

Partial Compliance and Risk of Rehospitalization Among California Medicaid Patients With Schizophrenia

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Objective: The objective of this study was to evaluate the relationship between compliance with an antipsychotic medication regimen and risk of hospitalization in a cohort of California Medicaid patients with schizophrenia. **Methods:** Compliance behavior was estimated by using a retrospective review of California Medicaid pharmacy refill and medical claims for 4,325 outpatients for whom antipsychotics were prescribed for treatment of schizophrenia from 1999 to 2001. Compliance behavior was estimated by using four different definitions: gaps in medication therapy, medication consistency and persistence, and a medication possession ratio. Patients were followed for one year and had an average of 19.1 dispensing events. Logistic regression models using each compliance estimate were used to determine the odds of hospitalization. **Results:** Risk of hospitalization was significantly correlated with compliance. With all definitions, lower compliance was associated with a greater risk of hospitalization over and above any other risk factors for hospitalization. For example, the presence of any gap in medication coverage was associated with increased risk of hospitalization, including gaps as small as one to ten days (odds ratio [OR]=1.98). A gap of 11 to 30 days was associated with an OR of 2.81, and a gap of more than 30 days was associated with an OR of 3.96. **Conclusions:** This study showed a direct correlation between estimated partial compliance and hospitalization risk among patients with schizophrenia across a continuum of compliance behavior. (*Psychiatric Services* 55:886–891, 2004)

Medication compliance, or adherence, among patients with schizophrenia has often been reported as an all-or-nothing behavior: the patient either is compliant or is not. This notion of noncom-

pliance as complete, willful cessation of all antipsychotic medications is not an accurate representation of actual medication-taking behavior among outpatient populations with schizophrenia. Recent studies using more

sophisticated assessments have found that a majority of patients with schizophrenia who are considered to be compliant with their antipsychotic medication regimens actually show a range of compliance behaviors, probably for many diverse reasons. The full range of compliance-spectrum behavior becomes apparent when patient self-report is contrasted with other, more quantitative, measures, such as the Medication Event Monitoring System (MEMS) (1), or when compliance is determined by blood samples taken during unscheduled home visits (2).

Thus the term “partial compliance” seems preferable to “noncompliance” in that the former explicitly acknowledges the common situation in which a person takes some, but not all, of his or her prescribed medication. Partial compliance may take several forms, including taking an amount that is consistently less than recommended, irregular (“on-and-off”) dosing behavior, and having discrete gaps in antipsychotic therapy—for example, in the case of patients who are unwilling or unable to refill a prescription.

It is important to note that partial compliance refers only to compliance behavior and does not reflect either the efficacy of the treatment or the person’s attitude toward taking medication. For example, partial compliance can be due to efficacy problems (such as cognitive dysfunction that leads to forgetting to pick up a refill), systems barriers (for example, a prescription is not refilled because insurance cover-

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age has run out), or an intentional decision to stop taking medication.

A number of studies have shown that most patients with schizophrenia are partially compliant (3,4). Docherty and colleagues (3) found that 90 percent of patients with schizophrenia had some degree of partial compliance. In this overall sample of 675 patients, medications were not available for 36 percent of patient-days of medication exposure. McCombs and colleagues (4) found that 92 percent of a sample of 2,010 patients with schizophrenia had at least one disruption in antipsychotic medication coverage during the course of a year and that the mean duration of therapy was only 142 days per year (4). Another study reported that among patients with early-episode schizophrenia, 63 percent of a sample of 182 had at least one gap in therapy over a one-year period, with most of these gaps extending over a month (5). However, comparison of partial compliance rates between studies is difficult, because the techniques used to measure compliance, as well as the definitions of compliance, vary from study to study.

