningful Noncompliance Measured by MEMS Cap and the Clinician Rating Scale[a]



[a]Adapted with permission from Byerly et al.[14] The between-group difference was significant at $p < .0001$.
Abbreviation: MEMS = Medication Event Monitoring System.

Compliance is also broader than just pill-taking. It includes making clinic appointments, participating in psychosocial treatment and rehabilitation, and other treatment-related activities. Assessments of medication compliance should include an evaluation of these other components of treatment.

There is also evidence that clinicians consistently underestimate the magnitude of noncompliance in their patients.[13] Byerly et al.[14] recently monitored compliance once a month during a 3-month study of 21 patients with schizophrenia (Figure 1). Compliance was assessed with electronic Medication Event Monitoring System (MEMS) caps that recorded how many times per day patients opened their pill bottles and by the Clinician Rating Scale, which categorizes patients' willingness to participate in treatment. On this rating scale, scores of 1 to 4 indicate reluctance or refusal to participate, and scores of 5 to 7, passive acceptance to active participation. Clinically meaningful noncompliance was defined as opening the pill bottle ≤ 70% of the required times during any month or receiving a score ≤ 4 on any of the monthly Clinician Rating Scale assessments. Evaluation with MEMS caps was significantly ($p < .0001$) more likely to detect clinically meaningful noncompliance than was assessment with the Clinician Rating Scale (62% versus 5%). This evidence suggests that psychiatrists may be unaware that patients are failing to take their medication and may assume that poor outcomes or psychotic relapses are related to an actual drug failure.

Patients also underestimate their level of noncompliance. Because methods of measuring compliance, such as

electronic monitoring and pill counting, can be costly or invasive, physicians often rely on patient reports to assess medication compliance. However, Lam et al.[15] found that patient reports were less likely to predict partial compliance than were plasma drug concentration evaluations and pill counting. For 3 months after being discharged from the hospital, 43 patients with schizophrenia were naturalistically followed to assess whether they were taking risperidone or olanzapine as prescribed. Compliance was defined as having ≤ 30% difference between baseline and 3-month plasma drug concentrations, taking ≥ 80% of one's pills, and rating one's compliance as 5 on a 5-point self-assessment of compliance, with 1 being the lowest level of compliance. Only 43.6% of patients were considered compliant by pill counting and even fewer—25.6%—by the plasma drug concentration evaluation. However, 67.5% of patients rated themselves as compliant. Although all of these methods of measuring compliance have a margin of error, patient reports appear to be the least reliable method of measuring medication compliance.

CAUSES OF PARTIAL COMPLIANCE

Partial compliance with treatment in schizophrenia or any illness in medicine cannot be explained by any single factor. For schizophrenia, there are a number of explanations. Weiden and colleagues[13] have provided a structure for evaluating the domains of nonadherence in schizophrenia. In this model, nonadherence to treatment interventions can be related to the disease features (e.g., suspiciousness regarding the treatment team), the treatment system (e.g., the use of appointment reminders), the treatment itself (e.g., unpleasant side effects of medications), interactions between the patient and therapist, patient characteristics (e.g., substance abuse), psychosocial factors (e.g., the family's attitude), and psychological factors (e.g., the role of stigma).

Van Putten[16] identified disease features in schizophrenia that were related to poor treatment adherence and reported that patients who had pleasant delusions, particularly grandiose delusions, were more likely to refuse their medications. This finding suggests that, for these individuals, the world of their delusions was preferred to their real lives. The result was poor medication compliance or outright refusal of medications.

There is also evidence that severity of psychopathology can influence treatment adherence. In a study of consecutive admissions to a day care program in New York, the severity of psychotic symptoms was the strongest predictor of medication noncompliance.[17] This association is supported by a study by Marder and coworkers,[18] who focused on the related issue of medication refusal. In their study, patients with more severe conceptual disorganization, hostility, and suspiciousness were more likely to refuse medication. The role of impaired cognition appears to be particularly important. Cuffel et al.[19] found that cognitive impairment was related to nonadherence. They also found that patients with cognitive impairment tended to report better adherence than actually occurred.

