# Poor Antipsychotic Adherence Among Patients With Schizophrenia: Medication and Patient Factors

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## Abstract

**Many patients with schizophrenia are poorly adherent with antipsychotic medications. The newer, atypical antipsychotics may be more acceptable to patients and result in increased adherence. We used national Department of Veterans Affairs (VA) pharmacy data to examine whether patients receiving atypical agents are more adherent with their medication and explored patient factors associated with adherence. Patients who received a diagnosis of schizophrenia or schizoaffective disorder between October 1, 1998, and September 30, 1999, were identified in the VA National Psychosis Registry. We calculated medication possession ratios (MPRs) for patients filling prescriptions for one ($n$ = 49,003) or two ($n$ = 14,211) antipsychotics during the year. We examined cross-sectional relationships among adherence, type of antipsychotic, and patient characteristics and explored adherence among patients switching antipsychotics during the year. Among patients receiving one antipsychotic, 40 percent had MPRs < 0.8, indicating poor adherence. African-Americans and younger patients were more likely to be poorly adherent. Cross-sectionally, patients on atypical agents were more likely to be poorly adherent (41.5%) than patients on conventional agents (37.8%). However, among a small group of patients switching from a conventional to an atypical agent ($n$ = 1,661) during the year, the percentage who were poorly adherent decreased from 46 percent to 40 percent. We describe the continuum of antipsychotic adherence among a large sample of patients with schizophrenia and confirm that poor adherence is common. African-Americans and younger patients are particularly at risk. Unfortunately, atypical antipsychotics may not be associated with substantial improvements in adherence. More intensive interventions are likely needed.**

**Keywords: Schizophrenia, antipsychotic medication, medication compliance.**

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Antipsychotic medications are a highly efficacious treatment for patients with schizophrenia. Fifty to 75 percent of patients with schizophrenia will relapse within a year if their antipsychotics are discontinued, compared to just 25 percent of patients who continue their medications (Hogarty and Ulrich 1977; Curson et al. 1985; Viguera et al. 1997). Unfortunately, poor adherence is a critical but weak link in translating this demonstrably efficacious treatment into an *effective* treatment that reduces relapse among patients in the community. Many patients do not enjoy the full benefits of antipsychotic medications because of poor adherence (Young et al. 1986; Scottish Schizophrenia Research Group 1987; Buchanan 1992; Bebbington 1995; Cramer and Rosenheck 1998).

Adherence with antipsychotics is likely influenced by a number of illness, patient, provider, and system-level factors (Becker 1990; Fenton et al. 1997; Kampman and Lehtinen 1999). Although the literature is mixed, patient factors such as ethnicity, age, cognitive functioning, degree of insight, symptom constellation, and substance abuse have been reported to influence adherence. Provider and system factors, such as the patient-provider relationship, the complexity of medication regimens, and family support, are also likely to be important (Becker 1985; Frank and Gunderson 1990; Owen et al. 1996; Fenton et al. 1997; Duncan and Rogers 1998; Olfson et al. 2000).

The side effects of antipsychotics, particularly extrapyramidal side effects, may play a major role in determining adherence (Van Putten 1974; Buchanan 1992; Fenton et al. 1997). Researchers have predicted that the newer atypical agents will increase adherence, primarily because patients might find these medications' side effect profiles to be more acceptable than the side effect profiles of the older, conventional agents (Casey 1997; Gaebel 1997; Marder 1998). Patients have reported a better qual-

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ity of life on atypical agents than on conventional agents, and patients' subjective response to antipsychotics has been linked to adherence and outcomes (Awad et al. 1995; Casey 1997; Garavan et al. 1998).

However, atypical agents are not free of side effects. Patients taking these agents may experience postural hypotension, sedation, anticholinergic side effects, and weight gain (Stanniland and Taylor 2000). These agents are also much more expensive than conventional agents, with the 2000 edition of *Redbook* indicating that the price for a 30-day supply of olanzapine or risperidone at typical doses is often more than 200 times the price of a 30-day supply of a conventional antipsychotic at typical doses (*Redbook* 2000).

