A Prospective Study of Risk Factors for Nonadherence With Antipsychotic Medication in the Treatment of Schizophrenia

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Objectives: This study aimed to prospectively identify the best single predictor and the best set of predictors of risk for nonadherence with antipsychotic medication in the treatment of patients with schizophrenia.

Method: We used data from 1579 patients in a 3-year, prospective, naturalistic, nonrandomized, multisite study of schizophrenia patients conducted from July 1997 to September 2003 (U.S. Schizophrenia Care and Assessment Program). Adherence with any oral antipsychotic medication was assessed using patient-reported medication adherence and an indirect adherence measure based on medical record prescription information. Patients who reported poor medication adherence or had a medication possession ratio ≤ 80% (percentage of days with prescriptions for any oral antipsychotic) during the first year after enrollment were defined as nonadherent (N = 296, 18.8%). Thirty-nine previously reported potential risk factors of nonadherence with antipsychotic medication were assessed at enrollment with valid and reliable measures. Risk factors represented patient-, environment-, and treatment-related domains, including sociodemographics, symptom severity, substance use, threat to safety of self and others, other illness-related factors, need for supervision, medication-related adverse events, and prior medication-utilization patterns.

Results: The best single predictor of future nonadherence was nonadherence during the 6 months prior to enrollment (odds ratio = 4.1, 95% confidence interval = 3.1 to 5.6, $p < .001$). The best set of predictors of nonadherence, ordered by strength of association, included prior nonadherence, recent illicit drug use, recent alcohol use, prior treatment with antidepressants, and greater patient-reported, medication-related cognitive impairment.

Conclusion: Nonadherence with antipsychotic medication is associated with a well-defined set of risk factors that can be used to identify patients who are predisposed to poor adherence.

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Antipsychotic medications are recognized as an essential component in the treatment of schizophrenia,[1] but only about half of patients take their medications as prescribed.[2,3] Nonadherence with antipsychotic treatment regimens was shown to be associated with poor treatment outcomes, including a 2-fold increase in hospitalization risk.[4,5]

Growing concerns about the adverse consequences of medication nonadherence have increased interest in monitoring adherence as an integral part of medication management[6] and in clarifying which risk factors are most strongly associated with nonadherence. Such key tasks may help identify patients predisposed to nonadherence, thus enhancing clinicians' ability to target these patients for adherence interventions.[2]

Prior research efforts have not led to consensus regarding which risk factors are most strongly associated with nonadherence in the treatment of schizophrenia.[2] There is, however, a general agreement that adherence is mediated by several factors broadly categorized as patient-, environment-, and treatment-related risk factors.[7] A comprehensive review of studies assessing risk factors for nonadherence with antipsychotic medications in schizophrenia[2] identified 7 factors as most consistently associated with nonadherence: poor insight, negative attitude or subjective response toward medication, previous nonadherence, substance abuse, shorter illness duration, inad-

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equate hospital discharge planning, and poorer therapeutic alliance. Although these factors were frequently associated with nonadherence, it is unclear if they are the best predictors of nonadherence.

Most studies of risk factors for medication nonadherence in the treatment of schizophrenia were conducted before atypical antipsychotics were introduced and may not be representative of the current treatment environment or reflect the different types of adverse effects these newer medications are associated with (e.g., diabetes, weight gain). Further, previous studies varied in patient populations, study designs, measures of adherence, and risk factors assessed, and most of these studies, with some exceptions,[8–12] typically assessed a few risk factors in a small sample at a single site. Additionally, most previous investigations were retrospective in design and rarely used rating scales to evaluate medication adverse effects.[2]

To address these methodological limitations and to expand on previous research, this study aimed to prospectively identify the best single predictor and the best set of predictors of risk for nonadherence with antipsychotic medication in the treatment of patients with schizophrenia. To enhance the ability to generalize findings to patients treated across different care settings, we examined data from a large, 3-year, prospective, nonrandomized, naturalistic, multisite study of patients treated for schizophrenia in various health care systems in the United States. In this study, we focused on 39 previously reported potential risk factors of nonadherence with antipsychotic medication representing patient-, environment-, and treatment-related domains.

