# Perspectives on Medication Adherence and Atypical Antipsychotic Medications

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***Introduction by the column editor:*** **The problem of noncompliance is one that affects all areas of medicine. Some opinion holds that it may be worse for psychiatric disorders, particularly the psychoses, and that the side effects of the older or conventional antipsychotics have played a major role in poor compliance. Side effects have also been proposed as the reason long-acting medications have been unpopular in the United States. This explanation, like many others, seems a bit simplistic and would not explain why European countries and Australia use ten times as many long-acting drugs as the United States.**

**The arrival of atypical antipsychotics, with their lower rate of extrapyramidal effects, was greeted positively as an advance on the older drugs. It was suggested that the lower rate of side effects would improve compliance. However, few data to support this suggestion have been reported.**

**In this month's column, Dr. Velligan and colleagues deflate that suggestion and detail the abysmal compliance level of a group of patients in Texas—some of whom were living in supervised residences—who were receiving atypical antipsychotics. Clearly, compliance is a complex issue and needs more attention than is now devoted to it.**

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Recent advances in medication treatments for patients with schizophrenia have included the development of a number of atypical antipsychotics that produce fewer extrapyramidal side effects and may have a broader range of efficacy than conventional antipsychotics (1). It has been widely assumed that the introduction of these second-generation antipsychotics would lead to improved treatment adherence for patients with schizophrenia. Although it may be that the improved side effect profiles of the novel antipsychotics have increased patients' willingness to take medications, little evidence exists that treatment adherence has been significantly improved by these antipsychotics. The continued decline in rates of depot neuroleptic use may in part reflect a belief that atypical antipsychotic medications have solved the nonadherence problem.

Recent studies that examined prescription fill rates have suggested that significant problems with adherence remain. One study reported that adherence was higher among outpatients taking atypical antipsychotics than among outpatients taking conventional antipsychotics. However, even in the group receiving atypical antipsychotics, adherence over 12 months was only 55 percent (2). In a study of more than 600 outpatients, Docherty and associates (3) found no differences in adherence rates between patients taking haloperidol and patients taking risperidone over a one-year period. In the sample as a whole, patients were in possession of their medication only 60 percent of the time. Prescription fill rates identify the number of days on which medication is available to the patient during a specified period rather than how much medication is actually taken. Therefore, fill rates may underestimate the problem of noncompliance.

In this column we describe our experiences with the first 68 patients recruited for participation in a five-year study of treatment adherence and outcomes in schizophrenia, funded by the National Institutes of Health. Although our study sample is still being recruited, our preliminary findings and clinical observations were sufficiently worrisome that we wanted to share them sooner rather than later. We briefly describe our preliminary data on adherence to the atypical antipsychotic medications and suggest ways to improve adherence.

## Methods

The sample was composed of 68 patients recruited at the time of hospital discharge. After participants had signed an informed consent document approved by an institutional review board, all medication intake was

monitored during a baseline blood draw period of about ten days to two weeks. During that time, our staff made home visits several times per day, depending on dosing schedule, to observe all medication taken. Initially, we did not monitor participants in board and care facilities with this intensity, assuming that the group-home staff would administer medication as prescribed by treating physicians. However, only 60 percent of all medication doses were administered to the first 14 participants discharged to board and care homes early in the study. A total of ten of these 14 participants missed multiple doses. This prompted us to observe all doses taken during the baseline period, even for participants residing in group homes.

Between the baseline period and three months, at the end of each month—approximately twice for each participant—study staff spoke by telephone with the participants or others living with them to determine whether the participants still lived at the same address. Assessments were then made at three months; they included blood level analysis, pill counts, pharmacy records, and self-report.

Of our initial 68 participants; 43 (63 percent) were men. A total of 26 (38 percent) were Hispanic, 21 (31 percent) were non-Hispanic white, and 21 (31 percent) were African American. The mean±SD age of the participants was 37.4±11.5 years. Of the original sample, 34 participants lived in group homes after discharge and 34 lived in private homes or apartments. Of the 68 participants recruited, 55 received both baseline and follow-up assessment. A total of 13 patients were lost to follow-up. Three were dropped from the study for dangerousness, two moved away to live with family, and one no longer wanted to participate in the study. The remaining seven patients were dropped because they were jailed or hospitalized at the time of follow-up. Although additional patients were hospitalized and jailed briefly during the follow-up period, they were available for assessment at three months and were not dropped from the study.

## Results

### *Adherence immediately after discharge*

None of the 68 participants completely refused to take medication during the baseline period. However, 4 percent of the participants (three of 68) refused at least one dose, and, as noted, ten of 14 group-home participants missed doses. In addition, seven other participants were not home or did not answer the door to take medications during at least one medication visit. Therefore, 17 participants (25 percent) had already missed medication doses during the ten-day to two-week period following hospital discharge, which was the baseline blood draw period.