It is well known that medication noncompliance is one of the most important modifiable risk factors for relapse among patients with schizophrenia (6,7). Estimates suggest that noncompliance causes about 40 percent of relapse (8). A review of seven studies demonstrated that noncompliant patients had a six-month to two-year relapse risk that was about 3.7 times that of compliant patients (9). First-episode patients, who potentially have the most to lose from repeated relapse, are similarly likely to experience relapse when their treatment is interrupted (10). However, these studies used the traditional definition of noncompliance—that is, complete discontinuation of antipsychotic medication. Thus the relationship between partial compliance and relapse risk is not known. An understanding of the role of partial compliance in relapse will help define the threshold between the extent of partial compliance and risk of relapse.

One approach for examining the effect of partial compliance on outcome is to use pharmacy claims data as a

conservative proxy measure for compliance behavior. Analysis of pharmacy claims has been used successfully for other chronic diseases—for example, hypertension and epilepsy—to show relationships between partial compliance and hospitalization (11–14). Claims records in administrative databases can be used to assess whether patients discontinue their medication therapy (stop taking their medication) or refill medications inconsistently (skip doses) (15–20).

The primary objectives of the analysis reported here were to determine the association between estimates of partial compliance and outcome, with the hypothesis that the lower the compliance, the greater the risk of hospitalization, and to evaluate the quantitative characteristics that define any potential relationship between partial compliance and hospitalization.

Methods

Study design and population

A 20 percent random sample of 1999–2001 California Medicaid data was used to evaluate the association between partial compliance and hospitalization. To be included, patients with schizophrenia—that is, patients with an *ICD-9-CM* code of 295.xx—had to have at least two dispensing events for antipsychotic medications during a six-month enrollment period (July 1 to December 31, 1999). Qualifying prescription claims included claims for all approved oral antipsychotic medications, including newer antipsychotics available before January 1, 2000.

Each patient was assigned an index date, defined as the date of the patient's first prescription during the enrollment period. Because it is possible that patients with new diagnoses would have significantly different compliance issues while being stabilized with medication therapy, the goal was to study patients who were already receiving antipsychotics. Therefore, patients were also required to have at least one prescription in the six months before their index date. The study was not examined by an institutional review board, because all personal identifiers were removed and the investigators were not aware of the patients' identities at any time.

Data were obtained for 12 months

after each patient's index date (the observation period). Because compliance patterns might be affected when patients are about to lose eligibility, patients included in the study were those who remained eligible for California Medicaid for an additional three months after the observation period. Patients were excluded if they were younger than 18 years at the start of the study period, if they had long-term-care visits (because of the possibility of incomplete records), or if their calculated medication use (number of units dispensed divided by days' supply was ten or more. The reason for the units-per-day restriction was that a use of ten or more times per day suggests data entry errors.

Patients who had a claim coded with an *ICD-9-CM* code for bipolar disorder (296.0x, 296.1x, or 296.4–296.8) at any point within the available data set were dropped from the analysis on the grounds that these patients might use drugs other than antipsychotics (for example, lithium) as a primary therapy (thus violating necessary assumptions for calculation of compliance variables). Patients who were receiving long-acting antipsychotics (haloperidol decanoate or fluphenazine decanoate) were excluded because of inconsistencies in the number of days' supply recorded.

Measures of partial compliance

Four measures of compliance were evaluated: gaps in medication therapy, medication consistency, medication persistence, and a medication possession ratio (MPR). Because the results from all measures were similar, the primary focus in this article is on gaps in medication, a measure that is conceptually straightforward and easiest to use in clinical practice. For this study, medication gap was defined as the longest period during which no medication appeared to be available. Contiguous periods in which no medication appeared to be available were based on dispensing date and recorded days' supply for each antipsychotic prescription. Four categories based on each patient's maximum gap in therapy were defined: zero days, one to ten days, 11 to 30 days, and more than 30 days. The mean number of gaps per patient and

Table 1

Characteristics of a sample of 4,325 outpatients for whom antipsychotics were prescribed for treatment of schizophrenia

Variable	N	%
Age (years)		
Mean±SD	44.2±12.3	
Range	18.1–89.7	
Median	43.1	
Gender		
Male	2,531	58.5
Female	1,794	41.5
Ethnicity		
White	2,406	55.6
African American	670	15.5
Asian	536	12.4
Hispanic	39	.9
Other	242	5.6
Unknown or missing	432	10
Medicare eligibility		
Yes	2,114	48.9
No	2,211	51.1
Hospitalized		
Yes	654	15.1
No	3,671	84.9

the mean gap duration (across all therapy gaps) were also calculated.