A challenging issue in antipsychotic adherence research is the lack of a universally accepted standard measure to differentiate adherent from nonadherent patients. Numerous adherence assessment tools have been described, all of which have their individual strengths and weaknesses.[13] Although patient reports are the most common methods of attempting to determine adherence, even refined interviewing strategies substantially overestimate adherence.[14] Faced with these challenges, this study assessed adherence using both patients' self-report and the annual medication possession ratio (MPR), the percentage of days with any antipsychotic during the first year following study enrollment. Although the MPR is typically derived from pharmacy-fill data, we used medical record–based MPR, reflecting the percentage of days with prescription for any antipsychotic during the first year following study enrollment. The MPR is an indirect measure of medication adherence commonly used with pharmacy-fill data and has been used to assess medication adherence in the treatment of chronic illnesses, including schizophrenia.[4,5,15–21] The MPR has been shown to be reliably associated with important treatment outcomes for schizophrenia patients, including relapse[5] and psychiatric hospitalization.[4,5,19–22]

METHOD

Data Source

Data were drawn from the U.S. Schizophrenia Care and Assessment Program (US-SCAP), a large (N = 2327), 3-year, naturalistic, prospective, observational study in the United States conducted from July 1997 to September 2003. The goal of US-SCAP was to understand the treatment provided to patients with schizophrenia in usual care settings. In brief, patients were enrolled from 6 regional sites (California, Colorado, Connecticut, Florida, Maryland, and North Carolina) and from diverse systems of care, including community mental health centers, university health care systems, the Department of Veterans Affairs Health Services (VA), and community and state hospitals. Institutional review board approval was received at each regional site, and informed consent was received from all patients. Of the 2327 patients, 78.1% completed 1 year of follow-up, and 21.2% were hospitalized at enrollment or during the 6 months prior to enrollment. At enrollment, most patients were treated with at least 1 antipsychotic medication (94.7%). Enrollment was not contingent on being treated with a specific antipsychotic or with any medication. Treatment decisions during the 3-year study were made by physicians and their patients, as they are in usual clinical practice, independent of study enrollment. Comprehensive details about US-SCAP are available elsewhere.[23,24]

The present study of risk factors for antipsychotic nonadherence included 1579 patients who were treated with any oral antipsychotics (no use of antipsychotics in depot formulation), had medical record information on prescribed medications, and responded to the inquiry about their medication adherence during the first year of the US-SCAP study.

Measures

Adherence measures. The adherence classification for each participant (adherent or nonadherent) was based on patient-reported medication adherence and medical record prescription information. Each participant's medication prescription information was systematically abstracted from the medical record every 6 months by trained and annually certified examiners who used an abstraction form developed for this study. To capture all patients' medication regimens, independent of service location, special efforts were made to abstract information on medications prescribed during patients' psychiatric hospitalizations. In addition, patients were queried about medications dispensed by sources outside of the patients' regular treatment site, and special efforts were made to collect that information.

Medication prescription information in patients' medical records was used to calculate an annual MPR, reflecting the percentage of days for which a prescription for any

oral antipsychotic medication was available during the 365 days following enrollment. Consistent with prior research,[4,15–21] MPR > 80% was defined as adherent and MPR ≤ 80% was defined as poorly adherent.

Patient-reported adherence with medication was assessed with a single rating scale, which was included in the SCAP Health Questionnaire (SCAP-HQ), a validated self-report measure developed and validated for the US-SCAP study[23] and administered at enrollment and at 6-month intervals thereafter. The medication adherence item was rated on a 5-point scale: (1) I never missed taking my medicine; (2) I missed only a couple of times, but basically took all the medicine; (3) I missed the medicine several times, but took at least half of it; (4) I took less than half of what was prescribed; and (5) I stopped taking the medicine altogether. Patients who chose alternative 1 or 2 were considered "adherent," whereas all others were classified as "poorly adherent." Patients who reported poor adherence at 2 consecutive assessments following enrollment (the 6-month and 12-month assessments) were considered nonadherent.

Because of our desire to identify most patients suspected to be nonadherent to oral antipsychotic treatment coupled with the limitations of all adherence assessment tools, any patient who had an MPR > 80% during the first year after enrollment and who reported being adherent at 2 consecutive assessments following enrollment (6- and 12-month assessments) was defined as adherent. All others were defined as nonadherent.

Risk factor measures. Thirty-nine previously reported potential risk factors of nonadherence with antipsychotic medication[2] were assessed at enrollment and at 12-month intervals thereafter. These risk factors, categorized into 3 domains—patient-related, environment-related, and treatment-related[7]—are presented in Table 1. The risk factors were assessed using instruments administered by trained and annually certified clinicians. Semistructured screening interviews with patients provided sociodemographic characteristics and psychiatric history. Symptomatology was assessed with the Positive and Negative Syndrome Scale (PANSS)[25] using the Davis and Chen[26] 5-factor scale scores, and the Montgomery-Asberg Depression Rating Scale (MADRS).[27] Global level of functioning was assessed with the Global Assessment of Functioning (GAF) scale.[28] Substance use, threat to safety of self and others, and other illness-related factors were measured with the SCAP-HQ. Medication-related adverse events were measured with the Abnormal Involuntary Movement Scale (AIMS),[29] the Simpson-Angus Scale (SAS),[30] and a patient-reported medication side effect scale on the SCAP-HQ. Tardive dyskinesia symptoms were determined by the Schooler and Kane criteria.[31] The US-SCAP, which was designed in 1996, did not measure adverse events that are of current interest, such as weight gain, diabetes, and hyperlipidemia.

