

Medication Adherence and Long-Term Functional Outcomes in the Treatment of Schizophrenia in Usual Care

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Background: Relatively little is known about the relationships between medication adherence and long-term functional outcomes in the treatment of schizophrenia. To extend previous research, we prospectively examined the relationships between adherence with any antipsychotic medication and functional outcomes among schizophrenia patients treated over a 3-year period, assessed the stability of adherence over time, and examined whether adherence in the first year predicts changes in functional outcomes over the following 2 years.

Method: Analyses included 1906 participants with DSM-IV diagnoses of schizophrenia or schizoaffective or schizophreniform disorder in a multi-site, 3-year, prospective, naturalistic study conducted in the United States between July 1997 and September 2003. Outcome measures were assessed at 6-month intervals using systematic medical record abstraction and structured interview of patients. Adherence with antipsychotic regimen was assessed using patient-reported adherence and the medication possession ratio (percent days with prescription for any antipsychotic), dichotomized into adherence and non-adherence. Analyses employed generalized estimating equations and mixed models with repeated measures.

Results: Nonadherence was associated with poorer functional outcomes, including greater risks of psychiatric hospitalizations, use of emergency psychiatric services, arrests, violence, victimizations, poorer mental functioning, poorer life satisfaction, greater substance use, and more alcohol-related problems (all $p < .001$). Adherence was relatively stable, with 77.3% of patients maintaining the same adherence status from the first year to the second year. Nonadherence in the first year predicted significantly poorer outcomes in the following 2 years.

Conclusions: Findings highlight the importance of adherence with antipsychotic medication in the long-term treatment of schizophrenia and its potential beneficial impact on the mental health and criminal justice delivery systems.

(*J Clin Psychiatry* 2006;67:453-460)

Received March 2, 2005; accepted July 24, 2005. From Eli Lilly and Co., Indianapolis, Ind. (Drs. Ascher-Svanum, Faries, Zhu, and Ernst) and the Department of Psychiatry and Behavioral Sciences, Duke University Medical Center, Durham, N.C. (Drs. Swartz and Swanson).

Eli Lilly and Co. sponsored this study. The U.S.-SCAP study was supported by Eli Lilly and Co. and administered by the Medstat Group.

Drs. Ascher-Svanum, Faries, Zhu, and Ernst are employees of Eli Lilly and Co. Dr. Swartz has served as a consultant for Eli Lilly and Co. Dr. Swanson has received grant/research support from Eli Lilly and Co.

Acknowledgments appear at the end of this article.

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Nonadherence to prescribed medication regimens has long been recognized as a worldwide problem that detracts from health system effectiveness.¹ Nonadherence is of particular concern in the treatment of schizophrenia because it is a major contributor to relapse and hospitalization,²⁻⁴ the costliest treatment component in human and economic terms.⁴ While continuous antipsychotic medication is recognized as a core component in the treatment of schizophrenia,⁵ only about half of patients are adherent with their antipsychotic medication regimens.⁶⁻⁸

Although the link between medication nonadherence and psychiatric hospitalization is well established in the field of schizophrenia, research investigating the associations between nonadherence and other clinical and functional outcomes is sparse. With the exception of substance abuse, which has been consistently linked to nonadherence,^{9,10} only a few studies have addressed the relationships between adherence and other outcomes such as risk of arrests, employment, housing, and quality of life in the treatment of schizophrenia.^{11,12} Notably, most previous studies, with only a few exceptions,¹⁰⁻¹² investigated the link between adherence and treatment outcomes using short or intermediate follow-up periods, mostly 1 year or less. Because schizophrenia is a chronic disorder, a longer follow-up period is necessary to assess the relationships between adherence and outcomes and to examine the stability of patients' medication adherence over time.

Understanding how adherence can affect sustained improvements in patients' long-term functional outcomes is

important for design and evaluation of treatment strategies. However, perhaps because improved functional status may lag behind improvements in psychotic or cognitive symptomatology,¹³ there is currently no information about whether current adherence status can predict distal functional outcomes in the treatment of schizophrenia.

Expanding on previous research, we used data from a large, multi-site, 3-year, prospective, naturalistic study of patients with schizophrenia spectrum disorders to assess adherence with antipsychotic regimen derived from patient-reported adherence and prescription information in patients' medical records. This study aimed to (1) assess the relationships between medication adherence and various functional outcomes over a 3-year period, (2) examine stability of patients' medication adherence over time, and (3) investigate whether adherence status during the first year predicts sustained changes in patients' functional outcomes during the following 2 years. This study used a longitudinal perspective and focused on outcomes that impact the mental health services and criminal justice systems.

