

Pharmacy Data Identify Poorly Adherent Patients With Schizophrenia at Increased Risk for Admission

MARCIA VALENSTEIN, MD, MS,*[†] LAUREL A. COPELAND, PhD,* FREDERIC C. BLOW, PhD,*[†]
JOHN F. MCCARTHY, PhD, MPH,* JOHN E. ZEBER, MHA,*[‡] LEAH GILLON, MSW,*
C. RAYMOND BINGHAM, PhD,*[†] AND THOMAS STAVENGER, RPh[§]

BACKGROUND. Health care organizations may be able to use pharmacy data to identify patients with schizophrenia and poor antipsychotic adherence.

OBJECTIVE. To determine whether a pharmacy-based measure of outpatient adherence, the medication possession ratio (MPR), is associated with adverse outcomes among patients with schizophrenia, as evidenced by increased psychiatric admission.

RESEARCH DESIGN. Cohort study linking pharmacy and utilization data for veterans with schizophrenia. MPRs were calculated by dividing the number of days' supply of antipsychotic medication the veteran had received by the number of days' supply they needed to receive to take their antipsychotic continuously. Using multivariate regression, the relationship between MPRs and psychiatric admission was examined.

SUBJECTS. Sixty-seven thousand seventy-nine veterans who received a diagnosis of schizophrenia and had outpatient antipsychotic medication fills between October 1, 1998 and Sep-

tember 30, 1999.

RESULTS. Patients with MPRs close to 1.0 had the lowest rates of admission. As patients secured progressively smaller proportions of required antipsychotic medication (and had smaller MPRs), rates of admission climbed. Among patients on one antipsychotic ($n = 49,003$), patients with poor adherence (MPRs < 0.8) were 2.4 times as likely to be admitted as patients with good adherence (MPRs from 0.8–1.1). 23% of poorly adherent patients but only 10% of adherent patients were admitted. Once admitted, poorly adherent patients had more hospital days. Patients who received excess medication also had higher admission rates.

CONCLUSIONS. Many health care systems may be able to use pharmacy data to identify poorly adherent patients with schizophrenia. These patients are at-risk for admission and may benefit from intervention.

Key words: Schizophrenia; medication adherence, admission. (Med Care 2002;40:630–639)

*From the Department of Veterans Affairs, Serious Mental Illness Treatment, Research, and Evaluation Center (SMITREC), Health Services Research and Development (HSR&D) Center for Excellence, Ann Arbor, Michigan.

[†]From the Department of Psychiatry, University of Michigan, Ann Arbor, Michigan.

[‡]From the Health Management and Policy, University of Michigan School of Public Health, Ann Arbor, Michigan.

[§]From the Department of Veterans Affairs, VISN 11 Headquarters, Ann Arbor, Michigan.

Supported by a HSR&D Research Career Development Award, RC-98350 to 1 and by the Mental Health Strategic Health Group of the Veterans Health Administration Headquarters.

Address correspondence and reprint requests to: Marcia Valenstein, MD, MS; Ann Arbor HSR&D COE; P.O. Box 130170; Ann Arbor, MI 48113-0170. E-mail marciav@umich.edu.

Received September 17, 2001; initial review November 5, 2001; accepted January 23, 2002.

DOI: 10.1097/01.MLR.0000021003.43524.64

Antipsychotic medications significantly reduce the symptoms of schizophrenia and are an essential part of the treatment of this disorder.^{1,2} Unfortunately, many patients with schizophrenia are poorly adherent with antipsychotic medication.³⁻⁷

Numerous articles have documented the frequency, predictors, and possible determinants of poor adherence among patients with schizophrenia, and clinicians are often reminded to discuss potential barriers to adherence with their patients.⁸⁻¹⁰ Nevertheless, poor adherence remains a persistent problem.