Information about psychiatric hospitalization (admission and discharge dates) and use of psychotropic medications was abstracted from patients' medical records. Patients were queried about use of medications and other psychiatric resources outside those of their regular treatment site, and systematic efforts were made to abstract offsite medical records.

Statistical Analysis

Comparisons between adherent and nonadherent patients concerning sociodemographic and clinical characteristics at enrollment were made using χ^2 tests for categorical variables and t tests for continuous variables. Pearson product-moment correlations were used to calculate the relationships between adherence status (adherent or nonadherent) during the first year following enrollment in the study and each of the 39 risk factors of nonadherence at enrollment. Risk factors with significant correlation coefficients ($p < .05$) were entered into a stepwise logistic model to help identify the best single risk factor and the best set of risk factors of nonadherence. To assess the robustness of the findings, we conducted a sensitivity analysis in which we repeated the stepwise logistic model using risk factors with correlation coefficients with $p < .001$ or better.

The ability of the "single best risk factor" to accurately predict future adherence was also calculated. This was summarized by the overall percentage agreement and the proportion of times the risk factor accurately predicted future adherence, as well as the positive predictive value and negative predictive value.[32] Positive predictive value is the proportion of patients who were adherent in the 1-year follow-up period among those classified at enrollment as adherent based on the risk factor. Negative predictive value is the proportion of patients who were nonadherent in the 1-year follow-up period among those classified at enrollment as nonadherent based on the risk factor. All statistical tests were 2-tailed, and significance was set at a .05 alpha level.

RESULTS

Patient Characteristics

This study included 1579 of 2327 enrolled patients. Excluded were patients treated with antipsychotics in depot formulation (397/2327, 17.06%), patients with incomplete medication information (278/2327, 11.95%), and patients who did not respond to the medication adherence item on the SCAP-HQ (73/2327, 3.14%) during the first year of the study. The sample comprised the majority of US-SCAP patients who completed the first year of the study (1579/1817, 86.90%). Patients were primarily outpatients (95.12%) in their early forties, mostly single, white males with a high school education or less. At enrollment, these patients were treated with at least 1 oral antipsychotic,

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Table 1. Measures of Risk Factors for Medication Nonadherence