METHOD

Data Source

We used data from the U.S. Schizophrenia Care and Assessment Program (U.S.-SCAP), a large, naturalistic, prospective, multi-site study in which patients treated for schizophrenia spectrum disorders were periodically assessed and followed for 3 years. The U.S.-SCAP was conducted between July 1997 and September 2003, and its goal was to understand the treatment of persons diagnosed with schizophrenia in usual care settings. Patients were recruited from diverse geographical areas including the Northeast, Southwest, Mid-Atlantic, and West. The 6 participating regional sites represented large systems of care, including community mental health centers, university health care systems, community and state hospitals, and the Department of Veterans Affairs Health Services. Institutional Review Board approval was obtained, and informed consent was received from all patients. Further details about the U.S.-SCAP are available elsewhere.^{11,12,14}

Sample

Since the study was designed as an observational study of the treatment of persons diagnosed with schizophrenia under usual care conditions, all adults aged 18 years or older with DSM-IV diagnoses of schizophrenia or schizoaffective or schizophreniform disorder were eligible for the study. Clinical chart diagnoses assigned in the past year were accepted *prima facie* and not verified by additional research diagnostic assessments upon enrollment. Participants were excluded if they were unable to provide informed consent or had participated in a clinical drug trial within 30 days prior to enrollment.

In order to minimize selection bias, outpatients were randomly selected from site medical information rosters of active clients; inpatients were selected by screening sequential admissions. Approximately 400 patients enrolled at each of the 6 study sites. Of 3332 patients who met inclusion criteria, 2327 (69.8%) enrolled, 765 (23.0%) refused, and 240 (7.2%) were not enrolled due to other reasons. Enrollment was not contingent upon being treated with a specific antipsychotic or with any drug and was independent of concurrent psychiatric or medical conditions, use of concomitant medications, or substance use. Patients could stay on medications received prior to enrollment, and decisions about medication changes, if any, reflected those made by the physicians and their patients.

The current analysis includes patients who had baseline measurements and at least 1 postbaseline measurement on any of the study's outcome measures during year 2 or year 3 of the study; the patients meeting these inclusion criteria numbered 1906 (82%).

Measures

Medication adherence. Adherence with antipsychotic regimens was based on prescription information in patients' medical records in combination with patient-reported adherence level. Trained and annually certified examiners administered the study measures and extracted antipsychotic prescription information from patients' medical records using a medical record abstraction form developed for the study. Assessments and medical record abstractions were conducted at enrollment and at 6-month intervals thereafter. Prescription data were used to calculate for each patient a medication possession ratio (MPR), defined as the cumulative number of days the patient had been prescribed any antipsychotic drug, divided by the number of days in the assessment period, and multiplied by 100. The assessment period was the 6-month interval for the first study objective and 1 year for the other 2 study objectives. The MPR is a proxy measure of medication adherence commonly used to quantify medication use in claims datasets¹⁵⁻¹⁷ and was found to be reliably associated with risk of psychiatric hospitalization.^{4,16,17} The MPR ranges from 0% to 100%, with higher values indicating greater time with any prescribed antipsychotic medication. Prior adaptations of the MPR to the study of adherence with antipsychotic regimens used 80%⁴ and 85% cutoffs¹⁶ to divide patients into adherent and nonadherent groups.

The patient-reported measure of adherence was derived from the SCAP Health Questionnaire (SCAP-HQ),¹⁸ which assessed a number of domains, including how regularly the patients reported taking their medications in the past 4 weeks: (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 with an MPR $\geq 85\%$ who also chose alternative 1 or 2 on the SCAP-HQ adherence item were considered "adherent," while all other patients were classified as "nonadherent."