Without systematic assistance, clinicians may be unable to successfully address many patients' adherence difficulties. Nonadherence may be covert, with clinicians failing to recognize that their patients are taking their medications erratically or have stopped their medication. Even when clinicians do recognize that their patients are poorly adherent, they may not have the time or resources to mount the multicomponent interventions that are necessary to increase adherence.¹¹ Successful interventions usually included multiple components, such as patient and family education, reduced barriers to access, ongoing monitoring, and systematic feedback, etc.¹¹

The rapid rise of organized health care systems presents new opportunities for addressing adherence problems among patients with chronic illnesses, including patients with schizophrenia. Organized health systems are increasingly accepting responsibility for the quality of treatment delivered by affiliated providers,¹² and many patients with serious mental illness are enrolling in managed Medicaid or Medicare programs.¹³ Managed care organizations and the public-sector organizations that have traditionally cared for these patients, such as the Veterans Health Administration (VA) and community mental health organizations, often have comprehensive pharmacy data and sophisticated information systems. Potentially, these organizations could assist clinicians in addressing adherence, by systematically identifying and intervening with poorly adherent patients.

Monitoring pharmacy data may be one of the few practical methods for assessing adherence in large patient populations; it is both less costly and less intrusive than other methods of monitoring adherence, such as medication blood levels, pill counts, or electronic monitoring devices (eg, MEMS-4, Apres Corporation, San Diego, CA)^{14,15} Researchers have made preliminary efforts to use

pharmacy data to monitor the quality of care of patients with bipolar disorder in a HMO setting.¹⁶

Pharmacy-based measures of adherence have been associated with important intermediate outcomes among patients with other chronic medical disorders,¹⁵ including patients with hypertension and epilepsy.¹⁷ However, only one study has reported a relationship between pharmacy data and the risk for admission among patients with schizophrenia.¹⁸ This study found that gaps of ≥ 3 months in Medicaid claims for antipsychotic agents were associated with increased rates of hospitalization among 434 patients with schizophrenia. Other studies have reported that nonpharmacy-based measures of adherence correlate with important outcomes among patients with schizophrenia.^{19,20}

Pharmacy data also offer an opportunity to explore the consequences of varying degrees of partial adherence. Many methods of assessing adherence cannot easily be applied in large patient populations or do not distinguish degrees of adherence. As a result, patients have often been characterized as either poorly adherent or adherent, although adherence is customarily a matter of degree.⁶ Depending upon the condition, drug, and pattern of ingestion, the association between partial adherence and outcomes may be more or less closely linked.

In this study, we examine whether a pharmacy-based measure of adherence, the medication possession ratio, is associated with an important outcome—psychiatric admission—among a large sample of patients with schizophrenia treated in the VA ($n = 67,079$). We also examine the relationship between varying degrees of adherence and admission. Finally, we explore whether patients who are identified as poorly adherent using pharmacy data remain in contact with the health care system. If pharmacy-based measures were associated with important patient outcomes, many organizations might find this a persuasive argument for using their data to systematically identify and intervene with these vulnerable patients.

Materials and Methods

Data on patient demographics, diagnoses, health care utilization, and outpatient pharmacy fills were obtained from the VA National Psychosis Registry for all VA patients receiving a diagnosis of a schizophrenia or schizoaffective disorder (ICD-9

codes for 295.x, excluding 295.5) between October 1, 1998 and September 30, 1999. If patients had more than one primary psychotic diagnosis noted during this period, the diagnosis noted during most treatment contacts was used. In study analyses, we used pharmacy data collected between October 1, 1998 and September 30, 1999 by the VA Pharmacy Benefits Management Group in Hines, Illinois and incorporated into the Psychosis Registry.

Study Sample

Seventy-four thousand three hundred ninety-four patients received a diagnosis of schizophrenia or schizoaffective disorder during a VA clinical encounter and had an outpatient prescription for an oral antipsychotic medication between October 1, 1998 and September 30, 1999. Previous studies have indicated that diagnoses of schizophrenia in claims data or VA administrative data are closely associated with clinical diagnoses of schizophrenia.^{21,22}

Because depot/decanoate medications are not consistently recorded in the VA pharmacy databases, we examined adherence only with oral antipsychotic medications in this study. Patients who were only on depot medications were not included and did not have MPRs calculated.