Characteristic	Measure
Patient-related factors	
Sociodemographic factors	
Age	Age at enrollment per screening interview
Gender	Male/female per screening interview
Ethnicity	White or nonwhite per screening interview
Marital status	Single or nonsingle at enrollment per screening interview
Education	High school education or less vs more than high school education at enrollment per screening interview
Symptom type and severity	
Depressive symptoms	Mean scale score on the MADRS at enrollment
Positive symptoms	Mean positive factor scale score[26] on the PANSS at enrollment
Negative symptoms	Mean negative factor scale score[26] on the PANSS at enrollment
Thought disorganization	Mean thought disorganization factor scale score[26] on the PANSS at enrollment
Hostility/excitement	Mean hostility/excitement factor scale score[26] on the PANSS at enrollment
Depression/anxiety	Mean depression/anxiety factor scale score[26] on the PANSS at enrollment
Substance use	
Alcohol use	Use of alcohol in the 4 weeks prior to enrollment (yes/no) per SCAP-HQ
Illicit drug use	Use of illicit drugs in the 4 weeks prior to enrollment (yes/no) per SCAP-HQ
Threat to safety of self or others	
Violent behaviors	Strike/injure another or threatened to strike/injure another in the 4 weeks prior to enrollment = score of 1, both items endorsed = 2, none endorsed = 0, per SCAP-HQ
Arrested/jailed	Arrested for crimes or spent a night in jail in the 6 months prior to enrollment = score of 1, both items endorsed = 2, none endorsed = 0, per SCAP-HQ
Victimized	A victim of any crime in the 4 weeks prior to enrollment (yes/no) per SCAP-HQ
Suicidal thinking	Thoughts of killing oneself in the 4 weeks prior to enrollment (yes/no) per SCAP-HQ
Other illness-related factors	
Prior medication adherence	Patient-reported medication adherence in the 4 weeks prior to enrollment on the SCAP-HQ (never missed medication or missed only a couple of times), or MPR > 80% in the 6 months prior to enrollment, calculation based on prescribed medications in patient's medical record
Age at illness onset	Age at illness onset per screening interview
Illness duration	Number of years elapsed between age at enrollment and age at illness onset, per screening interview
Level of functioning	Score on the GAF at enrollment
Insight	Score on the PANSS insight item (G12) at enrollment
Schizoaffective disorder	Diagnosis of schizoaffective disorder in patient's medical record (yes/no)
Prior psychiatric hospitalization	Any psychiatric hospitalization in the 6 months prior to enrollment (yes/no), per patient's medical record
Social activity	Mean score on the social activity scale for the 4 weeks prior to enrollment (3 items scored from 1 = at least once a day to 5 = none at all), per SCAP-HQ
Environment-related factors	
Need for supervision	
Supervised housing	Having supervised housing arrangement on the day of enrollment (eg, boarding homes, halfway houses, yes/no) per SCAP-HQ
Medication oversight	Receiving assistance with medication intake in the 4 weeks prior to enrollment (yes/no), per SCAP-HQ
Treatment-related factors	
Medication-related adverse events	
Abnormal involuntary movements	Mean item score on the AIMS at enrollment
Tardive dyskinesia	Meeting Schooler and Kane criteria for tardive dyskinesia at enrollment (yes/no), per AIMS (at least 1 item ≥ 3, or 2 items ≥ 2).
Extrapyramidal symptoms	Mean item score on the SAS at enrollment
Subjective adverse effects	Mean item score on the subjective medication side effect scale (5 items rated from 1 = not at all to 5 = extreme), per SCAP-HQ. Items assessed subjective reports of medications' (a) making one's thoughts clearer, (b) making one feel tired and sluggish, (c) interfering with normal thinking, (d) making one fidgety or restless, and (e) interfering with normal sexual functioning.
Subjective medication-related cognitive impairment	Mean score on the patient-reported medication-related cognitive impairment items on the SCAP-HQ (2 items [medication interference with normal thinking, and medication make thoughts clearer] rated from 1 = not at all to 5 = extreme)
Prior medication use	
Antiparkinsonian agents	Use of any antiparkinsonian agent (yes/no) in the 6 months prior to enrollment, per patient's medical record
Antidepressants	Use of any antidepressant (yes/no) in the 6 months prior to enrollment, per patient's medical record
Antianxiety agents	Use of any antianxiety agent (yes/no) in the 6 months prior to enrollment, per patient's medical record
Mood stabilizers	Use of any mood stabilizer (yes/no) in the 6 months prior to enrollment, per patient's medical record
Typical depot antipsychotics	Use of any typical depot antipsychotic (yes/no) in the 6 months prior to enrollment, per patient's medical record
Antipsychotic polypharmacy	Concurrent use of at least any 2 antipsychotics (yes/no) in the 6 months prior to enrollment, per patient's medical record
Sleep agents	Use of any sleep agents (yes/no) in the 6 months prior to enrollment, per patient's medical record

Abbreviations: AIMS = Abnormal Involuntary Movement Scale, GAF = Global Assessment of Functioning, MADRS = Montgomery-Asberg Depression Rating Scale, MPR = medication possession ratio, PANSS = Positive and Negative Syndrome Scale, SAS = Simpson-Angus Scale, SCAP-HQ = Schizophrenia Care and Assessment Program Health Questionnaire.

including typical antipsychotics (755, 47.82%) and atypical antipsychotics (1042, 66.00%), such as olanzapine (31.86%), risperidone (24.38%), or quetiapine (5.64%).

Most of the 1579 patients (81.2%) were deemed adherent, and 18.8% (N = 296) were considered nonadherent during the first year following enrollment. About half of the nonadherent were identified based on their self-report (135/296, or 45.61%), about half were identified based on MPR ≤ 80% (135/296, or 45.61%), and 8.78% were identified based on both self-reported nonadherence and MPR ≤ 80%. The adherent and nonadherent patient groups did not significantly differ at enrollment on several clinical and sociodemographic characteristics (Table 2), although the nonadherent patients were significantly more likely to use alcohol or illicit drugs, to be hospitalized for psychiatric purposes in the prior 6 months, to be of safety concern in the community (violent, arrested, victimized), to have poorer levels of functioning, and to be nonadherent in the 6 months prior to enrollment. They were also more likely to be depressed, to be treated with antidepressants in the prior 6 months, and to be more hostile, impulsive, and uncooperative, as measured using the hostility factor of the PANSS.

Nonadherent patients were less likely to be single, to be white, to be treated with antipsychotic polypharmacy or mood stabilizers, and to have medication oversight. Nonadherent patients also had significantly less extrapyramidal symptoms (EPS) as rated by clinicians (SAS) and reported by patients (SCAP-HQ, SAS) and had significantly lower utilization rates of antiparkinsonian agents, which are typically used to ameliorate EPS. The nonadherent participants reported, however, significantly greater medication-related cognitive impairment.