Outcome measures. Patients' medical records provided information about health care utilization such as prescribed psychiatric medications and psychiatric hospitalizations, whereas information about functional and quality-of-life outcomes was derived from the SCAP-HQ. This 102-item structured interview was developed for the U.S.-SCAP study and was administered at enrollment and at 6-month intervals thereafter. Items were drawn from existing measures such as the Lehman Quality of Life Interview,¹⁹ the Arkansas Schizophrenia Outcomes Module,²⁰ the Medical Outcome Study Short Form-12 (SF-12),²¹ and the CAGE, a screening tool for assessment of alcohol-related problems.²² The psychometric properties of the SCAP-HQ were found to be acceptable for application to large-scale studies in routine care based on a study of its internal consistency, convergent validity, test-retest reliability, and responsiveness to change.¹⁸

The SCAP-HQ and patients' medical records were used to assess the following outcome measures: (1) Health care utilization: psychiatric hospitalization (yes/no), number of hospitalization days for hospitalized patients during the past 6 months, and emergency psychiatric visits (yes/no) in the past 4 weeks. (2) Arrests, violence, and victimization: arrested or jailed (yes/no) during the past 6 months, violent toward others (yes/no) in the past 4 weeks, and victim of crime in the past 4 weeks (yes/no). (3) Other functional and quality-of-life measures: use of alcohol or illicit drugs in the past 4 weeks (yes/no), severity of alcohol-related problems per CAGE²² for patients reporting any alcohol use, paid employment in the past 4 weeks (yes/no), supervised housing arrangement on day of the assessment (yes/no) (e.g., boarding homes, halfway houses, hospitals, nursing homes), mental health and physical health functioning per SF-12,²¹ and level of satisfaction with social life, with fulfillment of basic needs, and with life in general in the past 4 weeks.

Statistical Analysis

Comparisons of baseline characteristics between the adherent and nonadherent groups included χ^2 tests for categorical variables and t tests for continuous variables. To calculate the association between adherence status and each outcome variable over the 3-year period, we used mixed models with repeated-measures regression analyses (MMRM)²³ for continuous outcome measures (hospitalization duration, mental and physical functioning, alcohol-related problems, and satisfaction with basic needs, with social life, and with life in general) and repeated-measures general linear models (generalized es-

timating equations, GEE)²⁴ for binary variables (psychiatric hospitalization, use of emergency psychiatric services, arrests, victims of crime, substance use, violent behavior, unemployment, and supervised housing). This first set of analyses assessed the relationship between adherence and outcomes at similar points of time (i.e., adherence during the first year and outcomes at 12 months, adherence during the second year and outcomes at 24 months, and adherence during the third year and outcomes at 36 months). The scores from the 7 assessments (patients' research visits over the 3-year study) were considered the dependent variables. The models included age, sex, race, assessment, and adherence classification (adherence or nonadherence) as independent variables.

To examine stability of adherence over time, we calculated concordance levels between adherence status in year 1 and year 2, between year 1 and year 3, and between year 1 and adherence in both years 2 and 3. Stability was calculated for the adherent and the nonadherent groups to provide an overall concordance level for patients who maintained the same adherence status from year 1 to the following 2 years. We also calculated Pearson product-moment correlations to assess the relationships between the continuous MPR measures for years 1, 2, and 3 of the study.

To assess the relationships between adherence status during the first year of the study and changes in patients' outcomes during the following 2 years, we again used an MMRM for continuous outcome measures and repeated-measures GEE for binary variables. These analytical methods address the correlation of repeated measurements on the same individual over time and handle differing numbers of repeated measures per individual. For each outcome measure, the outcome measure scores during years 2 and 3 were considered the dependent variables. Independent variables included the dichotomized adherence status, age, sex, race, assessment, and the baseline score of the dependent (outcome) variable. Although the statistical model does not force a linear or quadratic pattern over time and does not force the predicted values to be the same at years 2 and 3, it does force the difference between adherence and nonadherence groups to be the same during years 2 and 3. To assess the impact of this assumption, we performed another secondary repeated-measures model, adding a term for adherence status by assessment interaction. This model removes the assumption of equal effects over time.

As a further robustness check, analyses were repeated using MPR classification based on cutoff values of $\geq 80\%$ and $\geq 70\%$. Analyses were also repeated using MPR as a continuous rather than a dichotomous variable. Due to planned multiple comparisons, a step-down method was used to maintain an overall .05 significance level.²⁵ Unadjusted p values $\leq .05$ were considered indicators of a possible trend.

RESULTS

Patient Characteristics

Of 1906 patients who met inclusion criteria, 1786 (93.7%) completed at least 2 years, 1625 (85.3%) completed at least 2.5 years, and 1348 (70.7%) completed 3 years of follow-up. At enrollment, almost all patients (94.7%) were treated with at least 1 antipsychotic medication, including oral typical (36.7%), oral atypical (58.1%), and depot typical antipsychotics (19.6%).

