Antipsychotic Adherence Over Time Among Patients Receiving Treatment for Schizophrenia: A Retrospective Review

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Objective: Approximately 40% of patients with schizophrenia are poorly adherent to their antipsychotics at any given time. However, little is known about patients' adherence over time, although this has important services implications. We examined antipsychotic adherence over 4 years at the aggregate and the individual level among a large cohort of patients.

Method: We identified 34,128 Veterans Affairs patients who received a schizophrenia diagnosis and an antipsychotic fill in fiscal year (FY) 1999, completed schizophrenia visits in each of the next 4 years (FY2000, FY2001, FY2002, FY2003), and had valid medication possession ratios (MPRs) in each of these years. We examined whether patients had consistently good adherence (MPRs ≥ 0.8 in all 4 years), consistently poor adherence (MPRs < 0.8 in all years), or inconsistent adherence. We examined predictors of consistently poor or inconsistent adherence.

Results: The cross-sectional prevalence of poor adherence among the patient population remained stable over time; 36%–37% were poorly adherent in each year. However, 61% of patients had adherence difficulties at some point over the 4-year period. Approximately 18% had consistently poor adherence, 43% were inconsistently adherent, and 39% had consistently good adherence. Patients who were younger and nonwhite, with a substance use diagnosis, a psychiatric hospitalization, or predominant treatment with first-generation antipsychotics, were more likely to have consistently poor adherence.

Conclusions: Antipsychotic adherence is not a stable trait; most patients have difficulties with adherence over time. Health organizations and clinicians must emphasize adherence-enhancing interventions that can be provided on a longer term basis to the majority of patients.

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Antipsychotic medications reduce many of the symptoms of schizophrenia.[1] However, cross-sectional studies indicate that a significant percentage of patients with schizophrenia may be poorly adherent to their antipsychotic medications at any point in time, reducing treatment benefits. Cross-sectional studies report a wide range of adherence rates, with 2 comprehensive reviews indicating that the median rate of poor adherence is approximately 40%.[2,3]

Although there are considerable data regarding cross-sectional adherence, much less is known about adherence over time. One study in a single ambulatory schizophrenia disorders program (N = 162) used clinician reports as a measure of adherence.[4] This study reported that 50% of the patients whose clinicians considered them to be

"actively adherent" at admission to the program were considered nonadherent by 13.7 months, and 75% of the patients initially considered nonadherent by their clinicians were considered adherent by 9.1 months. If patients' level of adherence changes frequently over time, this change has important implications for clinical and organizational efforts to improve adherence among patients with schizophrenia.

On a cross-sectional basis, studies indicate that medication adherence is a complex behavior that is influenced by multiple patient, environmental, and treatment factors. Among patients with schizophrenia, cross-sectional predictors of adherence include demographics, clinical and functional status, medication side effects, quality of the relationship with the provider, psychosocial support, and health beliefs.[2,3,5–7] These factors may differ in the strength of their association with adherence, stability over time, and responsiveness to treatment interventions.

Although patient demographics have been inconsistently associated with adherence in many medical conditions, several studies report that patients with schizophrenia who are younger, unmarried, male, and African American and who have fewer years of formal education are more likely to be poorly adherent.[2,5–8] These demographic factors (age, race/ethnicity), although not mutable in themselves, may be imperfect markers for particular beliefs about psychiatric illnesses or medications that influence adherence. Such beliefs might be amenable to change.

Patients' clinical status, psychiatric symptoms, and substance use are also associated with treatment adherence,[2] and these factors may be subject to change. For example, concurrent substance use is common among patients with schizophrenia and is associated with poorer medication adherence.[2,9–12] However, some patients may become abstinent or reduce their intake of substances with time or with specific treatment interventions. Individuals with less insight into their illness tend to be less adherent to medications,[2,12–16] and recent studies indicate that deficits in cognitive functioning (e.g., conceptualization and memory) are associated with poorer adherence.[17,18] Medication adherence among the latter group of patients may improve with repeated concrete instructions, or memory aids, or with the involvement of family members in the management of their medications. Several, although not all, studies indicate that other potentially changeable factors, such as medication side effect burden, psychosocial support, positive relationships with providers, access to care, and the complexity of the medication regimen, are also associated with adherence.[2,7,15,19]

However, despite the potential changeability of many of the factors outlined above and clinicians' and researchers' efforts to target these factors and improve patient adherence, there are few assessments of patients' adherence over time in clinical settings. Little is known about changes in aggregate rates of adherence among patient populations with schizophrenia over time, and even less is known about changes in individual patients' adherence. We do not know whether the bulk of patients who are identified as poorly adherent in cross-sectional studies remains poorly adherent year after year or whether patients cycle in and out of periods of poor adherence. We also do not know how frequently changes in patients' adherence might occur.