Medication consistency is a measure of whether patients skipped doses when medication should have been available—that is, between the dates of the first and last prescriptions a patient had filled. Consistency was calculated, using a modified definition from the literature (21), as the percentage of time a patient appears to have medication available divided by the period during which the patient should have theoretically used all the available medication. A weighted average was taken across antipsychotic therapies. Medication persistence captures whether a patient discontinued all therapies. This calculation represents the number of days between the first and last prescription, divided by the fixed number of days in the study period.

The MPR was calculated in a manner similar to that used for therapy gaps and is a modification of the literature-based formula (15,16). The number of days a patient was not hospitalized and showed evidence of use of any antipsychotic medication (based on dispensing date and days' supply recorded on the prescription

claim) were summed. The MPR was calculated by dividing this sum by the number of ambulatory days in the study period. By evaluating the percentage of days over a fixed period, the MPR combines assessments of skipping doses (consistency) and discontinuation (persistence) into a single composite measure.

Measure of hospitalization

A marker was created to indicate whether a patient had at least one "mental health hospitalization" during the one-year, postindex observation period. Mental health hospitalizations were identified by using "mental health" ICD-9-CM diagnosis codes in the first (primary) diagnosis field. The following diagnosis codes were used: schizophrenia (295.xx), depression (296.2x, 296.3x, 296.9x, 300.4x, 309.0x, or 311.xx), anxiety (300.0x, 300.2x, 300.3x, 306.9x, 308.xx, 309.2x, 309.4x, or 309.9x), other psychoses (297.xx, 298.xx, 299.xx, 300.1x, 302.8x, or 307.9x), and dementia (290.xx, 291.2x, 310.9x, or 331.0). Use of a broad definition of psychiatric hospitalization ensured that no relevant psychiatric hospitalizations related to the index diagnosis of schizophrenia were missed.

Statistical analysis

The primary analysis evaluated the relationship between compliance and the presence of at least one mental health hospitalization during the one-year follow-up period. Logistic regression models predicting presence of at least one hospitalization in the postindex year were developed for each of the compliance measures. Medication gap models predicted hospitalization by using four gap categories: zero days, one to ten days, 11 to 30 days, and more than 30 days. Logistic models for consistency, persistence, and the MPR predicted hospitalization by using continuous measures. Interactions were included only if they added significantly to the explanatory power of the model; variables were dropped from the models if they were insignificant and had a negative impact on model fit. Compliance was also categorized and evaluated by using chi square tests.

For descriptive analyses, consis-

cy, persistence, and MPR mean scores as well as categorical frequencies are presented. For consistency and the MPR, the compliance categories defined less than 70 percent compliance as noncompliant and at least 70 percent compliance as compliant. Although no standard is available for identifying compliance categories, the literature suggests that a 70 percent cutoff is reasonable (3,22,23). The MPR was calculated in a manner such that no values exceeded 100 percent. The categories for persistence were less than 90 percent compliance and at least 90 percent compliance.

Results

Patient disposition and demographic characteristics

A total of 4,325 patients met the selection criteria. Patient characteristics are summarized in Table 1. The patients' mean age was 44.2 years; 58.5 percent were men, and 55.6 percent were white. Approximately half were also Medicare eligible (48.9 percent). A total of 654 patients (15.1 percent) had at least one psychiatric hospitalization. Analysis of the crude data also showed that age, ethnicity, and insurance status were associated with likelihood of hospitalization. Hospitalization was less likely with increasing age but more likely among patients who were African American and among patients who were eligible for Medicare (Table 2).