Exclusions

We excluded 770 patients from study analyses whose only outpatient prescriptions occurred on the dates of discharge from inpatient units with the conservative assumption that they received outpatient care outside of VA settings. We also excluded 3700 patients who had two or more outpatient prescriptions during VA institutional stays. These patients may have requested refills of their antipsychotic medication to be mailed before hospitalization, managed their own medications during nursing home stays, or received pass medications. Because the status of outpatient medications filled while patients were in institutional settings is unclear (mailed medications may have been lost, discarded, or stockpiled), using pharmacy data to measure adherence in these patients was problematic. Finally, we excluded 2,875 patients from study analyses who were exposed to ≥ 3 antipsychotics during the study year, because of difficulties in calculating adherence among pa-

tients with limited numbers of outpatient days following the prescription of several different antipsychotics (see below.)

The 7315 patients excluded from study analyses constituted 10% of the overall population of patients with diagnoses of schizophrenia and antipsychotic fills. Excluded patients were younger than patients included in the study (mean of 53 years vs. 55 years of age) and were less likely to be Hispanic. (Hispanic patients constituted 5% of the excluded group but 8% of the study sample.) Of the 67,709 study patients, 77% (52,389) were exposed to one antipsychotic drug during the year and 23% (14,690) were exposed to two different antipsychotic drugs during the year.

Study Measures

Medication Possession Ratio. Medication possession ratios were calculated for each patient in the sample by dividing the number of outpatient days' supply of medication the patient received during the study period by the number of days' supply they needed to receive if they were taking their outpatient medication continuously.

$MPR =$

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

We assumed that antipsychotic use should be continuous, reflecting guideline recommendations for the large majority of patients with schizophrenia.^{1,2} An MPR of 1.0 would indicate that the patient had received all the medication needed to take his medication as recommended, whereas an MPR of 0.5 would indicate that the patient had received medication sufficient to take only half of the recommended dose on a continuous basis. MPRs have been used in previous studies to assess adherence among patients with hypertension, diabetes, and other chronic disorders.^{23,24}

The numerator of the MPR, or the days' supply received by the patient, was calculated by adding the number of days' supply from each of the outpatient antipsychotic prescriptions filled during the year. If patients filled different dosage

strengths of the same medication on the same day, this was considered part of the same prescription. Outpatient prescriptions included medications that were given at the time of discharge from inpatient stays.

For patients receiving one antipsychotic during the year, the denominator of the MPR, or the days' supply needed, was calculated as the days between the date of first antipsychotic prescription and the end of the year or date of death. Any days that patients spent in institutional settings (in VA hospitals or nursing homes) were subtracted from the outpatient days' supply needed.

To obtain stable estimates, MPRs were calculated only for patients who had at least 90 days in noninstitutional settings, following their first antipsychotic prescription of the year. Of the 52,389 patients receiving one antipsychotic during the year, 49,003 had ≥ 90 noninstitutional days following their first prescription. The median number of days' supply needed for patients was 340 days.

In some analyses, MPRs were categorized. Patients with MPRs < 0.8 were considered to have "poor adherence," patients with MPRs from 0.8 to 1.1 were considered to have "good adherence," and patients with MPRs > 1.1 were considered to have "excess medication fills." This categorization reflects a frequently used "cut-off" of taking $\geq 75\%$ to 80% of prescribed medication to be considered adherent.²⁵⁻²⁷ Patients who received more medication than required to take their antipsychotics as prescribed (MPRs > 1.1), likely either lost their medications and requested additional fills or their providers frequently changed their doses and overlapped prescriptions.

Patients Treated With Two Antipsychotics

Major study analyses were conducted first for 77% of patients receiving just one antipsychotic medication during the year because of the more straightforward calculation of medication possession ratios among these patients. However, because 23% of patients were prescribed two different antipsychotics, we conducted exploratory analyses of the relationship between adherence and admission among these patients.

Patients treated with two different antipsychotics during the year either switched antipsychotic medications, received treatment with two antipsychotics concurrently, or had a brief trial of a second antipsychotic medication. MPRs were calculated

for each antipsychotic prescribed if there were ≥ 90 noninstitutional days following the first prescription of the medication. Because one antipsychotic alone is sufficient to meet the desired criterion of continuous antipsychotic treatment, the days' supply needed for any specific antipsychotic took into account whether a second antipsychotic was also being prescribed.

Of the 14,690 patients exposed to two antipsychotics during FY99, 8278 had ≥ 90 noninstitutional days following the first prescription of each of their two antipsychotics, and 14,211 had ≥ 90 noninstitutional days following the first prescription of at least one of their two antipsychotics. When patients had valid MPRs for two antipsychotic medications, the average of the two MPRs was calculated to reflect their overall adherence with antipsychotics during the study year.

