Partial Compliance and Patient Consequences in Schizophrenia: Our Patients Can Do Better

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Objective: The primary objective of this review is to evaluate the strategies used to improve patient compliance with antipsychotic medication in the treatment of schizophrenia.

Data Sources: An electronic literature search of relevant studies using MEDLINE and the Cochrane Library (January 1974–December 2002) was performed using the search terms *adherence*, *antipsychotic*, *atypical*, *compliance*, *conventional*, and *schizophrenia*.

Study Selection: English-language and non-English–language articles, references from bibliographies of reviews, original research articles, and other articles of interest were reviewed.

Data Extraction: Data quality was determined by publication in the peer-reviewed literature and the most important information was identified.

Data Synthesis: Atypical antipsychotics are associated with an improved side-effect profile and reduced risk of relapse compared with the older agents. Additional benefit may be provided by long-acting injectable formulations as they provide the confidence of continuous medication coverage.

Conclusions: Successful treatment of patients with schizophrenia requires acknowledgment that partial compliance will present a major barrier to achieving maximum outcomes. Ideally, all patients suspected of partial compliance should be considered suitable for treatment with a long-acting injectable atypical antipsychotic.

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Successful treatment of most chronic illnesses has been compromised by the difficulty in taking medication continually over an extended period of time. For example, medication compliance is estimated at 67% for asthma at 20 to 25 months, 25% for diabetes at 6 months, 67% for rheumatoid arthritis at 2 years, and 53% for hypertension at 6 months.[1–4] For psychotic disorders, the estimated rate of noncompliance may be as great as 80%, depending on the type of psychotic disorder and the length of follow-up.[5] We conducted a survey of 20 psychiatrists, asking them to rank a number of illnesses from 1 to 100 according to the difficulty in obtaining compliance sufficient to produce therapeutic benefit. Only weight-reduction therapy exceeded schizophrenia treatment as more difficult with which to achieve compliance (Figure 1). This review explores 3 principal questions about partial compliance in schizophrenia:

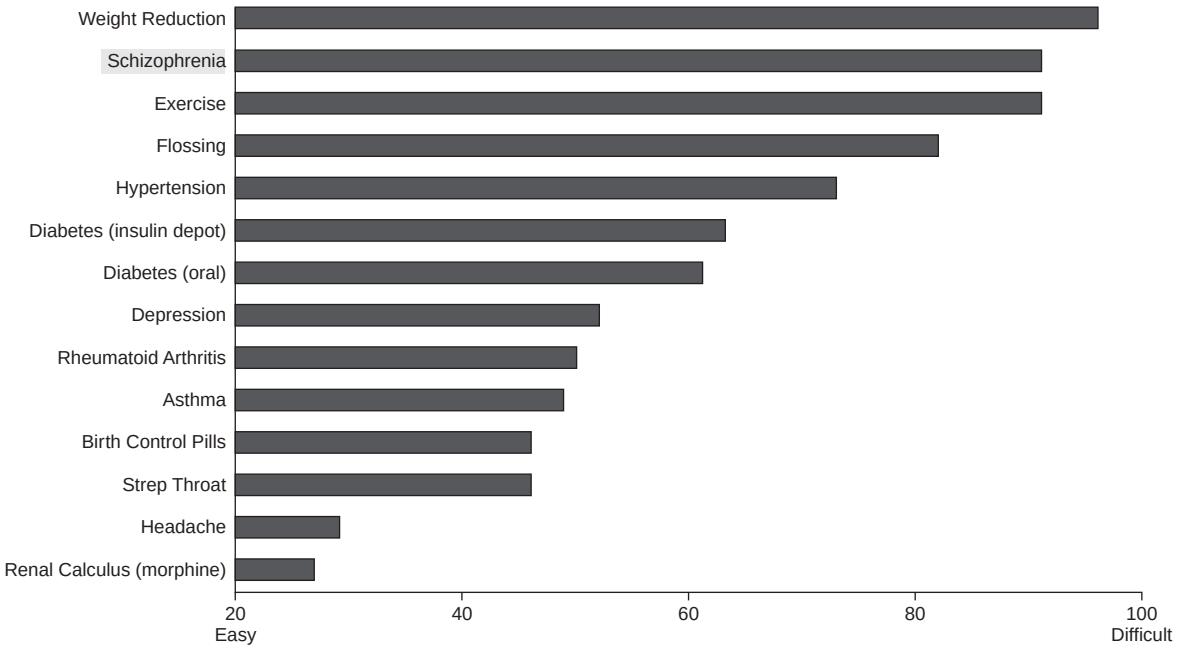
1. What is the extent of partial compliance?
2. How much compliance is sufficient to provide efficacy and prevent relapse?
3. Are we able to identify partially compliant patients with a degree of certainty?