Partial compliance and hospitalization

The patients in the study were on the more compliant end of the compliance continuum, as indicated by the mean compliance variables, shown in Table 3. Only 267 patients (6.2 percent) had a persistence level of less than 90 percent, yielding an average persistence of 97 percent. During the one-year observation period patients had a mean±SD number of dispensing events of 19.1±15.9 for 1.65±.87 different drug entities.

Figure 1 shows the percentage of patients hospitalized as categorized by medication gap within a one-year period. All pairwise comparisons with the reference group were significant ($p<.005$). As the maximum gap increased, the percentage of patients

hospitalized increased. For consistency and the MPR, significant differences ($p<.001$) in the percentages of patients with at least one hospitalization were found. Partially compliant patients had significantly higher rates of hospitalization. Patients who were less than 70 percent compliant by the MPR had higher rates of hospitalization than those who were at least 70 percent compliant (22.3 percent and 13.8 percent, respectively, $p<.001$). Similar results were observed for consistency (24.5 percent compared with 12.8 percent, $p<.001$). In addition, patients who were identified as being less than 90 percent compliant by the persistence measure had higher rates of hospitalization than those who were identified as being at least 90 percent persistent (25.1 percent and 14.5 percent, respectively, $p<.001$) (Table 3).

Compliance as a predictor of hospitalization

Having a maximum gap in use of medication that was as small as one to ten days in a one-year period was associated with a significantly increased risk of hospitalization (odds ratio [OR]=1.98) (Table 2). Compared with patients who did not have gaps in medication therapy, patients who had a one- to ten-day maximum gap had almost twice the odds of hospitalization. As the gap increased to 11 to 30 days and more than 30 days, ORs increased to 2.81 and 3.96, respectively.

Logistic regression results for the other three compliance measures were similar to the results for medication gaps. With a 10 percent improvement in consistency, persistence, or the MPR, the odds of hospitalization were lowered by factors of 16 percent, 9 percent, and 23 percent, respectively ($p<.01$). These models are consistent with the results observed for the maximum medication gap models. Odds of hospitalization were also significantly affected by Medicare eligibility, depending on the compliance variable (Table 4). Medicare eligibility and an increase in age of ten years were significant factors in the models for the MPR, consistency, and persistence.

Table 2

Odds of hospitalization for a sample of 4,325 outpatients for whom antipsychotics were prescribed for treatment of schizophrenia, based on the maximum gap model

Variable	OR estimate	95% CI	χ^2 [†]	p
Duration of maximum gap (days) ^a				
1 to 10	1.98	1.27–3.25	8.19	.004
11 to 30	2.81	1.8–4.64	18.57	<.001
More than 30	3.96	2.54–6.5	33.44	<.001
Ten-year increase in age	.82	.76–.88	28.28	<.001
Race ^b				
African American	1.31	1.03–1.65	4.94	.026
Other	.96	.76–1.21	.12	.725
Missing	1.02	.75–1.37	.02	.894
Medicare eligible ^c	1.58	1.32–1.89	25.7	<.001

^a Zero is the referent.

^b White is the referent.

^c Not Medicare eligible is the referent.