Further longitudinal information regarding patient-level adherence would have practical implications for clinicians and organizations attempting to improve adherence, providing guidance on the proportion of the patient population that may need adherence-enhancing interventions, on the best strategies for identifying patients who might benefit from adherence-enhancing interventions, and on the optimal duration of these interventions.

In this study, we use medication possession ratios (MPRs) constructed from U.S. Veteran Affairs (VA) pharmacy data to examine population trends in antipsychotic adherence and to describe longitudinal patterns of adherence among individual patients. We also examine patient and regimen factors that may be associated with consistently poor adherence.

METHOD

We obtained data on patient demographics, diagnoses, services, and pharmacy use from the VA National Psychosis Registry, which is maintained by the Serious Mental Illness Treatment Research and Evaluation Center (SMITREC) in Ann Arbor, Mich.[20] The Registry integrates outpatient pharmacy data from the VA Pharmacy Benefits Management Group with other VA administrative data for patients with psychoses diagnoses. The study was approved by the Ann Arbor VA Health System Institutional Review Board.

Patients were included in the study if they met the following criteria: (1) had a diagnosis of schizophrenia or schizoaffective disorder during a VA treatment encounter between October 1, 1998, and September 30, 1999 (fiscal year [FY] 1999), and filled an antipsychotic medication prescription during this year; (2) completed ≥ 1 visit for schizophrenia in each of the 4 subsequent years (FY2000, FY2001, FY2002, and FY2003); and (3) had valid MPRs calculated in each of the 4 study years. (See below.) Patients were considered to have completed a visit for schizophrenia if the provider recorded a diagnosis of schizophrenia for a treatment encounter. The total study population numbered 34,128 patients.

We also explored adherence among a broader cohort of patients (N = 52,560) that included both patients who met all the above criteria and patients who met the above criteria except that they did not complete visits for

schizophrenia in each of the study years. This allowed us to examine antipsychotic adherence among patients who had less consistent engagement in treatment, attending appointments for schizophrenia during only some years of the observation period.

VA administrative data have been widely used for health services and pharmacoepidemiologic research studies. Studies have indicated that diagnoses of schizophrenia recorded in VA inpatient administrative data and in Medicaid claims data closely reflect clinical diagnoses of schizophrenia.[21,22]

Study Measures

Patient characteristics. Patients' age, sex, and race/ethnicity (categorized as African American, Hispanic, white, other, or unknown) were obtained from the VA National Psychosis Registry. The category "other" included patients of Asian and Native American race/ethnicity.

Patients were considered to have a substance use diagnosis in FY99 or during the observation period if they received *International Classification of Diseases*, Ninth Revision, diagnostic codes 291, 292, 303.0, 303.9, 304.0 to 304.9, 305.0; or 305.2 to 305.9.

Medication regimen characteristics. We classified patients' antipsychotic treatment in each year as being predominantly first-generation agents if ≥ 90% of antipsychotic fills during the year were for first-generation agents, as predominantly second-generation agents if ≥ 90% of fills were for second-generation agents, or as exposure to both if neither type of antipsychotic accounted for ≥ 90% of fills during the year. Over the 4-year period, we classified predominant antipsychotic use based on whether ≥ 90% of the patient's antipsychotic fills during this period were for first-generation agents, or second-generation agents or if neither class of medication predominated during the 4-year period.

For each year, we classified patients as receiving predominantly high-dose antipsychotics during a year if ≥ 50% of their antipsychotic fills were for high doses during the year. Similarly, over the 4-year period, we classified patients as receiving predominantly high-dose antipsychotics during the 4-year study period if ≥ 50% of their antipsychotic prescriptions were for high doses during this period. High doses were defined using the Texas Implementation of Medication Algorithms guidelines.[23] For aripiprazole, doses were considered to be high if they were > 30 mg/day.