Only a few clinical trials have directly examined differences in adherence among patients taking conventional versus atypical agents. In some but not all of these trials, patients assigned to atypical agents have had lower rates of study withdrawal than patients assigned to conventional agents (Stanniland and Taylor 2000). In a 12-month randomized trial of clozapine or haloperidol, patients receiving clozapine continued their medication longer than patients receiving haloperidol (35.5 weeks compared to 27.2 weeks), but there were no significant differences in the weekly pill counts (Rosenheck et al. 2000). In the only published study comparing prescription refills in naturalistic settings, Medicaid patients with a variety of psychiatric diagnoses were more likely to "persist" with treatment if they were receiving conventional agents rather than atypical agents (Vanelli et al. 2001).

Department of Veterans Affairs (VA) pharmacy data present a unique opportunity to examine medication fills of patients receiving atypical versus conventional antipsychotics in a large population of patients treated in clinical settings. Dosage instructions, days' supply dispensed, and refill data are routinely recorded in national VA data bases, allowing the construction of pharmacy-based measures of adherence. These pharmacy-based measures, including the medication possession ratio (MPR), have been shown to correlate with important patient outcomes, such as blood pressure readings among hypertensive patients and anticonvulsant levels among patients with seizure disorders (Steiner et al. 1988). We recently demonstrated that MPRs are strongly associated with psychiatric admission among patients with schizophrenia (Valenstein et al. 2002).

In this study, we use MPRs constructed from VA pharmacy data to compare antipsychotic adherence among patients receiving conventional and atypical antipsychotic agents. We also examine patient factors that might be associated with adherence.

# Methods

Data on patient demographics, diagnoses, and pharmacy use came from the VA National Psychosis Registry, which is maintained by the Serious Mental Illness Treatment, Research, and Evaluation Center (SMITREC), located in Ann Arbor, MI (Blow et al. 2001). The registry integrates outpatient pharmacy data from the VA Pharmacy Benefits Management Group with other VA administrative data for patients with psychotic diagnoses.

**Study Sample.** Patients were included in this study if they (1) received a diagnosis of schizophrenia or schizoaffective disorder in the VA between October 1, 1998, and September 30, 1999 (fiscal year 1999) during an inpatient or outpatient encounter, (2) filled a prescription for one or two different *oral* antipsychotic medications as an outpatient, and (3) had more than 90 outpatient days following the prescription of at least one of their antipsychotic agents. If patients received more than one primary psychotic diagnosis during this period (e.g., schizophrenia during some treatment contacts and bipolar disorder during other contacts), the diagnosis noted during the majority of treatment contacts was used. Previous studies indicated that diagnoses of schizophrenia in VA inpatient administrative data and in Medicaid claims data closely reflect clinical diagnoses of schizophrenia (Lurie et al. 1992; Kashner 1998).

Patients were excluded from the study if they (1) received outpatient antipsychotic fills during institutional stays ($n$ = 3,700) or (2) filled prescriptions for three or more different antipsychotic medications during the year ($n$ = 2,875). Patients who received outpatient antipsychotic fills during institutional stays likely requested refills by mail before admission, managed their own medications during nursing home stays, or received pass medications. They were excluded because the status of "outpatient" fills occurring during institutional stays was unclear. These fills may have been lost, discarded, or stockpiled, making pharmacy-based adherence measurement problematic. Patients who received three or more different antipsychotics during the year, a small group, were excluded because of difficulties in calculating MPRs after the initiation of each of three different antipsychotics.

Our final study sample consisted of 63,214 patients with valid MPRs, of which 49,003 patients received just one antipsychotic drug during the year and 14,211 received two different antipsychotic medications during the year.

**Study Measures.** Patients' age, sex, and race (African-American, white, or other) were obtained from the VA

National Psychosis Registry. The category "other" included patients of Hispanic, Asian, and Native American origin. Patients were categorized into three age groups, consisting of patients (1) under the age of 45 years, (2) aged 45 through 64 years, and (3) aged 65 years or older.

Dummy variables were constructed that indicated whether a patient ever received an atypical antipsychotic, patient age group, sex, and race. We also constructed two additional dummy variables for ever receiving clozapine and for ever receiving an atypical antipsychotic other than clozapine.

**Measures for High Doses.** For an exploratory analysis examining the relationship between high antipsychotic doses and adherence, we constructed two variables. The first was an indicator variable that denoted whether patients *ever* received a "high dose" of antipsychotic medication. The second variable was the percentage of all prescription fills during the year that were high-dose fills.