COMPLIANCE, ADHERENCE, CONCORDANCE

Compliance relates to the extent to which patients' behavior corresponds with advice given by their physicians.[6] Our use of the term *compliance* is not intended to be judgmental. It is simply a statement of fact; there is no blame assigned to the prescriber, the patient, or the treatment regimen. *Adherence* and *concordance* are often used as synonyms for *compliance*. Unfortunately, many studies of compliance do not include a precise definition, and, as compliance is not an all or nothing phenomenon, patients are often "partially compliant." Patients who partially comply with their treatment regimen have accepted their diagnosis and requirement for treatment; however, they do not receive maximum benefit from their treatment regimen[7,8] and, therefore, may appear to be nonresponsive or only partially responsive to their antipsychotic therapy.

Physicians frequently question how much compliance is sufficient to ensure adequate antipsychotic coverage. Unfortunately, predicting a patient's outcome is never

Figure 1. Degree of Difficulty to Produce Adherence Sufficient for Therapeutic Effect: Psychiatrists' Assessment



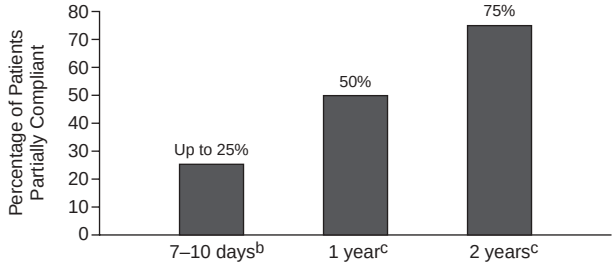
possible, and, often, the issue of partial medication compliance becomes evident in a patient only following multiple relapses. Identification of the problem post-relapse is too late for the patient, and earlier recognition and intervention are essential. Clinician assessments of compliance dramatically underestimate the level of noncompliance, thus, methods such as electronic monitoring are preferable.[9] In clinical practice, clinicians often rely on patient reports of medication compliance; a recent study reported that patients tend to overestimate their level of compliance.[10] Estimates of noncompliance with oral antipsychotics, using a median default rate, have ranged from 12% to 65% over a 6-month period.[11,12]

There are many ways to assess compliance, each with its own set of problems: evaluating refills, although refilling a prescription is only the initial step in taking a medication; counting pills, which is seen by many as intrusive and subject to manipulation; using multiple sources of history (e.g., patients and families), which frequently leads to divergent results and uninterpretable information; and measuring serum levels of the drug, which is easily manipulated, as it shows only recent medication activity.[13] It should be noted that the wide variation in assessed compliance rates with antipsychotic medication may be due, in part, to the methods used, including compliance measure (qualitative versus quantitative, self-report versus informant-report, direct versus indirect), observation period, and criteria for noncompliance (any deviation from medication regimen versus an acceptable range).[14]