Patients who experience side effects are less likely to take their medications as prescribed.[16] This is particularly true for side effects that are uncomfortable to the patient and result in dysphoric responses. Van Putten et al.[20] found that a patient's response to a single question a day or a week following the start of medication, such as "How does this medication agree with you?" was a powerful predictor of whether patients would take their drugs and, therefore, whether treatment was effective. Van Putten and colleagues also found that mild side effects, such as mild subjective akathisia, could result in poor compliance when patients experience discomfort every waking hour. This observation is important because it emphasizes that clinicians need to inquire about a range of side effects and how these effects are experienced by patients.

There is other evidence that a patient's perception of his or her medication can have an important influence on adherence. A study by Grunebaum et al.[21] evaluated medication adherence in residential facilities. A negative view of medication—one that is likely to have been derived from side effects—was significantly related to the number of days in which patients failed to take medication.

Poor adherence can also occur when patients do not understand the goals of drug treatment. This can be particularly important in long-term maintenance treatment where patients may not understand that medication is taken for the prevention of relapse and should be continued even when the individual is symptom-free. For example, Herz and Melville[22] found that many patients believed that their medication was not helping them because it failed to make them feel better. These patients failed to understand that the medications were prophylactic. Not surprisingly, Pyne et al.[23] found that patients who did not believe they were ill were more likely to be nonadherent. Adams and Scott[24] found that patients who were noncompliant differed from compliant patients in their understanding of the severity of their illness as well as their ability to control the outcome of their disorder. These observations point to the likely value of education as a means for improving medication adherence.

The best approach to managing partial compliance may be to assume that, for any number of reasons, most patients receiving antipsychotics are likely to begin missing a portion of their medication if their clinician waits long enough. This suggests that adherence monitoring should be a component of every patient's treatment. Blackwell[12] suggests asking about medication-taking behavior in a manner that is nonthreatening to patients and that does not result in a defensive response. For example, patients can be asked about problems they may have with remembering to take their medications. This nonjudgmental ap-

proach may be helpful in facilitating communication with patients about episodes of nonadherence as well as their explanations of why doses are missed.

NONADHERENCE RATES WITH ORAL AND DEPOT MEDICATION

Nonadherence with depot medications differs in a number of respects from nonadherence with oral medications. There is the obvious difference that patients receiving depot medications are not required to remember to take their medications each day. Moreover, under some conditions, patients are administered injections in their own residence, eliminating the need for making clinic appointments. In other words, important factors that can lead to partial compliance are eliminated. In comparing rates of adherence, it is also important to consider that patients are often assigned to a depot medication because of a history of noncompliance.

There is some evidence that managing patients with depot antipsychotics leads to higher rates of medication adherence. Young and coworkers[7] reviewed 26 studies and found a mean default rate of 25% for depot medications compared with 41% for oral antipsychotics. A study of patients from urban and rural environments found compliance rates exceeding 90% for both settings.[25] Weiden and colleagues[9] found that inpatients with a history of noncompliance who were switched to a depot agent had higher rates of medication compliance at 1 month than patients who remained on treatment with oral medication. However, this difference was not statistically significant by 6 and 12 months, which suggested to the authors that switching to a long-acting program is probably not sufficient for maintaining compliance in this population.

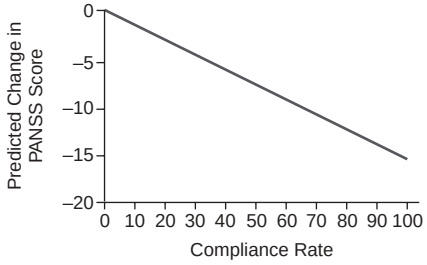
The advantage of depot medications for assuring treatment adherence may explain their advantages for lowering rates of psychotic relapse. Open-label studies—studies in which patients and clinicians were aware of the drug that the patient received—found much larger differences favoring depot over oral treatment. The difference probably results from the types of patients who enter these studies and the treatment conditions. Open-label studies usually take place in normal clinical settings and include typical patients who may be unreliable pill-takers. Double-blind studies usually include individuals who are selected because they are cooperative and compliant. Also, double-blind studies tend to have enriched staffs, and they tend to provide a higher quality of clinical care. As a likely result of these differences, double-blind studies are less conclusive. Nevertheless, in a review of 6 studies, Davis et al.[3] found that the results favored depot treatment in 5 of the studies. When the results were weighted for sample size, there was a statistically significant difference favoring depot. In addition, the comparison that lasted the longest[26] found an advantage for depot. In that study, relapse rates were similar for oral and depot medication during the first year following randomization, but lower for depot during the second year. In a meta-review from the Cochrane Schizophrenia Group, Adams and coworkers[27] found a statistically significant advantage for depot medications for global improvement, but not for other outcomes such as relapse and attrition. The authors acknowledge that the studies may be biased against depots, since few studies focused on the group of patients who are most likely to benefit from long-acting drugs, that is, noncompliant or partially compliant patients. On the basis of a similar literature review, the Schizophrenia Patient Outcomes Research Team (PORT)[28] concluded that there was an advantage for depot medications in preventing relapse.