We defined high antipsychotic doses as those that exceeded Patient Outcomes Research Team (PORT) guidelines for conventional antipsychotics (greater than 1,000 mg chlorpromazine equivalents) or that exceeded the upper ranges of atypical antipsychotic doses suggested by the Texas Medication Algorithm Project for Schizophrenia (> 6 mg per day of risperidone; > 20 mg per day of olanzapine; > 750 mg per day of quetiapine; and > 900 mg per day of clozapine), recognizing that the upper limits of effective doses for olanzapine and quetiapine remain uncertain (Miller et al. 1999).

**MPR.** MPRs were calculated from pharmacy data by dividing the number of *days' supply* of antipsychotic medication the patient *received* from the outpatient pharmacy during the study year by the number of *days' supply the patient needed to receive* if he or she was taking a full dose of medication continuously during outpatient periods.

$$\text{MPR} = \frac{\text{number of days' supply of antipsychotic received from outpatient pharmacy}}{\text{number of days' supply needed for continuous outpatient antipsychotic use}}$$

Consistent with treatment guidelines, we assumed that antipsychotic use should be continuous for the majority of patients with schizophrenia (American Psychiatric Association Work Group on Schizophrenia 1997). The numerator of the MPR, or the *days' supply received* by the patient, was calculated by adding the number of days' supply from each outpatient antipsychotic prescription filled during the year. Medications received at the time of discharge from inpatient stays were included in the outpatient supply.

For patients receiving only one antipsychotic drug during the year ($n$ = 49,003), the denominator of the MPR was calculated as the number of days between the date of first antipsychotic medication fill and the end of the year or the date of death. Any days that a patient spent in institutional settings (in VA hospitals or nursing homes) were subtracted from the outpatient *days' supply needed.* MPRs were calculated only if patients had ≥ 90 outpatient days following their first antipsychotic fill of the year.

Patients with MPRs of 1 received *all* the antipsychotics needed to take their full dose of antipsychotic continuously throughout the study period, whereas patients with MPRs of 0.5 received medication sufficient to take only half of their prescribed dose during this period. A small group of patients had MPRs ≥ 1.1, likely because of frequent changes in their antipsychotic doses and overlapping prescriptions. These patients also received enough medication to take their antipsychotics consistently but were likely somewhat less treatment-responsive (Valenstein et al. 2002).

**Categories of Adherence.** We used categories of adherence based on the MPR to facilitate discussion and comparison with previous articles addressing adherence. In these analyses, patients with MPRs < 0.8 were considered to have poor adherence, while patients with MPRs ≥ 0.8 were considered to have adequate adherence. This cutoff for poor adherence has been frequently used in the psychiatric and medical literature (Duncan and Rogers 1998; Adams and Scott 2000).

**Patients Receiving Two Different Antipsychotic Medications.** We conducted our major study analyses for patients receiving one antipsychotic during the study year because of the more straightforward calculation of MPRs among these patients. These patients also composed the majority (78%) of study subjects. However, we also explored adherence among 14,211 study patients exposed to *two* antipsychotics during the year. These patients either received concurrent treatment with two antipsychotics or switched antipsychotics during the year. Because only one antipsychotic medication is needed to meet the criterion of continuous antipsychotic treatment, the denominator, or *the days' supply needed,* for a specific antipsychotic took into account whether a second antipsychotic was initiated or was concurrently prescribed.

Because we could calculate valid MPRs for a particular antipsychotic medication only if the patient had ≥ 90 outpatient days following the initial fill, for some patients receiving two different antipsychotics during the year, we could calculate an MPR for only one of their two antipsy-

chotics. For these patients, this single MPR was used as the measure of adherence.

For patients who had ≥ 90 days following the prescription of *each* of their two antipsychotics, we calculated two drug-specific MPRs and averaged them to obtain an overall assessment of adherence.

**Data Analysis.** Simple descriptive statistics were completed, using frequencies and means (± standard deviations [SDs]).

Chi-square analyses were used to examine the significance of the relationships between adherence category (MPR < 0.8, y/n) and type of antipsychotic, gender, ethnic group (white, African-American, or other), and age group (< 45 years of age, 45–64 years, and ≥ 65 years). All relationships, except gender, were significant, and these covariates were included in the multivariate analyses reported in the article. In an exploratory chi-square analysis, we examined the relationship between an indicator variable for "ever receiving a high dose" of an antipsychotic and adherence categories.