Estimates today of sufficient doses of antipsychotic medication to ensure optimal coverage and prevention of symptom exacerbation and relapse would differ substantially from those of the late 1970s. In the earlier years of traditional antipsychotic treatment, patients were often treated with strikingly high doses of medication. Dosing studies, however, concluded that up to an 80% reduction of dosage was possible and led to the development of dosage-lowering strategies.[15] It was found that giving 2.5 to 10 mg of fluphenazine decanoate every 2 weeks did not result in more hospitalizations than did giving 12.5 to 50 mg every 2 weeks; however, it did result in more symptom exacerbations. It should be noted that this was continuous (not intermittent) treatment. Patients who received targeted or intermittent treatment at the onset of symptoms exhibited poorer outcomes.[15] Studies like these generated a much lower dose standard for the treatment of patients, and the practice is now well established: patients should be treated with the lowest possible dose.

The downside of this current practice is that patients are often now treated with the critical lower limit of medication and any further reduction through partial compliance presents a risk of relapse. In the past, when patients self-administered a lower dose as a consequence of partial compliance, they may still have been in the therapeutic range. Currently, however, further lowering of the dose as a result of partial compliance may substantially increase the risk of relapse. Although a precise estimate of the dose limit that constitutes a risk is impossible to determine, several clinicians consider adhering to < 70% of the

Figure 2. An Illustration of the Time Course of Antipsychotic Medication Compliance[a]



[a] Partial compliance in schizophrenia starts within days of medication initiation and prevalence increases over time.
[b]Data from Lam et al.[16]
[c]Data from Weiden and Zygmunt.[17]

prescribed regimen unsatisfactory. However, this will depend on such factors as the dosage prescribed, the half-life of the medication, patient characteristics, and level of environmental stress.

It is also important to note that rates of partial compliance with antipsychotic treatment in patients with schizophrenia increase over time with discharge from an inpatient facility. Surprisingly, a recent study showed that even under closely monitored conditions (staff monitoring, pill counts, patient reports, pharmacy records, and blood levels), 15% to 25% of the 51 patients enrolled were classified as noncompliant within 7 to 10 days.[16] This trend continues, according to the literature, with at least 50% of patients becoming partially compliant or noncompliant within 1 year, and 75%, within 2 years of discharge[17] (Figure 2).

FACTORS THAT INFLUENCE COMPLIANCE RATES IN PATIENTS WITH SCHIZOPHRENIA

Table 1 includes some of the factors that can contribute to reduced medication compliance in patients with schizophrenia. The management of schizophrenia—a chronic psychiatric disorder—necessitates long-term, continuous treatment to minimize rates of relapse and provide clinical benefit to patients.[18,19] As schizophrenia typically presents in late adolescence or early adulthood, individuals stricken with the illness and their family members often underestimate the burden and complexity associated with the treatment of a chronic illness. Most of these patients and their family members are only familiar with an acute model of disease: they take an antibiotic for 10 days or set a broken bone in a cast. Being unprepared for extended treatment is a real issue for both families and patients who may have never previously dealt with either a chronic or a mental illness. Furthermore, the nature of schizophrenia may contribute to partial compliance; the positive symptoms of this illness may distort insight,[20,21] the negative

Table 1. Factors Influencing Medication Compliance in Patients With Schizophrenia[a]

Poor insight
Negative attitude or subjective response toward medication
Previous noncompliance
Inadequate discharge planning or aftercare environment
Poorer therapeutic alliance

[a]Adapted with permission from Lacro et al.[14]