When taken together, these studies suggest that one of the best strategies for managing noncompliance is to change patients to a long-acting antipsychotic. As pointed out by Fenton et al.,[6] there can be a relatively high rate of noncompliance in patients assigned to depot medication. However, the treatment team can monitor whether patients are receiving injections more easily than it can monitor whether patients are taking their pills. Unfortunately, the only depot antipsychotic agents currently available in the United States are haloperidol and fluphenazine decanoates. Patients are frequently reluctant to accept these conventional antipsychotics, which are also referred to as first-generation antipsychotics, and clinicians who are concerned about reversible drug-induced motor side effects, such as extrapyramidal symptoms and the risk for persistent drug-induced movement disorders such as tardive dyskinesia, may be reluctant to prescribe them. This has led to a gradual reduction in the proportion of patients with schizophrenia who are being treated with depot medications. The introduction of atypical antipsychotics, also called second-generation antipsychotics, that are available in long-acting formulations may reverse this trend.

CHOICE OF MEDICATION

The introduction of atypical antipsychotics in the 1990s raised the hope that the greater tolerability of these agents would result in higher rates of compliance. This hope is supported by a study by Dolder and coworkers,[29] who analyzed prescription refill records for patients taking older antipsychotics and atypical antipsychotics. Patients who received older drugs were without medications for an average of 7 days per month compared with 4 days per month among those receiving newer drugs, suggesting a small advantage for the new drugs. In a Veterans Affairs Cooperative Study comparing clozapine and haloperidol, Rosenheck and coworkers[30] found significantly better compliance among patients assigned to clozapine. Another study failed to find a significant difference favoring atypi-

Figure 2. Predicted Change in Positive and Negative Syndrome Scale (PANSS) Scores by Compliance Rate[a]



[a]Adapted with permission from Docherty et al.[32]

cal antipsychotics, although there was a nonsignificant advantage for the newer agents.[31]

Unfortunately, there are no well-controlled trials comparing depot conventional antipsychotics and oral atypical antipsychotics. Establishing the benefits and drawbacks of depot conventional versus oral atypical drugs is a critical need, given the number of individuals who have been transitioned off treatment with long-acting agents.

IMPACT OF NONADHERENCE

Nonadherence with medication regimens is among the most common causes of psychotic relapse and the need for rehospitalization. Fenton et al.[6] reviewed 7 studies and found that noncompliance rates were an average of 3.7 times higher in patients who were rated as noncompliant. In a 1-year study of open-label treatment with conventional antipsychotics or risperidone, Docherty et al.[32] found that 90.4% of the 565 patients were only partially compliant with their medication regimen. The group of patients with high compliance rates, i.e., ≥ 70%, had a greater reduction in schizophrenic symptoms than did those with low compliance rates, i.e., ≤ 69%. Patients with high compliance had an 18.4-point decrease in Positive and Negative Syndrome Scale (PANSS) scores, but patients with low compliance had only an 11.8-point decrease. Also, multiple regression analysis predicted a 0.16 change in the total PANSS score for every 1% variance in compliance rates (Figure 2). For example, a 25% decrease in a patient's compliance rate results in a 4-point worsening in his or her PANSS score. Differences in compliance and change in PANSS scores between conventional antipsychotic– and risperidone-treated patients were not significant.