Antipsychotic Refill Gaps

A second, simpler measure of adherence was also calculated. Antipsychotic refill gaps were the number of contiguous months during the study year that patients did not have an outpatient fill of their antipsychotic medication. Patients were considered to have a 1 month gap in antipsychotic fills if no fills occurred during the calendar month, antipsychotic fills in previous months did not "cover" the calendar month, and no hospitalization of ≥ 10 days had occurred during the month.

Psychiatric Admissions

Psychiatric admissions were defined as (1) having an admission to a VA acute care facility with a primary psychiatric diagnosis or (2) being enrolled in psychiatric bed section at the end of the fiscal year. We ascertained whether a psychiatric admission occurred during either fiscal year 1999 (October 1, 1998 to September 30, 1999) or during fiscal year 2000 (October 1, 1999 to September 30, 2000). We also calculated total inpatient psychiatric days occurring during fiscal year 1999.

Data Analysis

Simple descriptive statistics of the study sample were completed with univariate analyses of frequencies and means ($\pm$ standard deviations). Bivariate analyses were used to examine the rela-

tionship between admission (yes/no) and categories of adherence, using χ^2 analyses. χ^2 analyses were also used to examine the relationship between admission and categorical patient characteristics: gender, ethnic group (white, black, or other), and age group (<45 years of age, 45–64 years, and ≥ 65 years).

Logistic regression analyses were used to investigate the relationship between the dependent variable, psychiatric admission, and MPR as a continuous independent variable, adjusting for covariates of ethnic group, gender, age group, and use of atypical agents. After visual inspection of the data, an MPR-squared term was included in this model.

Logistic regression analyses were also conducted examining the relationship between the dependent variable, psychiatric admission (yes/no), and adherence category, again adjusting for the listed covariates. Analysis of variance and linear regression analyses were used to examine the relationship between adherence categories and patients' total inpatient psychiatric days in 1999. Statistical analyses were completed using SAS System for Windows, Release 8.02 (SAS Institute, Cary, NC).

Results

Patient Characteristics

The demographics of patients who met study criteria (n = 67,079) are outlined in Table 1. Patients' mean age was 55.3 ($\pm$ 12.1) years. Most were men (95%) and either white (61%) or black (29%), reflecting the VHA patient population.

Medication Possession Ratios

Among patients receiving one antipsychotic medication, the mean MPR was 0.80 ($\pm$ 0.33); 40% of these patients had MPRs of less than 0.8 and 20% had MPRs less than 0.5. The mean MPR for the 14,211 patients exposed to two different antipsychotics was 0.85 ($\pm$ 0.33), and 38% had MPRs <0.8.

Patient Characteristics Associated With Adherence and Inpatient Use

In bivariate analyses, patient ethnic group, age group, and type of antipsychotic (conventional vs.

TABLE 1. Patient Demographics

Measure	Overall Cohort N = 67,079
Sex	
Male (n = 63,881)	95.2%
Female (n = 3,198)	4.8%
Race	
White (n = 37,013)	60.5%
Black (n = 17,947)	29.4%
Hispanic-White (n = 5,014)	8.2%
Hispanic-Black (n = 397)	0.7%
Asian (n = 577)	0.9%
American Indian (n = 195)	0.3%
(Missing data on race in 5,936 cases)	
Age Group	
<45 years (n = 18,928)	28.2%
45–65 years (n = 35,769)	53.3%
>65 years (n = 12,365)	18.4%
Mean Age	55.3 $\pm$ 12.1

atypical) were significantly associated both with the likelihood of psychiatric admission and with adherence category. Black patients, younger patients, and patients on atypical agents were more likely to be admitted during the study year and were also more likely to be poorly adherent than were white patients, older patients, and patients on conventional agents.

Relationship Between Adherence and Inpatient Use

In logistic regression analyses that examined the relationship among the dependent variable, psychiatric admission, and MPR, adjusting for covariates of ethnic group, age group, gender and antipsychotic type, the model, and the quadratic term for MPR were significant.