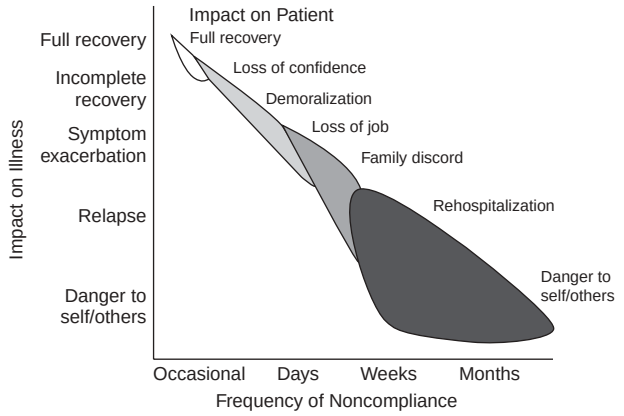
symptoms reduce will and drive,[22] and the cognitive deficits affect attention and memory,[23] all of which are necessary for consistent medication compliance.[24–27] Thus, it is hardly surprising that complex medication regimens are especially difficult for patients with schizophrenia who perform poorly on cognitive tests such as the Wisconsin Card Sort Test (WCST).[28]

Several studies have shown an association between poor cognitive function and noncompliance or partial compliance and confirm that compliance improvements can be attained using motivational or cognitive enhancement therapy.[25,26,29] Although poor baseline performance on the WCST predicted medication adherence in one study,[30] medication compliance was assessed on the basis of patient self-report, and neurocognitive status has been shown to bias compliance reporting in patients with schizophrenia.[25]

Unfortunately, the social stigma associated with treatment of psychotic disorders may also be a barrier to some patients' compliance with their prescribed regimen,[31] and, until recently, antipsychotic treatment–related side effects added to the stigma of the illness.[32–34] Extrapyramidal side effects and the risk of tardive dyskinesia are also major contributing factors to noncompliance in patients treated with antipsychotic medication.[35] It has also been suggested that weight gain induced by antipsychotics may affect compliance and morbidity.[36] Dosing schedule clearly influences compliance rates in the treatment of a number of nonpsychiatric diseases,[37] suggesting that a once-daily antipsychotic will promote compliance. The newer atypical antipsychotics olanzapine and risperidone have been shown to be efficacious in a once-daily dose,[38,39] unlike other atypical agents.

Environmental factors such as security and supportiveness correlate positively with compliance,[12] while patient characteristics such as age, gender, and ethnicity show no correlation with compliance rates.[40] Inadequate patient education and the resulting lack of understanding of the disease process may reduce compliance rates as patients fail to see the benefit of treating hallucinations and delusions with pharmacologic agents.[31] Patient attitude also plays a major role in compliance rates; patients may make a conscious decision not to comply with their medication regimen because they are in denial of their illness, or they may decide that they no longer require medication, believing they are "cured" following remis-

Figure 3. Downward Spiral Illustrating the Increasingly Detrimental Impact of Continued Partial Compliance on the Patient and on the Prognosis Over Time



sion of an acute psychotic episode.[41] When patients tell the clinician that they take an extra pill on a "bad day," it suggests that on a "good day" they may take less or no medication.

IMPACT OF PARTIAL COMPLIANCE

The impact of partial compliance or noncompliance with antipsychotic medication may be underestimated, since missing a dose or even stopping medication completely does not lead to immediate symptomatic consequences. In psychiatry, compliance is an important issue because the subtherapeutic drug levels achieved in patients with schizophrenia who only partially comply with their antipsychotic medication may be associated with both short-term and long-term negative outcomes such as symptom exacerbation, relapse, and self-injurious behavior.[41,42] Figure 3 illustrates the impact of continued partial compliance on the patient and on prognosis. Partial compliance is likely to precipitate symptom exacerbation, ultimately leading to increased hospitalization and relapse risk and thus poorer prognosis.[18,43,44]

Partial compliance or noncompliance with oral antipsychotics may be misinterpreted by clinicians as efficacy failure. It is important that psychiatrists are aware that the early warning signs of partial compliance with antipsychotic therapy may not be evident in patients treated with oral agents in time to intervene successfully; failure to note such warning signs may lead to relapse and rehospitalization. Studies have evaluated the difference in outcome between continuous medication compared with targeted medication reinitiated on the appearance of signs of relapse or prodromal symptoms.[15,18,19,45–47] Targeted treatment was associated with an increased risk of relapse and rehospitalization. It has been suggested that the majority of patients who require rehospitalization (73%) did not comply with their medication.[48] Thus, noncompliance bears a significant impact on relapse, rehospitalization, and patient outcome. Even with intensive monitoring for prodromal signs of relapse, medication discontinuation is associated with significant increase in risk of relapse and rehospitalization.