A logistic regression analysis explored the relationship between poor adherence (MPR < 0.8, y/n) and the independent predictors: antipsychotic type, ethnic group, age group, and gender. A second logistic analysis explored the relationship between poor adherence, with clozapine entered as a predictor in addition to "other atypical" use, adjusting for the same covariates. All predictors were entered into the model simultaneously. An exploratory multiple regression analysis was used to assess the relationship between the continuous MPR measure and these same independent predictors.

We also used a logistic regression analysis to examine the relationship between adherence category and the percentage of all antipsychotic fills that were "high dose" fills, including clozapine use, other atypical antipsychotic use, ethnic group, age group, and gender as covariates in this model.

Finally, we conducted an exploratory analysis that focused on adherence in the much smaller subgroup of patients who *switched* antipsychotics during the year and had valid MPRs for *both* of their two antipsychotics ($n$ = 3,303). Patients who received concurrent treatment were not included in these analyses.

In exploratory analyses of patients switching from one antipsychotic to a second antipsychotic, we used McNemar's chi-squares for paired data to explore whether there were significant differences in the percentages of patients who were poorly adherent on their first as opposed to their second antipsychotic of the year.

The criterion alpha level was set at 0.05 for all of these analyses. Statistical analyses were completed using SAS Proprietary Software Release 8.2 (TS2M0) (SAS Institute, Cary, NC).

# Results

**Patient Characteristics.** Reflecting the VA population, study patients ($n$ = 63,214) had a mean age of 52.3 years, and 95.2 percent were male. Most patients were white (61%) or African-American (29%). Exactly 49,003 patients (77.5%) were exposed to one antipsychotic during the year, and 14,211 (22.5%) were exposed to two different antipsychotics during the year.

**Use of Conventional and Atypical Antipsychotic Medications.** Of the 49,003 patients receiving just one antipsychotic medication, 53 percent received conventional agents and 47 percent received atypical agents. Of the 14,211 patients receiving two different antipsychotics, 71 percent received an atypical and a conventional agent, 21 percent received two different atypical agents, and 8 percent received two different conventional agents.

**MPRs.** Patients receiving just one antipsychotic during the year ($n$ = 49,003) had a mean MPR of 0.80 (SD ± 0.33). In exploratory analyses, the smaller group receiving two antipsychotics ($n$ = 14,211) had a mean MPR of 0.85 (SD ± 0.33).

There was substantial variation in patients' MPRs. Figure 1 shows the distribution of patients across the adherence continuum for patients receiving one antipsychotic. The distribution of MPRs for patients receiving two antipsychotics was similar. Approximately 40 percent of those receiving one antipsychotic during the year and 38 percent of those receiving two different antipsychotics had MPRs < 0.8, indicating poor antipsychotic adherence.

In addition to the substantial proportion of patients with poor adherence (MPRs < 0.8), there was a small group of patients with MPRs ≥ 1.1. Eleven percent ($n$ = 5,486) of those receiving one antipsychotic and 19 percent ($n$ = 2,686) of those receiving two antipsychotics during the year received more days' supply of medication than would be required to take their antipsychotics as prescribed. These patients likely received increases in their antipsychotic doses, with overlapping prescriptions (obtaining new fills before previous fills were exhausted). These patients are not poorly adherent by pharmacy-based criteria but were at increased risk for psychiatric admission and presumably less stable (Valenstein et al. 2002).

**Differences in Adherence Among Patients Receiving Conventional or Atypical Agents.** Table 1 outlines the mean MPRs and the percentages of patients with poor adherence (MPRs < 0.8) for each of 15 antipsychotic medications and for all patients receiving atypical antipsychotics or conventional antipsychotics.