Risk Factors of Nonadherence

The single best predictor of future adherence was patients' prior adherence. Adherent patients in the 6 months prior to enrollment were 4.14 times more likely to be medication adherent in the first year following enrollment in the study (odds ratio [OR] = 4.14, 95% confidence interval [CI] = 3.09 to 5.55, p < .001) (Figure 1). Prior adherence with antipsychotics accurately classified 78.5% of the patients in the year after enrollment. This accuracy level was driven primarily by a high positive predictive value (86.6%), the probability that a previously adherent patient will be adherent in the following year, and a moderate negative predictive value (43.9%), the probability that a previously nonadherent patient will be nonadherent in the following year. The positive predictive value was almost twice as high as the negative predictive value.

To identify the best set of risk factors of nonadherence, the 21 risk factors that significantly correlated with adherence (p < .05) (Table 3) were entered in the stepwise regression model. Of these, 5 were identified as the best predictors, ordered by strength of association: prior nonadherence in the 6 months prior to enrollment (OR = 4.1, 95% CI = 3.1 to 5.6, p < .001), illicit drug use in the 4 weeks prior to enrollment (OR = 1.8, 95% CI = 1.1 to 3.0, p = .025), alcohol use in the 4 weeks prior to enrollment (OR = 1.6, 95% CI = 1.1 to 2.2, p = .008), treatment with antidepressants in the 6 months prior to enrollment (OR = 1.4, 95% CI = 1.1 to 1.9, p = .020), and greater patient-reported, medication-related cognitive impairment (OR = 1.3, 95% CI = 1.1 to 1.5, p < .001). Figure 1 presents the odds ratios for the best predictors of adherence (inverse of nonadherence).

To assess robustness of the findings, analyses were repeated using risk factors that significantly correlated with adherence at p < .001 or better. This sensitivity analysis provided almost identical findings. The best predictors, ordered by strength of association, were prior nonadherence in the 6 months prior to enrollment (OR = 4.0, 95% CI = 3.0 to 5.4, p < .001); illicit drug use in the 4 weeks prior to enrollment (OR = 1.8, 95% CI = 1.1 to 2.9, p = .025); alcohol use in the 4 weeks prior to enrollment (OR = 1.5, 95% CI = 1.1 to 2.1, p = .015); greater patient-reported, medication-related cognitive impairment (OR = 1.3, 95% CI = 1.1 to 1.5, p < .001); and higher level of depressive symptoms, as measured by mean depression/anxiety factor scale scores[27] on the PANSS at enrollment (OR = 1.0, 95% CI = 1.0 to 1.0, p = .013).

Prior nonadherence was defined by 2 measures: the medication prescription records (MPR ≤ 80% in the 6 months prior to enrollment) and patient self-reported nonadherence (missing medications at least half of the time in the 4 weeks prior to enrollment). To assess which of these 2 measures contributed more to the prediction of future adherence, we repeated the stepwise regression model by entering 22 statistically significant variables (replacing the single categorical measure of "prior adherence" with the 2 individual adherence measures). Results showed that the 2 measures of prior nonadherence are comparable predictors of nonadherence. Patients who reported being nonadherent in the 4 weeks prior to enrollment were 3.1 times more likely to be nonadherent in the first year following enrollment (OR = 3.1, 95% CI = 2.0 to 4.8, p < .001). Patients who had an MPR ≤ 80% during the 6 months prior to enrollment were 3.1 times more likely to be nonadherent in the first year following enrollment (OR = 3.1, 95% CI = 2.2 to 4.3, p < .001). In comparison, the measure that incorporated both medical record information and patients' self-reported adherence offered better prediction (OR = 4.1, 95% CI = 3.0 to 5.6, p < .001).

DISCUSSION

This prospective study of the factors associated with greatest risk for nonadherence with antipsychotic med-

Table 2. Characteristics of Nonadherent and Adherent Patients at Enrollment[a]