COMPLIANCE RATES WITH ORAL ANTIPSYCHOTICS

Both classes of antipsychotics, conventional and atypical, are available in oral formulations. Conventional antipsychotics are potent antagonists at the dopamine (D_2) receptor, while the more recently developed atypical antipsychotics have additional high affinity for serotonin receptors.

Two recent studies have shown surprisingly little difference in prescription refill rates between oral atypical and conventional antipsychotic medication. In a 1-year naturalistic study, Mahmoud et al.[50] found that 5% of those taking conventional antipsychotic medication had no missed doses compared with 7% taking atypical antipsychotics. The mean number of days per year without prescription refills favored the atypical medication, but only by 15 days (110 days versus 125 days); for approximately one third of the year, patients in both groups could not have taken their prescribed antipsychotic medication because the prescription was not refilled.[50] In a second study, patients treated with conventional antipsychotics were without medication for an average of 7 days per month while patients treated with atypical agents were untreated for only 4 days per month. At 12 months, there was a higher, though not statistically significant, compliance rate in patients treated with atypical compared with conventional agents (mean ± SD = 54.9% ± 26.0% vs. 50.1% ± 30.6%; p = .11).[40] The significance of this study is that it was carried out in the Veterans Administration Hospital system, where medication cost was not a factor.

A comparison of clozapine with haloperidol in 423 patients in a double-blind, randomized, multicenter trial showed no difference in compliance rates.[51] In addition, a retrospective study of 60 inpatients also found no significant relationship between compliance and the type of antipsychotic medication.[52] In the absence of a difference in compliance rates with various oral agents, the treatment decision should be based on efficacy and tolerability data.

Atypical agents have been shown to provide at least comparable efficacy compared with that of the earlier conventional agents in randomized clinical trials. A review of studies comparing risperidone and haloperidol concluded that risperidone provided greater clinical efficacy with a better side-effect profile.[53] Furthermore, beneficial effects of the atypical antipsychotics on the treatment of negative symptoms have been demonstrated.[54] As

motor side effects are associated with high D_2 receptor occupancy, the multi-receptor action of the newer atypical agents with less D_2 receptor affinity provides a lower risk of extrapyramidal side effects. In a 1-year study involving 397 patients with schizophrenia or schizoaffective disorder, the scores on the Extrapyramidal Symptom Rating Scale (ESRS) were reduced in the risperidone-treated patients and increased in the haloperidol-treated patients.[55] The difference between the 2 antipsychotics was significant on each measure of the ESRS.

Additionally, the newer atypical antipsychotics are regarded more positively than older conventional agents in terms of efficacy.[56] In a double-blind, randomized, prospective study, 397 adult outpatients with clinically stable schizophrenia or schizoaffective disorder were assigned to treatment with oral risperidone or oral haloperidol for a minimum of 1 year. At study endpoint, the risk of relapse was estimated at 34% in the risperidone treatment group and 60% in the haloperidol-treated group ($p < .001$).[55] Furthermore, the mean change from baseline to endpoint on the Positive and Negative Syndrome Scale (PANSS) for schizophrenia was significantly greater in patients treated with risperidone than in patients treated with haloperidol for total scores ($p < .001$) and in 4 of the 5 subscores (positive symptoms [$p = .004$], negative symptoms [$p = .003$], disorganized thought [$p = .01$], anxiety/depression [$p = .005$]).[55]

Overall, no consistent significant differences exist between compliance with oral atypical and oral conventional antipsychotics. However, as one study provides strong support that the use of an atypical antipsychotic can substantially reduce the risk of relapse in patients with schizophrenia even under the circumstance of equivalent compliance as evaluated by pill counting,[55] atypical antipsychotics are likely to provide superior efficacy. The combination of an atypical antipsychotic with strategies to maximize compliance should therefore improve treatment outcomes.