**Figure 1. Frequency distribution of MPR values for patients receiving one antipsychotic (N = 49,003)**

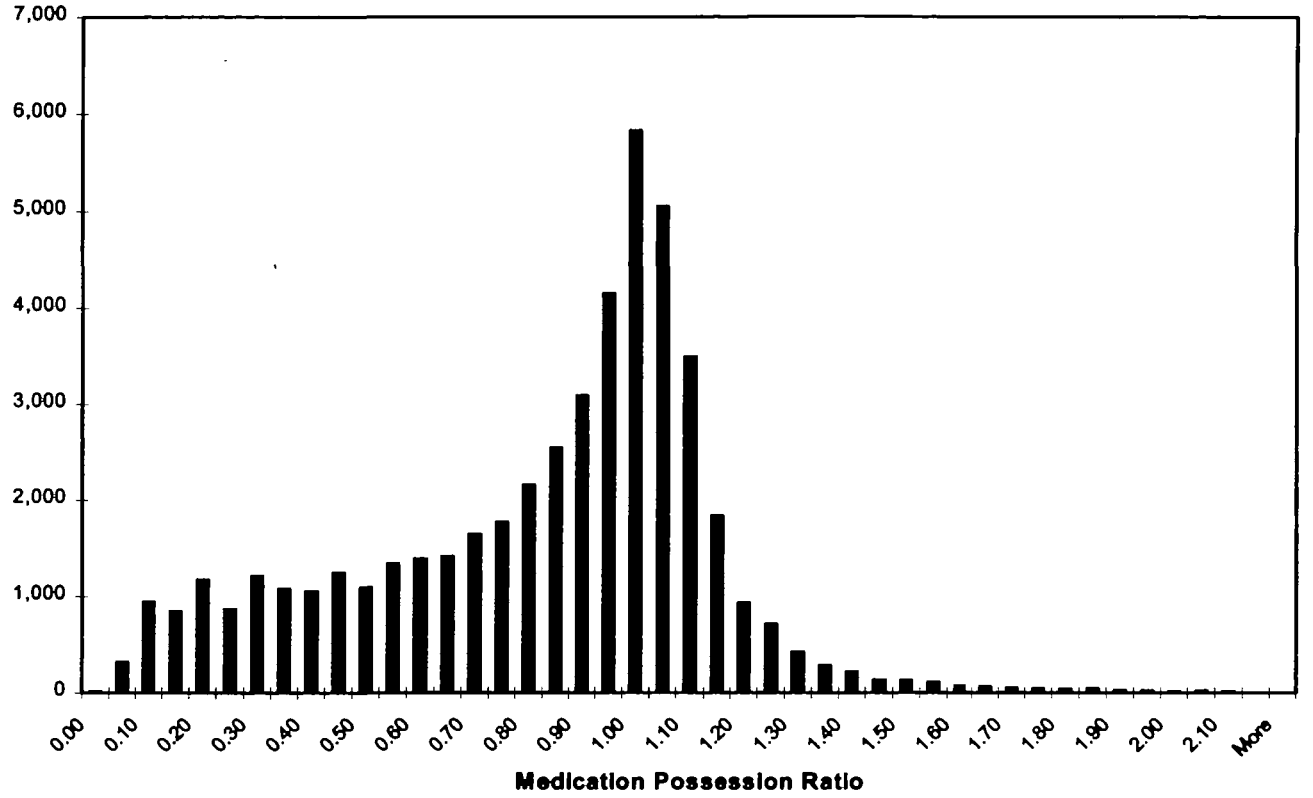


**Table 1. Adherence with antipsychotic medications for patients receiving one antipsychotic**

| Antipsychotic medications | Mean MPR | % patients with MPR < 0.8 |
|---|---|---|
| Clozapine (*n* =935) | 1.01 | 4.6 |
| Olanzapine (*n* = 10,665) | 0.80 | 41.9 |
| Quetiapine (*n* = 298) | 0.74 | 49.0 |
| Risperidone (*n* = 11,174) | 0.78 | 44.0 |
| **All patients on atypical antipsychotics (*n* = 23,072)** | **0.79** | **41.5** |
| Chlorpromazine (*n* = 2,616) | 0.83 | 34.5 |
| Fluphenazine (*n* = 2,623) | 0.78 | 40.3 |
| Haloperidol (*n* = 7,141) | 0.78 | 42.0 |
| Loxapine (*n* = 1,130) | 0.87 | 29.3 |
| Mesoridazine (*n* = 346) | 0.89 | 26.6 |
| Molindone (*n* = 143) | 0.83 | 32.9 |
| Perphenazine (*n* = 3,151) | 0.78 | 42.7 |
| Pimozide (*n* = 11) | 0.85 | 27.3 |
| Thioridazine (*n* = 3,732) | 0.85 | 32.8 |
| Thiothixene (*n* = 2,799) | 0.84 | 35.0 |
| Trifluoperazine (*n* = 2,239) | 0.82 | 37.1 |
| **All patients on conventional antipsychotics (*n* = 25,931)** | **0.81** | **37.8** |
| **All patients on oral antipsychotics (*n* = 49,003)** | **0.80** | **39.6** |

*Note.*—MPR = medication possession ratio.