[†]df=1

Discussion

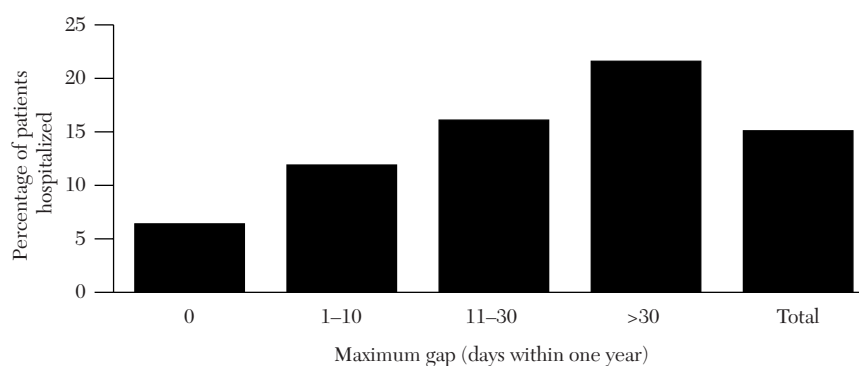
The major finding of this study was the direct relationship between measures of partial compliance and risk of hospitalization: the lower the level of compliance, the greater the risk of hospitalization. We emphasize that this finding is not as intuitive as it might appear. Most published studies showing the link between noncompliance and relapse define noncompliance as persistent and complete discontinuation of antipsychotic medication. From that perspective, the cohort in our analysis was mostly compliant, and even then a relationship was observed between partial compliance and hospitalization risk. This association behaves more like a continuous function than a categorical func-

tion—that is, once any degree of partial compliance was indicated by the data, there did not seem to be any low-end cutoff below which hospitalization risk reverted to that of the reference cohort (no indication of partial compliance). This observation held for all four compliance measures. These results suggest that relatively small changes in overall compliance are meaningfully associated with changes in the risk of hospitalization.

Partial compliance seems to be associated with increasing risk of relapse in the long-term treatment of schizophrenia. We found that medication gaps as small as one to ten continuous days in a one-year period were associated with a twofold increase in hospitalization risk. These

Figure 1

Percentage of patients with schizophrenia who were rehospitalized, by maximum gap in therapy^a



^a All pairwise comparisons were significant at $p<.005$.

Table 3

Compliance and use of prescription medications in a sample of 4,325 outpatients for whom antipsychotics were prescribed for treatment of schizophrenia

Variable	Mean±SD	Hospitalized		Not hospitalized	
		N	%	N	%
Gap in medication therapy					
Maximum gap (days) ^a	28.4±45.2				
0 days ^b		21	6.4	306	93.6
1 to 10 days ^c		203	11.9	1,507	88.1
11 to 30 days ^d		188	16.1	978	83.9
More than 30 days		242	21.6	880	78.4
Consistency ^e	.88±.2				
<70 percent compliant		173	24.5	532	75.5
≥70 percent compliant		444	12.8	3,018	87.2
Persistence ^f	.97±.11				
<90 percent compliant		67	25.1	200	74.9
≥90 percent compliant		587	14.5	3,471	85.5
Medication possession ratio ^g	.86±.18				
<70 percent compliant		150	22.3	522	77.7
≥70 percent compliant		504	13.8	3,149	86.2

^a Overall $\chi^2=70.6$, $df=3$, $p<.001$

^b For 0 days versus 1 to 10 days, $\chi^2=8.33$, $df=1$; for 0 days versus 11 to 30 days, $\chi^2=19.97$, $df=1$; for 0 days versus more than 30 days, $\chi^2=39.10$, $df=1$

^c For 1 to 10 days versus 11 to 30 days, $\chi^2=10.67$, $df=1$; for 1 to 10 days versus more than 30 days, $\chi^2=48.10$, $df=1$

^d For 11 to 30 days versus more than 30 days, $\chi^2=11.11$, $df=1$

^e $N=4,167$, because consistency was not calculated unless the patient had at least three dispensing events for a single drug; $\chi^2=63.7$, $df=1$, $p<.001$

^f $\chi^2=22.0$, $df=1$, $p<.001$

^g $\chi^2=32.1$, $df=1$, $p<.001$

results are consistent with those of other studies that have demonstrated the negative consequences of partial compliance. Valenstein and colleagues (23) found that patients who had poor compliance were 2.4 times as likely to have inpatient admissions compared with patients who had good compliance. In addition, patients who had poor compliance had a greater total number of psychiatric inpatient days (a mean of 33 days per

year) compared with patients who had good compliance (a mean of 24 days per year).