COMPLIANCE WITH LONG-ACTING INJECTABLE ANTIPSYCHOTICS

There are a number of advantages to long-acting injectable medications that are not often considered. The major advantage of administering a "depot" antipsychotic is the promotion of compliance.[31] Although depot antipsychotics cannot eliminate noncompliance, they do prevent covert noncompliance,[44] since compliance to long-acting injectable agents can be immediately identified.[57] Even with missed injections, there is time to intervene before the appearance of symptoms.[44] Thus, compliance failure can be differentiated from efficacy failure in patients treated with long-acting injectable agents, thereby reducing the use of rescue medications and the need for switching to a second-choice antipsychotic.

The majority of evidence indicates that depot medications can increase compliance and reduce relapse rates.[42,58] One study showed that inpatients switched from an oral to a depot antipsychotic had significantly better compliance at 1 month; however, this effect declined over time, suggesting that additional interventions are beneficial in maintaining the compliance benefits of depot medications.[43] Furthermore, treatment guidelines recommend the use of depot medications for patients who are suspected of noncompliance with oral medication.[59]

Relapse rates are reported to be lower in patients who are treated with conventional depot versus conventional oral antipsychotics in a number of trials[60–63]; however, one study that compared oral pimozide and fluphenazine decanoate does not support this.[64] Potential explanations for the lack of effect seen in this study are the agents employed and the duration of treatment. However, a meta-analysis of studies comparing oral and depot conventional antipsychotics revealed a highly significant reduction in relapse rates with the use of long-acting formulations ($p = .0002$, Mantel-Haentzel test).[42] It should be noted that clinical trials may minimize the differences between oral and depot medications that occur as a result of differences in compliance. The procedures required in a clinical trial make it more likely that participants will comply with medication.[65] Furthermore, the use of such preparations frees the patient from taking daily pills and facilitates consistent contact with the treatment team.[31] Such clinical benefits of long-acting injectable antipsychotics support the extensive use of such preparations in patients with schizophrenia; however, conventional depot antipsychotics represented only 55.1 million days of therapy in 2001, which represents only a 5.0% share of the overall antipsychotic market.[66]

Long-acting injectable preparations of a number of antipsychotics such as flupenthixol, fluphenazine, zuclopenthixol, and haloperidol have been available since the 1960s. However, in the United States, only fluphenazine and haloperidol are available, and, importantly, all the long-acting injectable preparations available until this year are of the conventional subtype of antipsychotics.[67] In addition, long-acting injectable conventional antipsychotics are formulated as oil-based preparations, which cause injection site pain and reactions. Such conventional depot preparations are also associated with a number of other limitations such as extrapyramidal side effects and weight gain.[44,68] Thus, there is an urgent need within the field of psychiatry to develop a long-acting, injectable atypical antipsychotic agent that will allow patients to achieve symptom control in a convenient and effective manner. The first long-acting injectable preparation of an atypical antipsychotic, risperidone, is due to be released shortly in the United States. This preparation of risperidone, designed for intramuscular administration every 2 weeks, has been developed as an aqueous suspension of risperidone,

thus eliminating some of the pain associated with oil-based injections of the current injectable antipsychotics.[69]

Some patients prefer not to use conventional, long-acting injectable preparations, for reasons such as aversion to injections, injection site pain, fear of adverse events, and feelings of "being controlled."[31] Thus, it is important that physicians work closely with their patients to establish the benefits of an injectable preparation and spend time over a series of patient visits promoting patient acceptance of this form of treatment. Interestingly, a review of 6 studies demonstrated that patients expressed a preference for long-acting injectable medication in 5 of the studies. In the sixth study, the preference for an oral agent was specifically the atypical antipsychotic risperidone.[70]

As a significant proportion of patients with schizophrenia are only partially compliant with their therapeutic regimen,[48] the administration of a long-acting preparation may provide significant advantages. Long-acting injectable formulations should not be considered solely for use in patients who are thought to be unable to comply with oral medication; long-acting injectable preparations may provide significant clinical benefit to a range of patients with psychotic symptoms if prescribed routinely,[71] as they should immediately identify, and thereby minimize, covert noncompliance.