There was only a small difference in the proportion of patients with poor adherence on atypical antipsychotics or conventional antipsychotics; 41.5 percent of patients on atypical agents were poorly adherent compared to 37.8 percent of patients on conventional agents. Patients on clozapine ($n$ = 935), who must meet stringent visit and monitoring requirements to continue on this medication, were least likely to be poorly adherent: only 4.6 percent of patients on clozapine had MPRs < 0.8. In contrast, 27 to 49 percent of patients on other antipsychotic medications had MPRs < 0.8.

Among patients taking one antipsychotic during the year, logistic regression analyses adjusting for sex, race, and age group showed a statistically significant but clinically small association between the type of antipsychotic (atypical vs. conventional) and poor adherence. Patients on atypicals had an odds ratio (OR) of 1.11 (95% confidence interval [CI] 1.07, 1.16) for poor adherence compared to patients on conventional agents. When clozapine was considered separately and analyses examined the relationship between type of antipsychotic (clozapine, "other atypical," or conventional agent) and adherence, patients receiving clozapine had an OR of 0.08 (95% CI 0.06, 0.11) for poor adherence compared to patients on conventional agents while patients receiving other atypicals had an OR of 1.19 (95% CI 1.14, 1.23).

Multiple regression analyses examining the relationship among the continuous variable, MPR, and the type of antipsychotic produced similar results. Again, clozapine was associated with higher MPRs than conventional agents (better adherence, $p < 0.0001$) and "other atypical" agents with slightly lower MPRs than conventional agents (poorer adherence, $p < 0.0001$). We note that the variance in MPR that could be explained by antipsychotic type, age group, and ethnic group was only 6 percent.

**Patient Factors Associated with Adherence.** Among patients on one antipsychotic, 54 percent of African-Americans were poorly adherent compared to 32 percent of whites and 45 percent of "other" racial/ethnic groups. Patients < 45 years of age were more likely to be poorly adherent (46%) than patients aged 45 to 64 (38%), who in turn were more likely to be poorly adherent than patients 65 years or older (33%). These patient characteristics were also associated with adherence among patients receiving two antipsychotics. In logistic regression analyses adjusting for gender and type of antipsychotic, younger patients (< 45 years) had an OR of 1.31 (95% CI 1.25, 1.37) for poor adherence compared to patients 45 to 65 years of age, and African-Americans had an OR of 2.38 (95% CI 2.28, 2.49) for poor adherence compared to whites.

**Exploratory Analyses of Relationship Between Adherence and High Antipsychotic Doses.** Among patients on one antipsychotic, those with poor adherence were less likely to have *ever* received a high antipsychotic dose during the year; only 3.4 percent of patients with MPRs < 0.8 received at least one high-dose fill compared to 10.3 percent of patients with MPRs ≥ 0.8. Those on two antipsychotics showed a similar pattern. In logistic analyses that examined the relationship between categories of adherence and percent of *all* fills that were "high dose," adjusting for type of antipsychotic, race, sex, and age group, each additional 10 percent increase in "too high" doses was associated with a decrease of approximately 9 percent in the odds of poor adherence.

**Exploratory Analyses of Adherence Among Patients Switching Antipsychotic Medications.** Finally, we conducted exploratory analyses that examined adherence among the subset of patients *switching* antipsychotics medication who had valid MPRs for each of their two antipsychotics ($n$ = 3,303). Table 2 outlines the percentages of patients with poor adherence on their first antipsychotic of the year and their second antipsychotic of the year—for each of four "treatment pathways": patients starting on conventionals and switching to atypicals (the most common pathway), patients starting on atypicals and switching to conventionals, and patients switching medications within the atypical or conventional antipsychotic categories.