Patients with MPRs close to one, indicating good adherence, had the lowest rates of psychiatric admission. As patients' MPRs decreased, their rates of admission progressively increased. Patients with excess medication fills also had increased admission rates. Figure 1 shows the proportion of patients admitted to inpatient psychiatric care across the MPR continuum.

In logistic regression analyses examining the relationship between psychiatric admission and

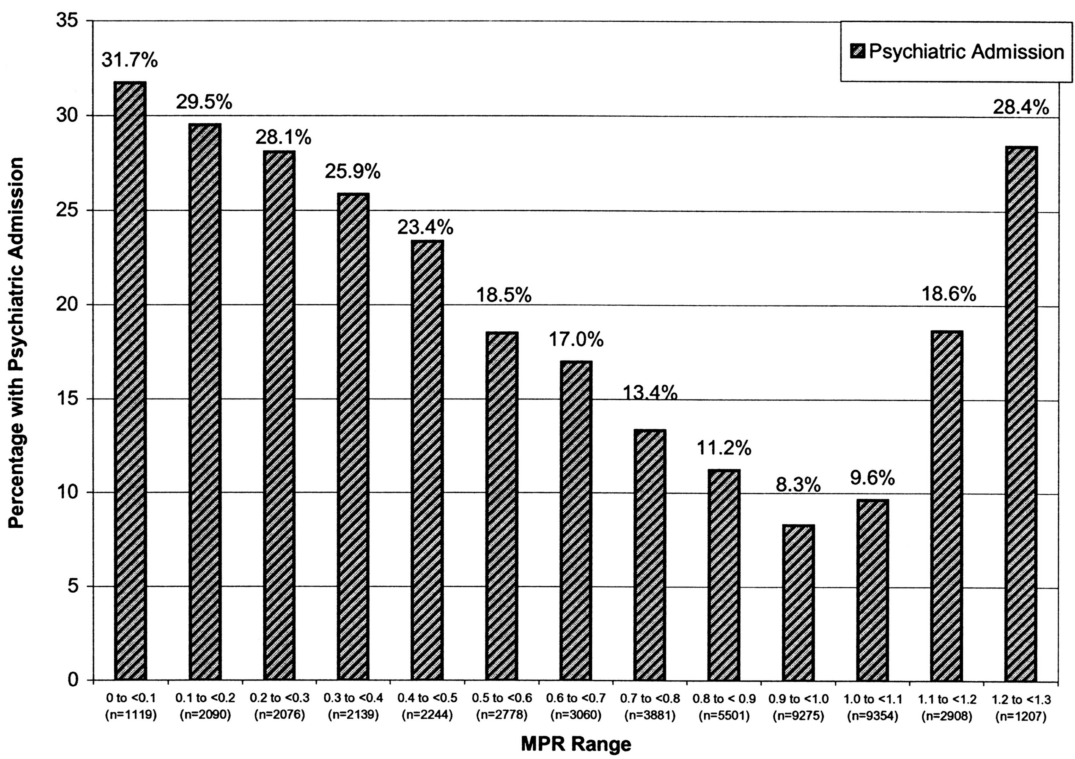


FIGURE 1. MPR and percentage of patients with a psychiatric admission in FY 99 (N = 48,148).

adherence category, patients with poor adherence (MPRs <0.8) were 2.4 times as likely to be admitted during the study year than patients with good adherence (95% CI, 2.3, 2.6; $P < 0.0001$). Table 2 lists the odds ratios for the association between psychiatric admission and each independent variable in the model.

Poor adherence during outpatient periods in the study year (October 1, 1998 to September 30, 1999, Fiscal Year 1999) was also associated with psychiatric admission in the following year (Fiscal Year 2000), although not as strongly. Patients who were poorly adherent during fiscal year 1999 were 1.6 times (95% CI, 1.6, 1.7) as likely to be admitted during fiscal year 2000 as patients who had good adherence.

Although the overall rates of admission were higher, the relationship between admission and MPR among patients receiving two antipsychotics during the year was similar to the relationship between admission and MPR among patients receiving just one antipsychotic. Again, patients with MPRs close to 1.0 had the lowest rates of admission. Patient age group, ethnic group, and

receiving atypical antipsychotics continued to be associated with admission.