At enrollment (Table 1), the nonadherent patients, who comprised 19.7% of the sample, were younger and more likely to be of nonwhite origin; to have more severe symptomatology; to have been previously hospitalized for psychiatric treatment; to have used emergency psychiatric services; to be substance users; to have more severe alcohol-related problems; to have been arrested, victimized, and violent; to have poorer mental health functioning; and to be less satisfied with social life, with fulfillment of basic needs, and with life in general. Compared with the nonadherent group, the adherent patients were more likely to complete the 3-year follow-up period (72.2% vs. 64.6%, $p = .004$). The groups did not significantly differ on the other outcome variables at enrollment, including hospitalization days, a variable that required logarithmic transformation due to the skewness of the data.

Because the nonadherent group was smaller than expected, we examined the adherence status of 421 patients who were excluded from the sample because they dropped out of the study prior to completing 1 postenrollment assessment during year 2 or year 3 of the study. The excluded group was found to include 28.7% nonadherent patients, suggesting that early dropout of these patients may have decreased somewhat the proportion of nonadherent patients identified in this study.

Adherence and Outcomes Over 3 Years

A summary of the associations between adherence status and each outcome variable over the 3-year study is presented in Table 2 for continuous outcome measures and in Table 3 for binary outcome measures. Nonadherence was associated with significantly greater risks of psychiatric hospitalizations; with use of emergency psychiatric services; with being arrested, violent, or victimized; with substance use, alcohol-related problems, and poorer mental functioning; and with less satisfaction with social life, fulfillment of basic needs, and life in general (all $p < .001$). Adherence status was not significantly related to unemployment, hospitalization days, physical functioning, or supervised housing.

Stability of Adherence

Patients' adherence status was relatively stable over time, as most patients (77.3%) maintained the same adherence status in year 2 as they displayed in the first year of

Table 1. Characteristics at Enrollment Among Patients With Schizophrenia

Characteristic	Nonadherent (N = 376)	Adherent (N = 1530)	p
Age, mean (SD), y	40.2 (11.2)	42.2 (11.1)	.002
Sex, male, %	62.8	60.3	.385
Race, %			
White	40.4	51.2	< .001
Black	42.6	35.6	.012
Hispanic	4.0	4.7	.599
Other	12.9	8.6	.101
Marital status, single, %	88.8	91.2	.160
High school education or less, %	67.9	68.7	.771
Age at illness onset, mean (SD), y	19.4 (8.7)	20.4 (8.8)	.065
Schizoaffective disorder diagnosis, %	31.6	33.7	.455
PANSS total score, mean (SD)	71.6 (18.2)	69.4 (18.3)	.046
Psychiatric hospitalization, % ^a	28.1	21.0	.006
Days hospitalized (among hospitalized patients), mean log (SD)	2.35 (0.78)	2.73 (1.11)	.454
Emergency psychiatric services use, % ^b	12.3	8.1	.012
Arrested, % ^a	12.0	4.2	< .001
Violent, % ^b	11.2	5.4	< .001
Victim of crime, % ^b	17.5	9.0	< .001
Substance use, % ^b	33.9	24.6	< .001
Alcohol-related problems, mean (SD) ^b	1.39 (1.27)	0.96 (1.15)	.004
Unemployed, % ^b	81.1	77.4	.120
Supervised housing at enrollment, %	28.8	33.7	.069
Mental health functioning, mean (SD) ^b	38.8 (13.3)	41.8 (13.4)	< .001
Physical health functioning, mean (SD) ^b	46.4 (11.4)	46.1 (10.1)	.658
Satisfaction with basic needs, mean (SD) ^b	4.6 (1.2)	4.8 (1.1)	< .001
Satisfaction with social life, mean (SD) ^b	4.4 (1.3)	4.5 (1.2)	.024
Satisfaction with life in general, mean (SD) ^b	4.4 (1.6)	4.7 (1.5)	.005

^aIn the 6 months prior to enrollment.

^bIn the 4 weeks prior to enrollment.

Abbreviations: log = logarithmic data transformation,

PANSS = Positive and Negative Syndrome Scale.

the study. Of 1530 adherent patients in the first year, 81.4% were adherent in year 2, 69.1% were adherent in year 3, and 61.9% were adherent in both years 2 and 3. In comparison, the nonadherent group displayed slightly less stable adherence status: of the 376 nonadherent patients in the first year, 39.1% were adherent in year 2, 37.3% were adherent in year 3, and 23.9% were adherent in both years 2 and 3. Overall, the correlations between MPR in years 1 and 2 ($r = .59$, $p < .001$) and between years 2 and 3 ($r = .65$, $p < .001$) were moderate in size, with a lower correlation between years 1 and 3 ($r = .35$, $p < .001$).