Patients were considered to have received antipsychotic polypharmacy if they had ≥ 90 consecutive days of overlapping supplies of 2 different antipsychotics.[24]

Measures of adherence. Data on medication fills and days' supply dispensed were used to calculate MPRs. MPRs were calculated for patients during each of 4 fiscal years (FY2000, FY2001, FY2002, FY2003) if patients had ≥ 90 noninstitutionalized days in a year (were alive and without extensive inpatient stays) and received < 3 different antipsychotic medications during the year. We did not calculate MPRs for patients with < 90 outpatient observation days or for patients with complex medication regimens that included 3 or more antipsychotics in a single year, because of difficulties in calculating adherence for patients with limited numbers of observation days following the prescription of each of several different antipsychotics. Of the 45,253 patients receiving VA treatment for schizophrenia in each of the 4 observation years, the large majority (75%) had valid MPRs calculated for each of these years.

MPRs were calculated by adding the number of days' supply of antipsychotic medication that patients received from the outpatient pharmacy during the study year and any days' supply from prescriptions of the prior year that would have covered days during the study period. Medications received at the time of discharge from inpatient settings are included in outpatient pharmacy supplies. The *number of days' supply received* was divided by the *number of days' supply needed* for patients to take their full dose of medication continuously during outpatient periods. Any days that patients spent in institutional settings (in VA hospitals or nursing homes) were subtracted from the outpatient days' supply needed.

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

For patients who received 2 different antipsychotic medications during the year, the denominator or the days' supply needed for a specific antipsychotic took into account whether a second antipsychotic was initiated or was concurrently prescribed. For these patients, we calculated 2 drug-specific MPRs and then calculated a mean MPR, weighted by the duration of taking each drug (number of days supply needed for each drug).

MPRs calculated from VA pharmacy data have been shown to correlate with important intermediate patient outcomes. Among patients with hypertension, MPRs for antihypertensive medications correlate with blood pressure readings, and among patients with seizure disorders, MPRs for anticonvulsants correlate with anticonvulsant blood levels.[25] MPRs for antipsychotic medications are inversely associated with psychiatric admission among patients with schizophrenia in VA and other health care settings.[12,26,27]

Adherence categories.

Cross-sectional adherence. We first categorized patient adherence during each of the 4 study years, on the basis of the patient's MPR for that year. Patients with MPRs < 0.8 during a specific fiscal year were considered to have *poor*

adherence during that year, while patients with MPRs ≥ 0.8 were considered to have *good adherence* during the year. Although studies do not yet suggest a specific threshold at which partial adherence with antipsychotics becomes problematic, taking 80% or more of one's prescribed medications has often been used as a traditional cut-point for good adherence, and this level appears to be a reasonable goal for patients and their providers.[12,28] (As outlined below, we also completed analyses in which we examined changes in the continuous MPR measure between years during the observation period.)

Patient adherence over time. We also categorized patients by their pattern of adherence over the 4-year observation period. Patients whose MPRs were ≥ 0.8 in all 4 study years were considered to have *consistently good adherence*, those with MPRs < 0.8 in all 4 years were considered to have *consistently poor adherence*, and those with MPRs ≥ 0.8 in some years but not all years were considered to have *inconsistent adherence*. We note that, theoretically, patients could have contiguous days without medication coverage that straddled 2 fiscal years, resulting in being categorized as consistently adherent across years. However, practically, this situation occurred in only 1% of the sample.

Stability of medication adherence (MPR) over time. Finally, we examined the stability of medication adherence by determining for each patient if a change of ≥ 0.2 in the MPR occurred between 2 consecutive years on at least 1 occasion during the 4-year observation period. In a previous study, differences of ≥ 0.2 in antipsychotic MPR were associated with absolute differences in rates of psychiatric hospitalization of approximately 5% to 7% in a year's time among patients with schizophrenia.[26]

Data Analysis

Simple descriptive statistics were completed, using frequencies and means. Cross-sectional relationships between MPRs in each year and independent variables for patient characteristics and regimen characteristics in each year were completed using generalized estimating equations (GEE) analyses. Patient characteristics included race/ethnicity, age, sex, substance use diagnosis during the year, and psychiatric hospitalization during the year. Variables for medication regimen characteristics included the predominant use of high antipsychotic doses during the year or the predominant use of first-generation agents, second-generation agents, or no predominant antipsychotic type during the year. GEE analyses properly estimate regression coefficients and variance when correlated data are used in analyses.[29] We used a GEE approach because of the clustered nature of our data, with observations nested within patients over the 4-year observation period.