Days in Hospital

A total of 8282 patients, or 17% of those patients receiving one antipsychotic medication, were admitted for psychiatric reasons during fiscal year 1999. Once admitted, patients with poor adherence had more total psychiatric inpatient days during the year (mean of 33 days) than patients with good adherence (mean of 24 days) ($F = 36.53$; $P < 0.0001$).

Patterns of Medication Taking and Treatment Contacts

In exploratory analyses, we examined the patterns of system contacts (medication refills and treatment visits) among the subset of poorly adherent patients on one antipsychotic who had >270 days of outpatient follow-up ($n = 14,485$).

TABLE 2. Odd Ratios for Inpatient Admission Among Patients Receiving One Antipsychotic

Independent Variable	Wald χ^2	P	Odds Ratio (95% CI)
MPR below 0.8 compared to MPR between 0.8–1.1	867.37	<0.0001	2.4 (2.3, 2.6)
MPR above 1.1 compared to MPR between 0.8–1.1	733.90	<0.0001	3.0 (2.8, 3.3)
Race			
Black compared to white	169.49	<0.0001	1.4 (1.4, 1.5)
Other compared to white	69.20	<0.0001	0.7 (0.6, 0.7)
On any atypical medication compared to being on conventional antipsychotics	456.49	<0.0001	1.8 (1.7, 1.9)
Age 20–45 compared to age 65 and older	324.66	<0.0001	1.9 (1.7, 2.0)
Age 46–65 compared to age 65 and older	129.06	<0.0001	1.4 (1.3, 1.5)
Female			
Compared to male	4.90	<0.0269	0.9 (0.8, 0.98)

Thirteen percent of these poorly adherent patients had no contiguous gaps in antipsychotic refills longer than a month, suggesting they took slightly less medication than prescribed over long periods of time or had short periods of discontinuation. Fifty-four percent had no contiguous gaps in antipsychotic fills longer than 3 months.

Many poorly adherent patients who had long gaps in refills (>3 months) maintained some degree of contact with the VA Health care system. Only 28% dropped out of treatment with gaps of >3 months in both prescription fills and system contacts (in or outpatient).

Discussion

Among patients with schizophrenia, a pharmacy-based measure of antipsychotic adherence, the medication possession ratio (MPR), is strongly associated with rates of psychiatric admission. Rates of admission are lowest for patients with MPRs close to one, those patients who secure sufficient medications to take their antipsychotics as prescribed. Rates of admission progressively increase as patients secure smaller percentages of the required antipsychotic supply. Patients who receive excess antipsychotic medication are also at increased risk for admission.

These data are consistent with previous reports of increased rates of relapse and admission among patients with poor adherence as assessed by other methods, such as self or clinician report, medication blood levels, or pill count.^{19,20} Our findings are also consistent with Svarstaad et al¹⁸ who

reported increased rates of admission among patients who had gaps of ≥ 3 months in Medicaid claims data for antipsychotics. However, with this large sample, we were able to use a finer measure of adherence and to delineate the relationship between admission and adherence across the “adherence continuum”.

Our data indicate that poor adherence remains a persistent problem, despite repeated admonitions to clinicians to be alert for adherence difficulties, address these issues with their patients, and adopt specific strategies to improve adherence, such as frequent nonjudgmental inquiries about medication use, depot antipsychotic medications, or promoting family involvement.^{8,28} Fully 40% of patients in this large national sample remained poorly adherent with their antipsychotic medication.

Our data also indicate that pharmacy-based measures of adherence flag patients who are at increased risk for poor outcomes. In this study, admission rates for patients with poor adherence (MPRs <0.8) were more than twice those of patients with good adherence.

Although some of the observed admissions may have resulted from poor medication adherence and subsequent relapse, study data do not allow us to completely disaggregate the relationship between medication adherence, relapse, and hospitalization. Some admissions may have resulted from behavioral problems that led both to poor adherence and admission. Patients may not have been receiving evidence-based psychosocial interventions that would have contributed to both

stability and adherence or they may have discontinued their medications because of lack of effectiveness or because of side effects. Nevertheless, this at-risk group seems likely to benefit from both a careful evaluation of the reasons for poor adherence AND an evaluation of whether their other treatment needs are being met.