Adherence in Year 1 and Distal Outcomes

Health care utilization. Adherence status in the first year was not associated with significant changes during

Table 2. Summary of the Associations Between Adherence Status and Continuous Outcome Measures: Longitudinal Assessment Over 3 Years Among Patients With Schizophrenia^a

Outcome Measure	F	df	Nonadherent, Mean (SD)	Adherent, Mean (SD)	p ^b
Days hospitalized, mean log	0.54	694	2.64 (0.97)	2.80 (1.03)	.462
Alcohol-related problems	18.1	869	1.21 (1.31)	0.88 (1.10)	< .001
Mental functioning	36.9	1892	39.0 (13.7)	42.7 (13.1)	< .001
Physical functioning	0.0	1893	45.5 (11.0)	45.7 (10.4)	.952
Satisfaction with basic needs	28.1	1893	4.59 (1.19)	4.88 (1.09)	< .001
Satisfaction with social life	5.7	1893	4.33 (1.32)	4.60 (1.23)	.017
Satisfaction with life in general	13.5	1893	4.42 (1.59)	4.78 (1.50)	< .001

^aHigher score denotes better outcome for all except log days hospitalized and alcohol-related problems.

^bp Values are based on longitudinal data analysis of variance models, with the scores over the 3-year period for each outcome variable as the dependent variable and age, sex, race, assessment number, and the time-varying covariate adherence classification per medication possession ratio as the independent variables.

Abbreviation: log = logarithmic data transformation.

Table 3. Summary of the Associations Between Adherence Status and Binary Outcome Variables: Longitudinal Assessment Over 3 Years Among Patients With Schizophrenia^a

Outcome Measure	Nonadherent (N = 376; visits = 1998) ^b	Adherent (N = 1530; visits = 10,184) ^c	χ^2	Odds Ratio ^d	95% CI	p ^e
Hospitalized, %	26.6	14.1	54.3	1.68	1.46 to 1.93	< .001
Emergency psychiatric services use, %	10.0	6.0	23.1	1.61	1.33 to 1.95	< .001
Arrested, %	8.4	3.5	29.8	1.87	1.49 to 2.34	< .001
Violent, %	10.8	4.8	44.7	1.98	1.62 to 2.42	< .001
Victim of crime, %	15.1	7.8	46.6	1.78	1.51 to 2.10	< .001
Substance use, %	31.1	21.5	14.9	1.25	1.12 to 1.40	< .001
Unemployed, %	77.9	76.6	1.6	1.08	0.96 to 1.22	.204
Supervised housing, %	31.5	31.4	3.2	1.09	0.99 to 1.20	.073

^aHigher score denotes worse outcome.

^bNumber of visits with non-missing data ranged from 1732 to 1998 across the outcome measures.

^cNumber of visits with non-missing data ranged from 9406 to 10,184 across the outcome measures.

^dOdds ratio > 1.00 denotes higher likelihood of the outcome in nonadherent patients.

^ep Values are based on longitudinal generalized linear models, with the scores over the 3-year period for each outcome variable as the dependent variable and age, sex, race, assessment number, and the time-varying covariate adherence classification per medication possession ratio as independent variables.

Abbreviation: CI = confidence interval.

the following 2 years in hospitalization days for patients who had at least 1 psychiatric hospitalization (Table 4). Compared with adherent patients, those who were nonadherent during the first year were 1.55 times more likely to be hospitalized in the following 2 years (odds ratio [OR] = 1.55, 95% confidence interval [CI] = 1.21 to 1.98) and 1.49 times more likely to use emergency psychiatric services in the following 2 years (OR = 1.49, 95% CI = 1.12 to 1.98) (Table 5).