Among patients switching from a conventional agent to an atypical agent during the study period ($n$ = 1,661), a larger proportion were poorly adherent (46%) on their first antipsychotic of the year, a conventional agent, than on their second antipsychotic of the year, an atypical agent (40%; McNemar's test statistic = 14.3, $p < 0.001$). Among the smaller group of patients switching from atypicals back to conventionals ($n$ = 504), 49 percent were poorly adherent on their first medication (the atypical), and 64 percent were poorly adherent on their second medication (the conventional; McNemar statistic = 28.6; $p < 0.0001$). Thus, there were small increases in adherence among patients switching from a conventional to an atypical agent and larger decreases in adherence among patients switching back from an atypical to a conventional agent during fiscal year 1999.

## Discussion

To our knowledge, this is the largest study examining adherence with antipsychotic medication among patients with schizophrenia. Data from this large, national cohort ($n$ = 63,214) confirm previous reports of poor adherence among these patients; fully 40 percent of patients with

**Table 2. MPRs among patients switching from one antipsychotic medication to a second during the year[1]**

| Treatment pathways | MPR on first antipsychotic | MPR on second antipsychotic | McNemar's test |
|---|---|---|---|
| Treatment pathway 1 ($n$ = 1,661) | Conventional agent first<br>MPR < 0.8: 45.8% | Atypical agent second<br>MPR < 0.8: 40.2% | McNemar's statistic = 14.3; $p < 0.0001$ |
| Treatment pathway 2 ($n$ = 504) | Atypical agent first<br>MPR < 0.8: 49.0% | Conventional agent second<br>MPR < 0.8: 63.9% | McNemar statistic = 28.6; $p < 0.0001$ |
| Treatment pathway 3 ($n$ = 885) | Atypical agent first<br>MPR < 0.8: 48.1% | Atypical agent second<br>MPR < 0.8: 46.7% | McNemar statistic = 0.48; nonsignificant |
| Treatment pathway 4 ($n$ = 253) | Conventional agent first<br>MPR < 0.8: 54.5% | Conventional agent second<br>MPR < 0.8: 52.6% | McNemar statistic = 0.27; nonsignificant |

*Note.*—MPR = medication possession ratio.

[1] Analyses were conducted for subgroups of patients switching antipsychotic medications during the year who had valid MPRs for both medications. Eliminating clozapine patients from these analyses ($n$ = 14) did not substantially change the results.

schizophrenia receiving one antipsychotic and 38 percent of those receiving two antipsychotics were poorly adherent with their antipsychotic medications. This finding is consistent with previous studies that used a variety of methods to assess adherence among patients with schizophrenia (Cramer and Rosenheck 1998). However, our large sample and continuous measure of adherence allow us to give a finely nuanced view of adherence across the "adherence spectrum" (figure 1).

The high rates of poor adherence demonstrated in this and other studies are troubling, given the consequences of antipsychotic discontinuation and haphazard antipsychotic use. Previous studies have reported that patients who discontinue antipsychotics may be two to five times as likely to relapse as other patients, leading to unnecessary suffering and increased costs (Davis et al. 1993; Fenton et al. 1997; Robinson et al. 1999). In a previous study, using the same patient sample for the major study analyses, we demonstrated that patients with MPRs < 0.8 were 2.4 times as likely to have a psychiatric admission as were patients with MPRs between 0.8 and 1.1 (Valenstein et al. 2002). Thus, the consequences of poor adherence can be dramatic for patients with schizophrenia.

Researchers and clinicians have long believed that addressing one of the most important "costs" of antipsychotic treatment, medication side effects, would increase adherence—and that atypical agents would prove more acceptable to patients than conventional agents.

Disappointingly, in this study we did not find substantially higher levels of adherence among patients treated with atypical antipsychotics, with the important exception of clozapine. Indeed, cross-sectionally, patients on atypical agents were slightly less likely to be adherent with their medication than patients on conventional agents. This finding is congruent with a recently published article that examined "persistence" in antipsychotic refills among a diagnostically heterogeneous group of Medicaid patients. In this study, patients filling prescriptions for atypical antipsychotics were less likely to persist with treatment than those filling prescriptions for conventional antipsychotics (Vanelli et al. 2001).

We believe this unexpected finding is explained, in part, by selection effects. The first atypical agent, clozapine, became available in 1989, and other atypicals followed. Clinicians may have preferentially switched poorly adherent patients to atypical agents in the early to mid-1990s, while leaving patients with better adherence on the conventional agents. In exploratory analyses, we found modest increases in adherence among patients switching from a typical to an atypical agent and decreases in adherence among patients switching back to

a conventional agent from an atypical agent during fiscal year 1999.