Organizations that regularly monitor pharmacy data have the opportunity to identify these at-risk patients in a timely fashion and perhaps forestall adverse outcomes. Because admission rates (and likely other adverse outcomes) increase gradually as adherence decreases, organizations may choose different “adherence thresholds” at which they will intervene. Organizations might identify patients with low MPRs in the previous year, because these patients continue to be at increased risk. Alternatively, organizations might prospectively calculate MPRs at the end of each month to identify patients who have newly fallen below a specified threshold. Organizations might also use a less precise but simpler measure of adherence—missed monthly refills. Patients who miss two to three monthly fills over a year’s time would have MPRs between 0.84 and 0.75. Patients who miss two or three contiguous months of antipsychotic fills may be particularly at risk for hospitalization. However, even with this simpler measure, organizations will need to consider inpatient days and the days’ supply received with each medication fill when deciding if adherence has become problematic.

For those organizations contemplating whether to intervene with poorly adherent patients, our data suggest that approximately 70% of these patients will maintain some level of contact with the system and be relatively easy to contact. The remaining 30% may require community outreach efforts to reengage them in treatment.

We note that patients with low MPRs are not the only vulnerable group flagged by pharmacy data. In this sample, patients who secured more medication than necessary to take their prescribed antipsychotic doses were also at increased risk for admission. This finding is consistent with a previous report that MPRs for antihypertensive medications correlated with improved blood pressure control until they became greater than one, at which point blood pressure control deteriorated.¹⁷

High antipsychotic MPRs may serve as a marker for less stable patients. Clinicians may be frequently increasing these patients’ doses, giving them new prescriptions of different dosage

strengths. Alternatively, these patients may be disorganized, and clinicians may be replacing mislaid medications. Although patients with high MPRs form a much smaller group than patients with low MPRs, they may also merit special attention.

In study analyses that adjusted for important covariates, we found that several patient factors were associated with increased rates of psychiatric hospitalization. Black patients, younger patients, men, and patients on atypical agents were at higher risk for admission after adjusting for adherence. Previous studies have suggested that younger patients and men may be at increased risk for admission,^{19,29} and some^{30,31} but not all¹⁹ studies have reported that black patients are more likely to be admitted than white patients. Younger men may be more likely to be admitted because they exhibit more uncontrolled or violent behavior. Black patients may be more likely to be admitted because they present with different symptom constellations,^{32,33} have less access to alternatives to inpatient care such as partial programs or intensive outpatient services, or receive less appropriate pharmacological management.^{34,35}

In this sample, patients on atypical agents were more likely to be admitted than patients on conventional agents, possibly because of selection effects. Patients who were less stable may have been preferentially switched to the newer atypical agents in the years before the study and remained at higher risk during the study period.

Limitations

As noted above, study data demonstrate a strong association between poor medication adherence and admission, but do not allow us to disaggregate the relationship between adherence, behavioral problems, and hospitalization. Our measure of adherence, the MPR, also has limitations. Some patients may have received sufficient medication from the pharmacy to take their antipsychotic medication as prescribed but failed to ingest the medication; others may have filled antipsychotic prescriptions outside of the VA, resulting in incorrectly low MPRs.

Nevertheless, extensive out-of-VA services use is unlikely to explain study findings, as this would require both substantial out-of-system use and increased rates of VA hospitalization among patients treated in other systems. Only 19% of

veterans with schizophrenia receiving VA mental health treatment report any outside health service use, including outside general medical use.³⁶ Also, public health care systems outside of the VA have strengths and weakness but do not appear to offer significantly poorer care.³⁷

Finally, we note that we did not study medication adherence among patients using depot/decanoate medications. Patients on depot antipsychotics may have better levels of adherence than patients using oral medications. However, oral antipsychotics are a major modality of treatment in the US, newer antipsychotics are not yet available in depot form, and many patients will only accept oral medications. Therefore, a study of adherence with oral medications remains germane.

Conclusion

Pharmacy data can be used to identify patients with schizophrenia who are poorly adherent with their antipsychotics and at risk for poor outcomes. These patients may benefit from a thorough evaluation and increased attention to both medication adherence and other aspects of care. Patients may require changes in their pharmacological regimen, the addition of psychosocial interventions, such as family interventions, treatment of substance abuse, or structured interventions targeting adherence.³⁸ If health care organizations identify and intervene with these vulnerable patients, their outcomes might be substantially improved.

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