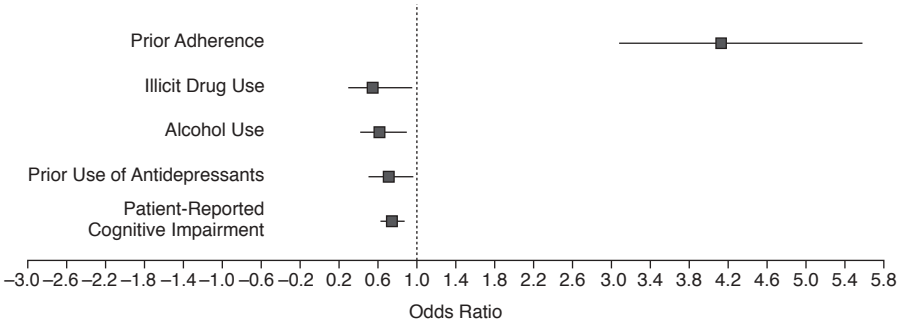
Characteristic	Nonadherent (N = 296)	Adherent (N = 1283)	N	p Value
Patient-related factors				
Sociodemographic factors				
Age, mean (SD), y	41.57 (11.21)	42.38 (11.30)	1579	.264
Gender, male, %	61.82	59.47	1579	.456
Ethnicity, white, %	52.56	59.03	1572	.043
Single marital status, %	53.22	62.39	1574	.004
High school education or less, %	64.73	68.81	1565	.177
Symptom type and severity				
Depressive symptoms, MADRS score, mean (SD)	16.37 (10.67)	14.06 (10.20)	1524	< .001
Positive symptoms, PANSS, mean (SD)	18.03 (7.04)	17.41 (6.57)	1521	.156
Negative symptoms, PANSS, mean (SD)	16.92 (6.78)	17.14 (7.38)	1551	.640
Thought disorganization, PANSS, mean (SD)	17.11 (5.89)	17.02 (5.47)	1521	.804
Hostility/excitement, PANSS, mean (SD)	6.63 (2.91)	6.15 (2.64)	1552	.007
Depression/anxiety, PANSS, mean (SD)	13.29 (4.85)	11.88 (4.78)	1548	< .001
Substance use				
Alcohol use, %	29.15	19.78	1569	< .001
Illicit drug use, %	12.54	4.78	1572	< .001
Threat to safety of self or others				
Violent behaviors, %	10.51	5.79	1573	.005
Arrested/jailed, %	9.83	4.31	1570	< .001
Victimized, %	17.29	9.24	1572	< .001
Suicidal thinking, %	26.55	24.11	1559	.384
Other illness-related factors				
Prior medication adherence, %	52.56	84.51	1565	< .001
Age at illness onset, mean (SD), y	19.25 (9.02)	20.30 (8.98)	1452	.084
Illness duration, mean (SD), y	22.1 (12.7)	21.9 (11.7)	1452	.776
Level of functioning, GAF, mean (SD)	40.53 (13.46)	43.18 (13.29)	1564	.002
Insight (PANSS item), mean (SD)	2.93 (1.59)	3.04 (1.59)	1552	.325
Schizoaffective disorder diagnosis, %	38.26	35.92	1486	.475
Prior[a] psychiatric hospitalization, %	24.66	18.16	1579	.011
Social activity, mean (SD)	2.77 (1.09)	2.67 (1.04)	1571	.135
Environment-related factors				
Need for supervision				
Supervised housing, %	27.99	33.39	1563	.075
Medication oversight, %	19.35	25.18	1550	.040
Treatment-related factors				
Medication-related adverse events				
Abnormal involuntary movements, AIMS mean (SD) item score	0.48 (0.58)	0.45 (0.57)	1557	.393
Tardive dyskinesia symptoms, %	32.38	28.64	1524	.213
Extrapyramidal symptoms, SAS mean (SD) item score	0.42 (0.42)	0.49 (0.48)	1556	.016
Subjective adverse effects, mean (SD) item score	2.19 (0.74)	2.00 (0.70)	1441	< .001
Subjective medication-related cognitive impairment, mean (SD) item score	2.40 (0.97)	2.16 (0.91)	1517	< .001
Prior[a] medication use				
Antiparkinsonian agents, %	34.46	42.24	1579	.014
Antidepressants, %	49.32	40.84	1579	.008
Antianxiety agents, %	11.49	11.69	1579	.921
Mood stabilizers, %	26.69	33.59	1579	.022
Typical depot antipsychotics, %	5.07	2.96	1579	.070
Antipsychotic polypharmacy, %	12.50	17.85	1579	.027
Sleep agents, %	1.69	1.40	1579	.711

[a]During the 6 months prior to enrollment.
Abbreviations: AIMS = Abnormal Involuntary Movement Scale, GAF = Global Assessment of Functioning, MADRS = Montgomery-Asberg Depression Rating Scale, PANSS = Positive and Negative Syndrome Scale, SAS = Simpson-Angus Scale.

ication identified a small and well-defined set of predictors. Among 39 studied risk factors belonging to patient-, environment-, and treatment-related domains, the best predictors of medication nonadherence were prior nonadherence, recent illicit drug use, recent alcohol use, prior treatment with antidepressants, and greater patient-reported, medication-related cognitive impairment. Among these 5 predictors, prior adherence with antipsychotics was the single best predictor of future adherence. This is not surprising, because past behavior is often the best predictor of future behavior. This well-documented phenomenon is found across different areas of investigation, including the prediction of violent[33] and suicidal[34] behaviors in patients with schizophrenia.

Prior adherence has rarely been studied in previous research of medication adherence in schizophrenia. How-

Figure 1. Odds Ratios and 95% Confidence Intervals for the Best Predictors of Future 1-Year Adherence With Antipsychotics



ever, the few studies that assessed this risk factor[9,12,35,36] consistently demonstrated its significant association with medication nonadherence, and one of these studies[9] reported results that were identical to this study's (OR = 4.1, 95% CI = 1.3 to 12.2).