However, study data indicate that any improvements that occur in adherence as a result of using atypical agents appear to be small. A substantial proportion (42%) of patients on atypical agents remain poorly adherent. Only clozapine was associated with markedly higher rates of adherence—perhaps because of its superior efficacy, because of the requirements for close monitoring, or because only the relatively "adherent" patients who come for regularly scheduled blood draws and appointments can continue on this medication.

Other atypical agents may fail to markedly improve patient adherence because their side effects remain problematic or because factors other than side effects are more important in determining patients' adherence with medication. Patients' degree of insight, cognitive functioning, and substance abuse all have been demonstrated to affect medication adherence (Fenton et al. 1997). Several studies have reported that patients may be more sensitive to the perceived benefits of antipsychotic medication than side effect burden when making decisions about adherence (Adams and Scott 2000; Rosenheck et al. 2000).

As reported by a few but not the majority of studies, we found that African-Americans and younger patients were less adherent with antipsychotic medication than whites or older patients (Fenton et al. 1997; Duncan and Rogers 1998; Rosenheck et al. 2000). Race is likely an imperfect flag for other factors that underlie adherence, such as personal or family health beliefs, differences in antipsychotic management, and differences in access to services. Previous studies have reported that clinicians may prescribe higher doses of antipsychotics and provide more aggressive pharmacological management in emergency settings for African-Americans than for whites (Segal et al. 1996; Lehman and Steinwachs 1998; Surgeon General's Office 2000). African-Americans may also have different levels of access to or use of mental health services that support adherence, such as frequent outpatient visits (Kales et al. 2000). Younger patients may be less adherent because they are less likely to appreciate the severity of their illness or the need for medication. They may also be more likely to have concurrent substance abuse (Kessler et al. 1994).

Although several researchers have hypothesized that high doses of antipsychotics might result in poorer medication adherence because of increased side effects, we found that poorly adherent patients were actually *less* likely to receive high doses. We suspect that providers prescribe higher than recommended doses when patients are unstable but keep their regular appointments (adherent with appointments). We also suspect that physicians often carefully assess adherence before moving patients to high antipsychotic doses.

**Limitations.** MPRs are a useful but imperfect measure of adherence. Patients may fill antipsychotic prescriptions on a regular basis and have MPRs suggesting good adherence yet fail to ingest their medications. Patients may also have low MPRs, suggesting poor adherence, but fill their antipsychotic prescriptions regularly outside of the VA.

However, patients in active VA care have a strong inducement to fill their prescriptions within the system because of favorable benefits coverage. In previous work, we have also demonstrated a strong relationship between patients' MPRs and psychiatric hospitalization, giving evidence of the validity and usefulness of this measure (Valenstein et al. 2002). The MPR produces overall estimates of adherence that are in line with previous reports and shows higher levels of adherence among patients who are closely monitored (patients receiving clozapine). Thus, although an imperfect measure, the MPR appears to be sufficiently robust to allow meaningful comparisons of adherence among patient subgroups.

We caution readers that although African-American patients were more likely to be poorly adherent than whites in this sample, we were unable to adjust for many factors that might underlie such differences, such as personal or family health beliefs or differences in mental health service access and use. As in much of the literature, patient demographic characteristics are associated with adherence, but these factors explain only a small part of the observed variation. The use of atypical antipsychotics also has a weak association with adherence and explains only a small portion of the variation in adherence.

**Summary.** In summary, this study confirms previous reports of extensive nonadherence among patients with schizophrenia. Using an unobtrusive measure, we were able to examine adherence among a large sample of patients treated in diverse naturalistic settings. Poor adherence was seen in every demographic subgroup but was particularly common among African-Americans and younger patients.

Unfortunately, our data indicate that any improvements that occur in adherence with the use of the atypical antipsychotics are not likely to be dramatic. Although atypical agents may have fewer extrapyramidal side effects and improve patients' quality of life, many patients remain poorly adherent and do not enjoy the full benefit of these expensive medications. More intensive multicomponent interventions may be needed to improve adherence and reduce excess morbidity among these vulnerable patients.

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