### *Clinical observations*

Observations during our first home visit suggested that discharge instructions were routinely misunderstood. In many cases, as a result of short lengths of stay, individuals had been discharged from the hospital while still experiencing high levels of psychotic symptoms. It is unlikely that they were able to attend to and remember the instructions delivered by the hospital treatment team. We found that several participants were planning to take both the recently prescribed antipsychotic and the antipsychotic that was prescribed before their index hospitalization, not understanding that one medication was intended to replace the other. We frequently found bottles of the same medication from both inpatient and outpatient pharmacies. When questioned, participants reported that they were planning to take medications from both bottles. On several occasions, we found bottles containing different strengths of the same medication. Patients had apparently combined bottles labeled with the same medication name in an effort to be efficient. Without our monitoring, this practice would have resulted in participants' taking less than their prescribed dose on an unspecified number of occasions. Furthermore, we discovered while counting pills that different types of medications, such as antipsychotics and mood stabilizers, were mixed in the same bottles. When questioned, participants were unable to identify accurately the different pills in these containers.

We also found evidence of nonadherence or partial adherence that predated the participants' index hospital admission and participation in the study. We found between two and 22 bottles of antipsychotic medications that had not been taken. The amount of unused medications found in only this small sample of patients is suggestive of the potentially large amount of health care dollars wasted on nonadherence.

### *Living environment*

Multiple problems with living environment and daily routines were identified as barriers to treatment adherence. The places where several individuals kept medications—for example, in their cars or at the homes of relatives—made it unlikely that they would be able to take all doses prescribed. Many participants were asleep at several dosing times, and if our staff had not woken them during the baseline period, they would probably have missed more than 50 percent of their doses. Participants' lives were often chaotic and unstructured. Several slept at the home of a different relative each night of the week. Many did not eat regular meals or follow a regular hygiene routine that could be linked with taking medication.

Even participants who resided in group homes missed doses of medication during the initial follow-up period. If group-home participants were not present at medication distribution times or failed to appear at the distribution desk, residential care staff were rarely able to follow up to see that medications were taken at a later time.

### *Three-month follow-up*

In the period between baseline and three-month assessment, 25 percent (17 of 68) of these patients were readmitted to the hospital, and 12 percent (eight of 68) went to jail or became homeless. With preestablished criteria for each assessment method, we divided the 55 participants assessed at discharge and three months into adherent and nonadherent groups. For each method, participants who were

taking at least 80 percent of their prescribed dose were considered adherent by our study criteria.

By pill count, only 40 percent of participants were adherent, and only 9 percent of these participants took all doses prescribed during the three-month period. Analysis of blood level data suggested that the adherence rate was only 23 percent. In contrast, 55 percent of participants reported that they were perfectly adherent.

## Discussion and conclusions

Adherence to oral antipsychotic medications remains a significant problem among persons with schizophrenia. The low level of adherence observed in this group of patients is likely to have contributed to the high rates of relapse and readmission we found. These participants, who were recently released from a state psychiatric facility, are likely to be among the most vulnerable to relapse as a result of low levels of adherence. Our preliminary data suggest that rates of adherence to atypical antipsychotics are even lower than described in recent studies that examined prescription fill rates. During our baseline period, we made certain that all medication prescribed was in the possession of our patients. It is clear that availability was a necessary but not sufficient condition for patients' taking the medication.

Furthermore, the low rate of adherence we found for participants in this study may underestimate the problem. Pill counts and other measures were available only for participants who were in the community three months postdischarge. Some of the participants who were nonadherent and who were readmitted, or who experienced other poor outcomes such as jail, were not included in the rates of adherence estimated at three months. In other words, some of the least adherent participants had already been eliminated from the sample before this assessment.

Partial adherence creates significant problems for the treating physician. It creates difficulties in determining whether medications are working adequately, whether dosing is appropriate, and whether concomitant medication is needed. We have observed that medication changes and the addition of concomitant medications are more likely to occur among patients who are not fully compliant with prescribed medication.

The wide availability of atypical antipsychotic agents has not fulfilled the promise of improved treatment adherence. Although these second-generation medications may have increased the willingness of patients to take medication, many barriers to adherence remain. Several plausible explanations exist. Although side effects are reduced with atypical antipsychotics, side effects may be only one small component of the adherence picture. Judging from our study, the ability to comply with medication—to remember to take it and to establish routines that promote regular adherence—is a much larger issue. Despite the increased availability of better medications, the increasing fragmentation and gross underfunding of mental health delivery systems is likely to have contributed to the poor outcomes observed in our sample. Finally, the expectation that ordering atypical antipsychotic medications for patients should solve or greatly reduce the adherence problem in schizophrenia may be unrealistic, given the fact that low levels of adherence are the rule for both physical and psychiatric disorders.

Both psychosocial and pharmacologic methods should be employed to improve medication adherence. Environmental supports such as special pill containers labeled with day and time, alarms, and signs to cue appropriate medication taking have been found to be successful in rehabilitation programs (4,5). Depot neuroleptics may also be used to improve rates of compliance, particularly among patients willing to take medications. Unfortunately, many individuals may find the side effects of first-generation antipsychotics problematic.

Our data support the importance of developing long-acting forms of second-generation antipsychotics. In addition, it is important to increase the awareness among health care professionals that these newer medications are not necessarily more likely to be taken by patients than were the conventional antipsychotics. ♦

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