IMPROVING MEDICATION COMPLIANCE IN SCHIZOPHRENIA

Patients who are persistently noncompliant and exhibit a lack of treatment response may in fact be masking the value of some antipsychotic medications. Continually switching these patients from one antipsychotic to another or adding adjunctive medication may or may not induce a transient improvement.[72] Practically speaking, the most straightforward way to improve compliance would be to simplify the dosing schedule. In practice, continuing medical care and interaction with the treatment team become important to improving compliance.[73] Providing adequate patient education regarding side effects and disease progression may also help to improve compliance and build an alliance between the patient and the treatment team.[74] Cognitive-behavioral interventions such as "compliance therapy" have been shown to improve insight, attitude, and compliance for a sustained period of time.[75]

Patient noncompliance with oral medication is, of course, dramatically affected by the administration of long-acting injectable formulations of the currently available antipsychotics. There is a drawback, however, as all long-acting injectable antipsychotic agents available to date are conventional agents and are, therefore, associated with significantly higher risk of motor side effects compared with the atypical agents. Studies have clearly demonstrated that most patients who have had experience with depot formulations will choose a depot medication when given the option between a conventional oral versus depot and will choose an atypical oral antipsychotic agent over a conventional depot agent. The need for a long-acting injectable formulation of the atypical antipsychotic agents could not be more compelling. Furthermore, although assurance of patient compliance may be achieved with the use of a long-acting injectable antipsychotic, it has been demonstrated in the United States that clinicians prescribe long-acting injectable antipsychotics relatively infrequently despite high rates of noncompliance with oral agents.[44] It is suggested that this effect may be due to clinicians prescribing atypical antipsychotics as a first-line therapy and reserving the use of conventional long-acting formulations to those patients with a history of noncompliance and relapses.

CONCLUSIONS

Up to 80% of patients with psychotic disorders fail to comply with their medication regimen at some point during the course of their treatment.[5] Early warning signs of such partial compliance may be confused by some clinicians with nonresponse to treatment and may result in switching these patients to alternative oral antipsychotic medication, adding adjunctive medication, or, even worse, relapse or rehospitalization. The reduced incidence of adverse side effects, such as motor disorders, with atypical antipsychotic agents has the potential to improve compliance rates in patients receiving continued medication for schizophrenia, yet the improvements in compliance rates observed with atypical agents are surpisingly small compared with those observed with conventional agents.

Administration of long-acting injectable preparations of an antipsychotic will increase patient contact with the treatment team and provide confirmation of whether patients have taken their medication. Furthermore, it allows physicians a means of distinguishing nonresponse from noncompliance. Currently, however, the use of long-acting injectable preparations is limited by clinicians' reluctance to prescribe conventional depot agents when atypical oral agents are available, lack of patient acceptance of injectable agents, and fear of adverse events associated with the use of conventional antipsychotics. Strategies to improve patient compliance with antipsychotic medication are warranted in order to give patients the greatest opportunity for success, even for patients receiving the newer oral atypical agents. The need for earlier recognition, intervention, and future prevention of partial compliance by clinicians is essential to successful treatment of our patients with schizophrenia.

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

Disclosure of off-label usage: The authors of this article have determined that, to the best their knowledge, pimozide is not approved by the U.S. Food and Drug Administration for the treatment of schizophrenia, and flupenthixol and zuclopenthixol are not approved for use in the United States.

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