Another study found that partially compliant patients were 49 percent as likely as compliant patients to have an inpatient hospitalization (24). Most recently, Gilmer and coworkers (25), in an analysis of a California Medicaid database, also found that rates of psychiatric hospitalization were lowest among patients who were compliant

with their antipsychotic medication regimens (25). These data suggest that patients who do not achieve satisfactory responses to treatment may be experiencing partial compliance problems rather than medication efficacy problems. Steps taken to improve compliance offer an important treatment option that should be considered along with other options, such as combining or switching antipsychotic medications.

Several limitations of this study should be noted. One of the most important limitations is that pharmacy claims data do not provide insights into the reasons for partial compliance. Partial compliance is a behavioral finding with no attributable underlying cause. For example, there is no way to know whether partial compliance in our study sample reflected an intentional decision to stop taking medication or was unintentional, perhaps due to service barriers such as discontinuity of care (26).

Furthermore, the causality of the association between partial compliance and hospitalization has not been established. For example, it is possible that patients who do not fully respond to their medication would be more likely to have medication gaps and that the common shared risk is incomplete medication efficacy (27). We did not attempt a test of temporal contiguity between noncompliance and hospitalization, but such a test could be considered for a future analysis.

The database we used had technical limitations. The use of Medicaid claims data as a proxy for partial compliance relies on minimal coding er-

Table 4

Odds of hospitalization for a sample of 4,325 outpatients for whom antipsychotics were prescribed for treatment of schizophrenia, based on compliance models^a

Endpoint	Consistency			Persistence			Medication possession ratio		
	OR estimate	χ^2	df	OR estimate	χ^2	df	OR estimate	χ^2	df
10 percent improved compliance	.84**	86.42	1	.91*	9.07	1	.87**	48.76	1
Ten-year increase in age	.83**	22.18	1	.81**	29.04	1	.82**	27.78	1
African American versus white	—	—	—	1.4	8.19	1	—	—	—
Medicare eligible	1.55**	21.65	1	1.55**	23.81	1	1.54**	23.84	1

^a Only variables that were significant in the model are shown.

* $p<.01$

** $p<.001$

rors (28,29). Patients' discontinuation of use of Medicaid services may not be reflected in a timely fashion (28); Medicaid patients may not be representative of the population as a whole; and claims data may not include potential confounders, such as medical history and lifestyle factors (28). Calculations for compliance variables are dependent on accurate claims information pertaining to dates, days' supply of medication, the patient's being discharged on the same medication as at admission, and the assumption that there are no other sources of medication supply—for example, medication samples. These latter problems could lead to an overestimation of the association between medication gaps and hospitalization. Although the use of pharmacy claims methodology has the potential advantage of assessment of large cohorts of patients over longer periods, potential sources of error lie in the assumption that claims data are a proxy for partial compliance. Although these factors may have introduced bias into our analysis, the analysis plan minimized sources of differential error between the reference group and the partial compliance group.

Given these factors, however, it should be noted that medical claims data almost certainly overestimate compliance, because claims data can report only whether the prescription was filled, not whether the medication was taken correctly or at all (28). Furthermore, the reference group likely included some patients who could be more accurately described as partially compliant. Thus the actual relationship between partial compliance and hospitalization is likely to be stronger than could be identified from our data. Factors other than partial compliance, many of which would not be captured in a claims database, including social support—or lack thereof—and substance abuse, can affect hospitalization rates.

Conclusions

The results of this study suggest that enhancing compliance across the range of partial compliance behaviors can reduce the risk of hospitalization among patients with schizophrenia. Future studies will explore the impact of par-

tial compliance on other aspects of schizophrenia, such as the duration and severity of illness. Ultimately, enhanced compliance, through improved pharmacologic drug delivery interventions or behavioral interventions, could reduce the toll of relapse and rehospitalization associated with the long-term treatment of schizophrenia. ♦

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