We used a multinomial logistic regression model to assess the predictors of patterns of adherence (inconsistent adherence and consistently poor adherence compared with consistently good adherence) over the 4-year period. Predictors were entered simultaneously and included patient race/ethnicity, age, sex, substance use diagnosis in the year prior to or during the study period, psychiatric hospitalization in the year prior to or during the study period, and medication regimen variables, including the predominant use of high doses during the study period and the predominant use of first-generation agents, second-generation, or both agents (no predominance) during the study period. The statistical significance level was set at .05 for all of these analyses. Statistical analyses were completed using SAS software version 9.1 (SAS Institute, Inc., Cary, N.C.).

Table 1. Characteristics of the Patient Cohort and Medication Regimens (N = 34,128)[a]

Patient Characteristic	Value
Age, mean (SD), y	51.2 (11.2)
Gender, N (%)	
Male	32,589 (95.5)
Female	1539 (4.5)
Race/ethnicity, N (%)	
White	18,924 (55.5)
African American	8830 (25.9)
Hispanic	2852 (8.4)
Other	427 (1.3)
Unknown	3095 (9.1)
Substance use diagnosis at any time, FY99–03, N (%)	11,993 (35.1)
Psychiatric hospitalization at any time, FY00–03, N (%)	12,080 (35.4)
Antipsychotics used predominantly, FY00–03, N (%)[a]	
First-generation antipsychotics	7930 (23.5)
Second-generation antipsychotics	16,931 (50.2)
Both antipsychotic types, no predominance	8899 (26.4)
Predominant use of high-dose antipsychotics, FY00–03, N (%)[a]	2159 (6.4)

[a]368 patients had MPRs = 0 in all 4 years and were not included in the calculations assessing predominant antipsychotic use or the use of high-dose antipsychotics. Thus, percentages reflect a denominator of 33,760 rather than 34,128 patients.
Abbreviation: FY = fiscal year.

RESULTS

Patient Characteristics

Table 1 outlines the demographic and clinical characteristics of the patient cohort and medication regimen characteristics. Consistent with the VA patient population, the cohort was predominantly male (95%) and older (mean age of 51.2 years). Most patients were white (56%) or African American (26%). Approximately 35% had a psychiatric hospitalization and 35% had a substance use disorder noted in the year prior to or during the observation period.

Regimen Characteristics

The percentage of patients who had 90% or more of their fills for second-generation agents increased in each

Table 2. Aggregate and Patient-Level Adherence to Antipsychotic Medication Over Time (N = 34,128)

Observation Year	Aggregate MPR, Mean (SD)	Patients With Poor Adherence, N (%)	MPR in Patients With Good Adherence, Mean (SD)	MPR in Patients With Poor Adherence, Mean (SD)
FY2000	0.81 (0.32)	12,679 (37.2)	1.01 (0.15)	0.47 (0.25)
FY2001	0.80 (0.34)	12,660 (37.1)	1.01 (0.15)	0.45 (0.26)
FY2002	0.81 (0.35)	12,278 (36.0)	1.02 (0.16)	0.43 (0.27)
FY2003	0.80 (0.36)	12,588 (36.9)	1.02 (0.16)	0.42 (0.27)

Abbreviations: FY = fiscal year, MPR = medication possession ratio.

Table 3. Pattern of Adherence to Antipsychotic Medication Over 4 Years (N = 34,128)

Variable	MPR Over 4-Year Period, Mean (SD)	N (%)
Level of adherence		
Consistently good adherence	1.03 (0.16)	13,434 (39.4)
Inconsistent adherence	0.79 (0.29)	14,711 (43.1)[a]
Consistently poor adherence	0.33 (0.25)	5983 (17.5)
Changes in MPR ≥ 0.2 in consecutive years		21,066 (61.7)

[a]19.8% of patients had 1 year of poor adherence, 12.8% had 2 years with poor adherence, and 10.6% had 3 years with poor adherence. (A total of 43% had at least 1 year of poor adherence.)
Abbreviation: MPR = medication possession ratio.

year of the observation period; 48% of patients were predominantly treated with second-generation agents in FY00, 56% in FY01, 62% in FY02, and 66% in FY03. Over the 4-year period, 50% of patients had ≥ 90% of their antipsychotic fills for second-generation agents.

Approximately 7% to 9% of patients in the sample received predominantly high doses of antipsychotics in each study year, with 6% receiving predominantly high doses over the 4-year period.