Risk of arrests, violence, and victimization. Compared with adherent patients, the nonadherent during the first year were 2.22 times more likely to be arrested (OR = 2.22, 95% CI = 1.53 to 3.24) and 1.82 times more likely to be victims of crime in the following 2 years (OR = 1.82, 95% CI = 1.42 to 2.34) (Table 5). The nonadherent group was more likely to have been arrested prior to enrollment. Both prior arrest and nonadherence status predicted a greater risk of arrests during the study follow-up period. Figure 1 illustrates this link by graphing the percentage of patients with at least 1 arrest during the 3-year follow-up by adherence status and by arrest status prior to enrollment. Patients who were arrested prior to

enrollment were more likely to be arrested again during the following 2 years than those without prior arrest (p < .001). However, nonadherent patients had a greater risk of being arrested than adherent patients, regardless of prior arrest status. This difference was statistically significant for the group without prior arrests (p < .001) and for the group with prior arrests (p = .046). Adherence status in the first year of the study was, however, not significantly associated with changes in violent behaviors in the following 2 years.

Other functional and quality-of-life outcomes. Compared with nonadherence, adherence in the first year of the study was associated with significant and sustained improvements over the following 2 years in mental functioning, satisfaction with social life, satisfaction with basic needs, and general life satisfaction (Table 4). Further, compared with adherent patients, the nonadherent patients in the first year of the study were 1.36 times more likely to consume alcohol or drugs in the following 2 years (OR = 1.36, 95% CI = 1.07 to 1.72) and had significantly greater severity of alcohol-related problems (Tables 4 and 5). Significant associations were not found

Table 4. Summary of the Relationships Between Adherence in Year 1 and Changes in Continuous Outcome Variables in Years 2 and 3 Among Patients With Schizophrenia^a

Outcome Measure	Predicted Difference ^b	F	df	p ^c
Days hospitalized (among hospitalized patients), mean log	0.0	0.1	144	.876
Alcohol-related problems	0.4	9.1	295	.003
Mental functioning	-3.0	30.2	1854	< .001
Physical functioning	-0.7	2.5	1854	.113
Satisfaction with social life	-0.2	20.0	1873	< .001
Satisfaction with basic needs	-0.1	7.2	1857	.007
Satisfaction with life in general	-0.3	18.9	1884	< .001

^aHigher score denotes better outcome for all except log days hospitalized and alcohol-related problems.

^bPredicted difference in least squares means between the nonadherent and adherent groups (nonadherent – adherent) from the mixed-effects model.

^cp Values are based on mixed-effects model with medication possession ratio as binary (< or ≥ .85) covariate and baseline score, sex, age, race, and assessment as other factors. Data from years 2 and 3 are considered dependent variables. Abbreviation: log = logarithmic data transformation.

Table 5. Summary of the Relationships Between Adherence in Year 1 and Changes in Binary Outcome Variables in Years 2 and 3 Among Patients With Schizophrenia^a

Outcome Measure	Odds Ratio ^b	95% CI	χ ²	p
Hospitalized	1.55	1.21 to 1.98	12.1	.001
Emergency psychiatric services use	1.49	1.12 to 1.98	7.4	.007
Arrested	2.22	1.53 to 3.24	17.5	< .001
Violent	1.26	0.89 to 1.78	1.7	.195
Victim of crime	1.82	1.42 to 2.34	22.2	< .001
Substance use	1.36	1.07 to 1.72	5.9	.016
Unemployed	1.18	0.92 to 1.51	1.7	.188
Supervised housing	0.95	0.71 to 1.28	0.1	.751

^aMedication possession ratio p values are based on generalized estimating equations model with medication possession ratio as binary covariate and baseline score, sex, age, race, and assessment as other factors. Data from years 2 and 3 are considered dependent variables.

^bOdds ratio > 1.00 denotes higher likelihood of the outcome in nonadherent patients.

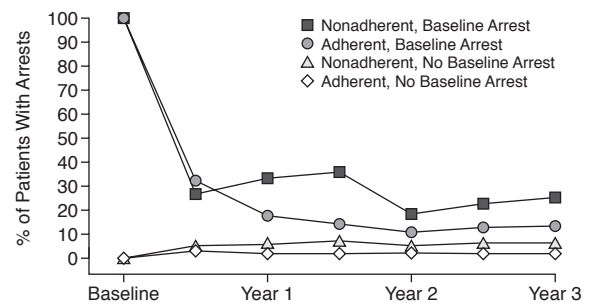
Abbreviation: CI = confidence interval.

for employment status or supervised housing. Following adjustment for multiple comparisons, all but substance use remained significant. Substance use became a trend (p = .096).