We also found that prior adherence status has a relatively high level of accuracy (79%) in predicting future adherence or nonadherence with antipsychotic medication. This high level of accuracy was driven primarily by high positive predictive value (86.6%), the probability that a previously adherent patient will be adherent in the following year. To the best of our knowledge, this study is the first to examine the predictive utility of risk factors for nonadherence in schizophrenia. Understanding the predictive utility can help clinicians decide which patients would most benefit from medication adherence interventions, including a switch to antipsychotics in long-acting formulations.

Previous studies have shown that actuarial predictions are often more accurate than clinical predictions[37] and that clinicians tend to underestimate the magnitude of nonadherence among their patients.[38] Thus, although medication nonadherence is a complex phenomenon driven by multiple factors,[6,7] using the often accessible medical record information on patients' prescriptions for antipsychotics in the prior 6 months and patient-reported adherence in the past month may help enhance clinicians' accuracy in identifying patients at risk for future nonadherence. Interestingly, the 2 measures of prior adherence—MPR per medication prescription records and patients' self-reports—were found to be comparable and reasonable predictors of adherence, although their combined use offered a greater predictive ability. These findings have important implications for clinical practice, suggesting that in the absence of access to patients' prescription records, patients' self-reports offer valuable information, although concurrent use of both adherence measures is preferable.

The clinical utility of prior adherence as a single marker of future adherence will require further study and should be evaluated with caution, because prior adherence status in this study correctly identified most of the adherent but only about half of the nonadherent patients. The relatively high accuracy level of this predictor was driven by a high base rate of adherence in our sample (81%), which may have overestimated patients' true adherence rate. The poorer accuracy in predicting adherence for previously nonadherent patients may also stem from their greater tendency to exhibit unpredictable behaviors. In this, as in another study,[9] nonadherent participants were found to be more impulsive and unpredictable, prone to substance use, violent behaviors, and arrests. Because past behavior is the best predictor of future behavior, one would expect that future behaviors of these patients, including medication adherence, would be less predictable. Furthermore, the relatively low rate of nonadherence among study participants may also stem from providers' recognition of nonadherence in their patients and initiation of interventions to improve nonadherence in high-risk patients. This study did not, however, collect information on medication intervention efforts.

Although the rate of nonadherence found in this study (19%) was much lower than the 40% to 50% nonadherence rate reported in past research,[3,4,15,19] this rate appears to be consistent with 6 studies[5,7–9,12,39] in which nonadherence rates ranged between 15% and 20%. Interestingly, in a recent large (N = 2960), multicenter, prospective, observational study of schizophrenia patients in Germany,[39] 17.1% of the participants were deemed nonadherent per providers' ratings, and 11.7% were deemed nonadherent per self-report measure. Although lower rates of nonadherence may reflect a tendency to enroll more adherent individuals in prospective longitudinal studies, it is notable that a similarly low rate of nonadherence (15.5%) was found in a large retrospective study (N = 4325) using

Table 3. Correlation Coefficients Between Risk Factors and Medication Adherence in the Following Year

Risk Factor	r
Patient-related factors	
Sociodemographic factors	
Age	0.028
Gender, male	–0.029
Ethnicity, white	0.051*
Marital status, single	0.073**
Education level	0.034
Symptom type and severity	
Depressive symptoms (MADRS)	–0.088**
PANSS	
Positive symptoms	–0.036
Negative symptoms	0.012
Disorganized thoughts	–0.006
Hostility/excitement	–0.069**
Anxiety/depression	–0.114***
Substance use	
Alcohol use in prior 4 weeks	–0.089***
Illicit drug use in prior 4 weeks	–0.125***
Threat to safety of self or others	
Violent	0.057*
Arrested/jailed	–0.086***
Victimized	–0.101***
Suicidal thinking	–0.022
Other illness-related factors	
Adherence in prior 6 months	0.306***
Age at illness onset	0.045
Illness duration	–0.010
Level of functioning (GAF)	0.077**
Insight (PANSS item)	–0.025
Schizoaffective disorder diagnosis	–0.019
Psychiatric hospitalization in prior 6 months	–0.064*
Social activity	–0.038
Environment-related factors	
Supervised housing arrangements	0.045
Medication oversight	–0.052*
Treatment-related factors	
Medication-related adverse events	
Abnormal involuntary movements (AIMS)	–0.022
Tardive dyskinesia	–0.032
Extrapyramidal symptoms (SAS)	0.057*
Subjective medication adverse effects	–0.104***
Patient-reported medication-related cognitive impairment	–0.100***
Medication use in prior 6 months	
Antiparkinsonian agents	0.062*
Antidepressants	–0.067**
Antianxiety agents	0.0002
Mood stabilizers	0.058*
Depot typical antipsychotics	–0.045
Antipsychotic polypharmacy	0.056*
Sleep agents	–0.009

*p < .05.
**p < .01.
***p < .001.
Abbreviations: AIMS = Abnormal Involuntary Movement Scale, GAF = Global Assessment of Functioning, MADRS = Montgomery-Asberg Depression Rating Scale, PANSS = Positive and Negative Syndrome Scale, SAS = Simpson-Angus Scale.