Olanzapine and risperidone were the most commonly prescribed antipsychotic medications in each observation year, with haloperidol being the third most commonly prescribed agent until FY03, when quetiapine replaced it in the top 3. Doses of most of these medications remained relatively stable over the years, with olanzapine and quetiapine showing slight increases in prescribed doses in succeeding observation years.

Approximately 6% of the study population received antipsychotic polypharmacy in FY00, with slight increases over the following years; 8% received polypharmacy in FY03.

Adherence Over Time

As shown in Table 2, the cross-sectional percentage of cohort patients with poor antipsychotic adherence remained relatively stable from year to year during the 4-year observation period (36%–37% in each year).

Despite a high degree of stability in cross-sectional adherence among the patient population, there was considerable variation in the adherence of individual patients over time (Table 3). Among patients with schizophrenia visits in each of the 4 years (N = 34,128), 43% were inconsistently adherent. Approximately 20% were poorly adherent for 1 year, 12.8% for 2, and 10.6% for 3 years of the 4 observation years. Approximately 18% demonstrated consistently poor adherence across all 4 years, and 39% demonstrated consistently good adherence. Thus, a majority of patients (61%; N = 20,694) with regular appointment attendance had 1 or more years during the observation period in which they were poorly adherent and in need of additional supports.

Because 14,711 patients had inconsistent adherence, most (71%) of the 20,694 patients who might have been identified as poorly adherent on a cross-sectional basis (in any of the 4 study years) also had at least 1 year during the 4-year study period during which they were adherent. Conversely, a majority (52%) of the 28,145 patients who might have been identified as having good adherence on a cross-sectional basis (in any study year) had at least 1 year during the 4-year period during which they were poorly adherent. When we examined adherence in consecutive years, we found that 17% of the patients who had good adherence in FY00 had difficulties with adherence in FY01. Conversely, 30% of patients who had difficulties with adherence in FY00 had good adherence in the following year.

Because patients who completed treatment visits for schizophrenia in each of 5 consecutive years are likely to represent a more adherent subset of the entire VA population with schizophrenia, we explored antipsychotic adherence among a broader group of patients who had schizophrenia diagnoses and antipsychotic fills in FY99 and valid MPRs in each of the next 4 years but who did not necessarily complete treatment visits for schizophrenia in all 4 study years. Not surprisingly, among this broader group that included patients with gaps in appoint-

Table 4. Predictors of Inconsistent Adherence or Consistently Poor Adherence Compared With Predictors of Consistently Good Adherence

Patient Characteristic	Relative Risk Ratios for Consistently Poor Adherence (95% CI)	Relative Risk Ratios for Inconsistent Adherence (95% CI)
Male vs female	1.09 (0.92, 1.27)	0.94 (0.84, 1.05)
Age (per 5-year increase)	0.96 (0.94, 0.98)	1.01 (1.00, 1.02)
Race/ethnicity		
African American vs white	3.81 (3.53, 4.12)	1.77 (1.66, 1.88)
Hispanic vs white	3.54 (3.16, 3.97)	1.76 (1.60, 1.93)
Other vs white	1.61 (1.20, 2.16)	1.27 (1.03, 1.57)
Unknown vs white	1.88 (1.67, 2.11)	1.35 (1.24, 1.47)
Substance use diagnosis	1.84 (1.71, 1.98)	1.38 (1.31, 1.46)
Psychiatric hospitalization	1.48 (1.37, 1.59)	1.47 (1.39, 1.55)
Predominant use of second-generation antipsychotics vs first-generation agents during FY00–03	0.87 (0.80, 0.94)	0.95 (0.89, 1.01)
No predominant antipsychotic type vs predominant use of first-generation agents during FY00–03	0.86 (0.78, 0.94)	1.03 (0.96, 1.10)
Predominant use of high-dose antipsychotics during FY00–03	0.43 (0.37, 0.50)	0.66 (0.60, 0.73)

Abbreviation: FY = fiscal year.

ment attendance (N = 52,560), 71% had 1 or more years during which they were poorly adherent with antipsychotic medications. Approximately 33% demonstrated consistently poor adherence, 38% were inconsistently adherent, and 29% demonstrated consistently good adherence.

Stability of Medication Use

When we examined whether patients with schizophrenia visits in all years had substantial changes in their MPRs from year to year, rather than simply categorizing adherence in each year as good or poor, we found that 62% of patients had at least 1 change in their MPR of ≥ 0.2 between consecutive years.