To clarify whether the group differences on outcome variables were driven by improvements in 1 group, deteriorations in the other, or both, we calculated the least squares mean change for each group across the 3-year period. Results indicate that group differences were primarily driven by significant improvements in the adherent group (p < .05), along with some worsening for the nonadherent group on mental functioning, satisfaction with social life, and alcohol-related problems.

The relationship between adherence in the first year and distal outcomes in the following 2 years was assessed

Figure 1. Percent of Patients With Arrests During the 3-Year Follow-Up by Adherence Status and by Prior Arrest^a



^aPrior arrest is defined as at least 1 arrest in the 6 months prior to enrollment. Differences between nonadherent and adherent patients with prior arrests were significant, p = .046. Differences between nonadherent and adherent patients without prior arrests were significant, p < .001.

using a statistical model that assumes equal effects over time (at years 2 and 3). To assess the impact of this assumption, we performed another repeated-measures model that removes this assumption by including a term for adherence status by assessment interaction. The new interaction term was not significant for any outcome variable, and there were no differences in adherence effects assessed from the new model.

Robustness of Findings

The current findings, which were based on a dichotomized MPR at ≥ 85%, were found to be concordant across all outcome variables when using MPR dichotomized at ≥ 80% and ≥ 70%. The major difference was the size of the nonadherent groups, which decreased with lower MPR thresholds. Further, because previous research indicates that substance use negatively affects adherence, we repeated the analysis including substance use as a covariate. The findings remained unchanged. Moreover, we repeated the analyses using only MPR, as a continuous measure, to define adherence and found highly consistent findings.

DISCUSSION

We examined the relationships between adherence with antipsychotic medications and various functional outcomes in a large, diverse, and well-described patient sample over a 3-year period in the absence of research interventions. As in previous studies,^{7,8,16,17} MPR was used as a dichotomous measure of adherence, but unlike prior research, we used a prescription-based MPR rather than a pharmacy-fill-based measure, which was augmented by patient-reported medication adherence. Despite use of different measures, our findings are highly consistent with prior research on the link between nonadherence and

higher hospitalization risk,^{6,7,9,16,17} substance use,^{9,10} and violent behaviors.^{12,26,27}

This study provides the first demonstration that an adherence measure, based on MPR from readily available prescription information in patients' records and patients' self-reports, predicts sustained future changes in clinically and economically meaningful outcomes, including health care utilization, risk of arrests, and other functional and quality-of-life parameters. In addition, our findings demonstrate a long-term relationship between adherence and a broad spectrum of functional outcomes, indicating that adherence status is relatively stable over time in this chronically ill population. The current findings show that adherence to antipsychotic medication is associated with more favorable long-term outcomes and moreover that adherence in the first year predicts sustained long-term improvements in important outcome measures, including decreases in risks of psychiatric hospitalizations, arrests, victimizations, substance use, and severity of alcohol-related problems and improvements in mental health and satisfaction with social life and with life in general. We also found that adherence status is relatively stable over time, with the majority of patients maintaining their adherence status from the first year to the second year of the study.

Although the observational nature of the study does not provide a definitive test of cause-effect relationships, the findings suggest that the beneficial correlates may be the consequences of adherence or that adherence, as measured by MPR and patients' self-report, is a marker of other factors that may be linked to better outcomes. One such potential factor is patients' engagement in the treatment process, because adherent patients may be more engaged in outpatient treatment and thus experience more beneficial functional outcomes. Further research is needed to help define and measure patients' engagement in the treatment process and to clarify, for example, if greater engagement tends to improve patients' adherence with medication or if greater adherence to medication facilitates cooperation with treatment plans and leads to greater participation in outpatient treatment processes.

In this study, the functional gap between the adherent and nonadherent groups, which was already present at baseline, widened over time as a result of sustained improvements among adherent patients and some decline among nonadherent patients. These differential outcome trajectories bode well for the adherent group but signal alarm for the nonadherent group, who are at high risk of psychiatric hospitalizations, arrests, and victimizations. This relatively small group of patients, about 20% of the current sample, appears to consume a disproportionate amount of resources in the mental health system as well as the criminal justice system, as jails and prisons are becoming surrogate mental hospitals with large populations of severely mentally ill offenders.²⁸

Our analysis also identified the prescription-based MPR as a valid, timely, and simple tool to identify at-risk patients. Because prescription information is available in most patients' medical records, this tool may be more useful to practicing clinicians than the equally valid, but less accessible, pharmacy-fill-based MPR.^{7,8} Prescription-based MPR may help identify patients who have fallen below a specified adherence threshold, enabling timely assessment of causes of nonadherence and tailoring of treatment plans to better address patients' special needs. These efforts may include psychosocial and pharmacologic interventions aimed at improving patients' medication adherence and participation in treatment plans.²⁹