Weiden and Glazer[33] studied patients who were frequently readmitted to an inpatient unit in New York. Noncompliance with medication regimens was the most common reason for rehospitalization, followed by nonresponse to medications. Haywood and colleagues[34] also found that noncompliance with medications, along with alcohol and substance abuse, was the most important factor related to a need for rehospitalization, or the "revolving door" phenomenon.

The cost of partial compliance in schizophrenia is substantial. Weiden and Olfson[35] found that nonadherence in schizophrenia accounted for about 40% of the annual costs of rehospitalization.

Other studies indicated that patients who relapsed when they were not taking their medications tended to have more severe relapses than those who relapsed while they were taking medication.[36] Those who relapsed while not taking medications were more likely to require involuntary hospitalization and were more likely to have attempted suicide or to have committed a violent act. This finding is supported by Swartz and coworkers,[37] who found that the combination of noncompliance with medication and substance abuse was related to the risk for violence in the community.

The study by Johnson et al.[36] also found that patients with schizophrenia who experienced a relapse did not return to their prerelapse level of social adjustment 1 year after recovery. This finding is important because it emphasizes that the cost of relapse is much greater than just the cost of rehospitalization. The cost of relapse may be particularly severe for patients with jobs and family responsibilities since they have the most to lose.

Other evidence indicates that remaining stable can mean considerably more than just staying out of the hospital. In a double-blind multisite study that compared oral fluphenazine and fluphenazine decanoate for 2 years, Hogarty and coworkers[26] found that patients who received fluphenazine decanoate demonstrated a lower risk of relapse than those assigned to oral fluphenazine. Moreover, the best outcomes were found for patients who received fluphenazine decanoate supplemented by a form of social therapy. In other words, protecting patients against relapse with a depot drug may enhance their response to psychosocial treatments or rehabilitation.

CLINICAL RECOMMENDATIONS

The failure of patients to reliably take their medications is the most important cause of psychotic relapse in schizophrenia. As a result, managing partial compliance is an essential component of any long-term plan for managing schizophrenia. Moreover, partial compliance is a manageable problem with strategies that can be individualized for many patients.

One of the most effective strategies for improving medication adherence is to reduce medication side effects that are troubling to patients. The side effects that trouble patients vary among individuals. For example, the lassitude and difficulty initiating physical movement from akinesia can be troubling to patients who are attending school or working. Other patients who are concerned about their

appearance may find even mild weight gain to be unacceptable. As a result, there will not be a single antipsychotic that is best for every patient.

Nearly all patients will prefer atypical antipsychotics to conventional drugs. The most distinct advantage of the newer drugs is that they can be administered at doses that do not cause uncomfortable reversible movement disorders. This advantage contributes to patients feeling subjectively better while taking these agents and less likely to refuse drug treatment. This advantage for subjective response is likely to have a major impact on the willingness of patients to remain on treatment with their medications.

Educating patients about the nature of schizophrenia and the role of antipsychotic medications has been demonstrated to be effective for improving outcomes, according to the Schizophrenia PORT.[38] More recently, specific interventions have been introduced to improve medication adherence. For example, psychoeducational programs are able to improve overall treatment adherence.[39] A study by Herz and colleagues[40] found that patients who received a treatment program that included psychoeducation, family treatment, and monitoring of prodromal symptoms had decreased relapse rates. Other studies have found that social skills training that directly focuses on issues of treatment adherence can be effective.[41,42]

Finally, there is a large body of evidence indicating that switching partially compliant patients to a long-acting depot medication can be an effective strategy for improving treatment adherence. Studies carried out prior to the introduction of atypical antipsychotics found that depot drugs were effective for large populations of individuals with schizophrenia. Although centers in the United States often reserved these drugs for patients with a clear history of noncompliance, these agents are used for a much broader group of patients in Europe. As long-acting forms of atypical antipsychotics are introduced, it will be important for clinicians to reconsider this form of treatment.

Drug names: clozapine (Clozaril and others), fluphenazine (Prolixin and others), haloperidol (Haldol and others), risperidone (Risperdal).

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

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