We note that, when patients were categorized as having a change in adherence status between consecutive fiscal years (going from good to poor adherence or the reverse), approximately 92% to 93% of patients had changes in their MPR values ≥ 0.1, and 73% to 75% of patients had changes in their MPR values ≥ 0.2. In large population samples, differences of ≥ 0.1 or ≥ 0.2 in MPR are associated with absolute differences in hospitalization rates of 2% to 5% or 5% to 7% in a year's time, respectively, depending on the reference value of MPR.

Predictors of Cross-Sectional Adherence and Patterns of Adherence Over Time

In multivariate GEE analyses that examined cross-sectional relationships between adherence during the year and patient and medication regimen characteristics during the year, African American and Hispanic race, younger age, substance use diagnosis, and psychiatric hospitalization were associated with an increased likelihood of poor adherence. Cross-sectionally, high doses of antipsychotics were not significantly associated with the likelihood of poor adherence. However, patients who predominantly used second-generation agents during a study year had a significant but small reduction ($p = .0014$) in the likelihood of poor adherence during that year compared with patients who predominantly used first-generation agents.

In multinomial logistic regression models examining adherence patterns over time, several factors were associated with having consistently poor adherence or inconsistent adherence rather than consistently good adherence. As outlined in Table 4, older patients were less likely to have consistently poor adherence with the relative risk ratio (RRR) of consistently poor adherence compared with consistently good adherence being 0.96 for each 5-year increase in age. In contrast, patients who were African American (RRR = 3.81) or Hispanic (RRR = 3.54) or who had a substance use diagnosis (RRR = 1.84) or a psychiatric hospitalization (RRR = 1.48) in the year prior to or during the observation period were more likely to demonstrate consistently poor adherence than consistently good adherence.

Most of these patient characteristics, with the exception of age, had similar associations with inconsistent adherence compared with good adherence, although the effect sizes were smaller. Age was not significantly associated with inconsistent adherence.

Patients who were treated with predominantly high doses of antipsychotics over the 4-year period were less likely to have consistently poor or inconsistent adherence than patients who were not predominantly treated with high doses. Although patients who were treated with second-generation or both types of antipsychotics did not differ in the likelihood of inconsistent adherence from those treated predominantly with first-generation agents, these groups did show small but statistically significant decreases in the likelihood of consistently poor adherence.

CONCLUSIONS

Ongoing adherence with antipsychotic medications is essential if the outcomes of patients with schizophrenia are to be optimized.[12,26,27,30] However, developing interventions that improve patient adherence remains challenging. This study examined adherence with antipsychotic medication over a 4-year period among a large sample of patients with schizophrenia, providing information that may be useful to clinicians and organizations attempting to improve adherence. Study data allow us to comment on the proportion of the patient population with schizophrenia that may need adherence-enhancing interventions, potential processes for identifying patients who might benefit from these interventions, and the duration of time that the interventions might need to be in place.

We observed cross-sectional rates of poor adherence (36%–37% in each of the study years) that are generally congruent with those observed in prior cross-sectional studies of patients with schizophrenia, although somewhat below the median rate of 40% noted in 2 recent reviews.[2,3] Our cohort included patients who completed visits for schizophrenia in 5 consecutive years (the year of cohort entry and each of the 4 subsequent years). Patients who are in treatment for several consecutive years are likely more adherent than patients who are in treatment at any one time point.

Disappointingly, cross-sectional rates of adherence among our patient population did not change significantly over a 4-year study period. Although there are frequent articles about poor adherence in the psychiatric literature and repeated admonitions to clinicians to address adherence with their patients, improving adherence is difficult, and our study suggests that such changes are not occurring rapidly. This difficulty remains, even though second-generation agents were increasingly used during the observation period, and many had hoped that these medications might substantially increase adherence among patients with schizophrenia. Even though, in multivariate analyses, we found that predominant use of second-generation agents was associated with a significant but small increase ($p = .0014$) in adherence, such use has not resulted in large changes in adherence at the population level.

Despite stable rates of adherence across the population during the observation period, individual patients showed considerable variation in adherence over time. Most patients who were identified as nonadherent on a cross-sectional basis did not remain poorly adherent year after year, and many patients with good adherence at one time point had adherence difficulties in other years. When patients' adherence category changed, this usually represented substantial changes in the continuous MPR measure.