It is notable that the "specified threshold" is not a fixed parameter. Our choice of $\geq 85\%$ as MPR cutoff point to define adherence status was based on the sample's MPR distribution, although other MPR thresholds such as $\geq 70\%$ and $\geq 80\%$ provided similar results.^{7,17}

This study has a number of limitations. First, it is likely that we underestimated the patients' true nonadherence rate because of a higher study attrition rate among the nonadherent patients. Second, our measure of adherence relied on medical record prescription information and patients' self-reports. Recognizing that patients' self-report may not be reliable, and that adherence is often partial and a matter of degree, we repeated the analysis using only a continuous MPR to define adherence and found highly consistent results. Furthermore, although we identified about 20% of the patients as nonadherent, this rate is close to the 25.8% nonadherence rate previously calculated from pooled data of 86 studies reporting nonadherence with medication and scheduled appointments among psychotic patients treated in community psychiatry settings.³⁰ Moreover, the present findings are highly consistent with a large body of research in which diverse and predominately indirect adherence measures were used.^{4-7,9-12,16,17}

Another study limitation is its observational nature, which, despite its merits, does not permit delineations of cause and effect relationships between adherence and outcomes. Appropriate (apples to apples) comparisons between nonrandomized groups, such as the comparisons between adherent and nonadherent patients, depend on the use of statistical adjustments and the collection and accurate measurement of all key factors relating to the groups and outcomes. The study was designed to capture a wide variety of outcomes across multiple domains, and we have incorporated statistical adjustments for known potential confounding variables. However, we cannot eliminate the possibility that some confounding factor was not adequately measured or collected. For example, we discussed the difficulties with measuring and adjusting for "engagement in the treatment process." In addition, this study used patient-reported measures to assess functional outcomes, whereas the use of multiple sources of information, particularly for documenting violent behaviors,

arrests, and substance use, might have provided more valid outcome parameters.^{12,31}

This large, 3-year, prospective, naturalistic study of schizophrenia patients demonstrated that adherence with antipsychotic regimens, as measured by medical record-based–prescription information and patients’ self-reports, was associated with better long-term functional outcomes. We also demonstrated that adherence to medication is relatively stable over time and that adherence in the first year predicted sustained improvements in clinically and economically meaningful outcome parameters in the following 2 years. Findings suggest that the prescription-based MPR may help identify at-risk patients who constitute the costliest patient cluster in the mental health and criminal justice systems. Future research is needed to further elucidate cause and effect relationships, identify helpful interventions, and clarify which of the modifiable correlates are most amenable to change, in order to enhance patients’ adherence to beneficial medication regimens.

Acknowledgment: The authors wish to thank Michael D. Stensland, Ph.D., Eli Lilly and Co., for his statistical consultation. The authors wish to thank the site investigators and others who collaborated in the research. By site, they include Maryland: A. F. Lehman, M.D., M.S.P.H., University of Maryland School of Medicine, and G. Gallucci, M.D., M.H.S., Johns Hopkins Bayview Medical Center; Colorado: C. Harding, Ph.D., University of Colorado (previously); Florida: D. Shern, Ph.D., Florida Mental Health Institute, University of South Florida, and T. Saunders, M.S., Florida Mental Health Institute (previously); North Carolina: J. Swanson, Ph.D., L. A. Dunn, M.D., and M. Swartz, M.D., Duke University Medical School; California: R. L. Hough, Ph.D., and C. Barrio, Ph.D., Child and Adolescent Services Research Center and San Diego State University; Connecticut: R. A. Rosenheck, M.D., and R. Desai, Ph.D., VA Connecticut Health Care System; Medstat Group: P. Russo, Ph.D., M.S.W., R.N., L. Palmer, Ph.D., L. Torres, M.B.A., and B. Cuffel, Ph.D. (previously); Eli Lilly and Co.: D. Buesching, Ph.D., Bryan M. Johnstone, Ph.D., and T. Croghan, M.D. (previously); Consultants: D. Salkever, Ph.D., Johns Hopkins University, E. Slade, Ph.D., Johns Hopkins University (previously), and W. Hargreaves, Ph.D., and M. Shumway, Ph.D., University of California, San Francisco.

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