MPR to define nonadherence among schizophrenia patients with Medicaid health coverage. Furthermore, a review of 86 studies of adherence among psychotic patients treated in community settings[40] reported an average nonadherence rate of 25.8% and indicated that a larger study sample size was associated with lower rates of nonadherence. Although the reasons for this phenomenon are unclear, it may be one additional reason for the low adherence rate found in the present large study.

We also found substance use to be a significant predictor of future nonadherence, a finding consistent with most prior research.[8–11] Compared with this well-studied predictor, the other 2 significant risk factors in our study were not previously investigated. Prior treatment with antidepressants, an unexpected predictor, is most likely related to depressive symptoms, a risk factor previously found to be associated with poorer adherence.[41] Fifth among the best predictors identified was patient-reported, medication-related cognitive impairment. Cognitive deficits in schizophrenia patients are known to be associated with poor adherence,[42] but the relationship between patients' subjective perceptions of cognitive impairment and medication adherence has not been studied before. However, patient-reported, medication-related cognitive impairment could be considered a negative subjective response to medication, a previously identified major predictor of nonadherence.[2,35]

Several limitations of this analysis must be considered. First is the omission of several important risk factors of nonadherence, particularly therapeutic alliance, patients' attitudes toward the illness and the medication, and level of cognitive deficits. These risk factors were not assessed in US-SCAP but were previously identified as important factors that influence adherence with antipsychotic medications.[2,41] In addition, information concerning other potential risk factors for nonadherence, like treatment-emergent weight gain, was not collected in US-SCAP and thus could not be evaluated. A second limitation is the assessment of several risk factors with less than optimal measures, particularly insight, which was assessed with only 1 PANSS item rather than with a comprehensive and valid measure. The substance use measures were also imprecise, as they identified participants with self-reported alcohol or illicit drug use in the past 4 weeks (yes/no) rather than the amount and frequency of the substance use behaviors.

In addition, the MPR in this study was based on prescriptions in patients' medical records rather than the customary pharmacy-fill data. Although previous research in this patient population has demonstrated that pharmacy-fill claims data nearly always had a prescription for psychotropic medication documented either in the medical record or in a survey filled out by the case manager,[43] there are no studies assessing the quantitative correspondence between MPR based on medical record prescription notations and pharmacy fill data. It is, however, notable that these 2 types of MPRs have previously provided highly similar findings when assessing risk of hospitalization among nonadherent versus adherent schizophrenia patients. Both studies—one using VA pharmacy fill data[4] and the other using US-SCAP medical record prescription data[22]—have found the risk of psychiatric hospitalization

to be about twice as high among nonadherent as among adherent patients. Such consistent findings may help increase confidence in the potential correspondence between the 2 types of MPRs.

Among the strengths of this study is its prospective, naturalistic design and use of a large well-defined and diverse sample of schizophrenia patients, suggesting these findings are applicable to patients treated in large systems of care across the United States. Another strength is the use of comprehensive assessments with multiple valid and reliable instruments that enabled studying the link between numerous potential risk factors and future adherence. The comprehensive assessments helped improve on previous research that lacked in valid clinical rating scales, particularly for assessment of medication adverse events.[2] A third strength is the rigor with which medication information was collected in US-SCAP. In addition to abstraction of prescription information from medical records, this study collected information about medications prescribed during patients' psychiatric hospitalizations and about medications dispensed by sources outside of the patients' regular treatment site, when applicable. This methodological feature, which is absent in pharmacy claims databases, is particularly important because it increases confidence in the completeness of the medication data and in its derived adherence measure, the MPR. Lastly, this study measured adherence using information from 2 independent sources: the patients' medical records and the patients' self-reports, thereby minimizing pitfalls associated with reliance on a single and potentially less reliable source of information, such as patients' self-reports.[40]

Although medication adherence is driven by multiple, complex, and often overlapping risk factors, this study identified a small and well-defined set of strong predictors. More importantly, this study singled out a simple and relatively accurate predictor that may improve the accuracy of clinicians' ability to identify nonadherent patients. Although the clinical utility of past adherence as a predictor of future adherence will require further study, the fact that past behavior is the best predictor of future behavior bodes well for the use of this risk factor as predictor of adherence in the long-term medication management of patients with schizophrenia.

Drug names: olanzapine (Zyprexa), quetiapine (Seroquel), risperidone (Risperdal).

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