These findings represent mixed news for clinicians. On the positive side, our findings suggest that most patients who are noted to have adherence problems at any given time point have also recently demonstrated a capacity to be adherent and could presumably return to being adherent. Patients' adherence may improve during periods when there are positive changes in their life circumstances (e.g., more residential stability or social support), economic circumstances (e.g., increased ability to afford medication copayments), or treatment environment (e.g., easier access to care, or receiving medications that are more efficacious or have fewer side effects).

On the less positive side, our findings suggest that clinicians must always be vigilant regarding patients' medication adherence. The majority (61%) of patients with schizophrenia and regular appointment attendance had difficulties with adherence at some time over the 4-year period. When both patients with regular attendance and those with gaps in appointment attendance are considered, an even higher proportion (71%) had difficulties with antipsychotic adherence sometime during the observation period. Favorable conditions for adherence are likely difficult to maintain.

Clinicians must address adherence issues regularly in their routine interactions with patients and continually assist patients in developing habits and securing social and environmental supports that help maintain adherence.

Because patients often move in and out of being adherent, health care systems wishing to improve population adherence must focus on interventions that can be provided in an ongoing fashion rather than concentrating only on time-limited efforts. Although positive changes may result from time-limited efforts, such changes may be difficult to maintain over time. Organizations should not limit adherence-enhancing interventions only to those patients who might be identified as poorly adherent at any one time point, as this limitation will miss many patients who require support to maintain their adherence. More than half of the overall population with schizophrenia will likely need ongoing support if they are to achieve and maintain adherence.

In line with studies that have reported that patient factors such as younger age and nonwhite race/ethnicity are associated with higher cross-sectional rates of poor adherence, we found these factors to also be associated with consistently poor compared with consistently good adherence over time.

As noted above, these demographic factors may be imperfect flags for potential differences in health beliefs regarding psychiatric illness, susceptibility to additional illness episodes, or the acceptability and benefits of medication. Younger patients may be less likely to appreciate the severity of their illness or the need for ongoing medications, and minority patients may be less likely

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to find long-term psychiatric medications to be an acceptable treatment option.[2,31]

A substance use diagnosis prior to or during the observation period predicted consistently poor adherence, suggesting that substance use may be difficult to address among patients with serious mental illness or that patient factors that are associated with substance use contribute to poor adherence in an ongoing manner. A psychiatric hospitalization prior to or during the observation period also predicted consistently poor adherence. Patients who had been hospitalized may have more severe illnesses, impairing their ability to maintain stable housing or habits that support regular medication taking. These patients also may have had longer-term difficulties with adherence that precipitated their hospitalization.

Medication regimen characteristics appeared to have relatively modest effects on adherence. On a cross-sectional basis, high antipsychotic doses showed no association with the likelihood of poor adherence, but predominant use of high doses over a 4-year period was associated with less consistently poor and less inconsistent adherence. As we noted in a prior article,[5] providers may prescribe higher than recommended doses, particularly longer term, when patients are unstable but keep their regular appointments (adherent with appointments). Providers may also carefully assess adherence before moving patients to high doses of antipsychotics. The use of second-generation agents appears to be associated with a significant but small decrease in consistently poor adherence over time. However, many patients continue to have adherence difficulties even when using these newer medications.

Limitations

We note that MPRs are a useful, but imperfect, measure of adherence. For example, patients might have high MPRs, suggesting good adherence, yet be filling their prescriptions regularly without ingesting the medications. Alternatively, they may have low MPRs, suggesting poor adherence, but be regularly filling antipsychotic prescriptions outside of the VA system. However, cross-system use is generally low among VA mental health users,[32,33] and in this study, we examined adherence among patients who remained engaged in VA treatment over time. In previous work, we and other researchers have also demonstrated a strong relationship between patients' MPRs and psychiatric hospitalization, giving evidence of the validity and usefulness of this measure.[12,26,27]

Summary

Although some subgroups of patients may be at particular risk, the majority of patients with schizophrenia will have some difficulties with adherence over a 4-year period of time. Many will cycle in and out of periods of poor adherence. Clinicians must stay vigilant for poor adherence in the majority of their patients and recognize that improvements in adherence can subsequently be lost. Health care organizations wishing to improve patient adherence should emphasize interventions that can be implemented longer term or in an ongoing fashion and that can be offered to the majority of patients.

Drug names: aripiprazole (Abilify), haloperidol (Haldol and others), olanzapine (Zyprexa), quetiapine (Seroquel), risperidone (Risperdal).

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

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