A Longitudinal Study of Medication Nonadherence and Hospitalization Risk in Schizophrenia

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Objective: Previous cross-sectional studies have suggested an association between medication nonadherence and hospitalization for individuals with schizophrenia. However, such analyses typically measure adherence averaged over long time periods. We investigated the temporal relationship between nonadherence and hospitalization risk using a daily measure of medication availability.

Method: Our observational cohort included 1191 patients with schizophrenia (ICD-9 criteria) enrolled in Maine and New Hampshire Medicaid programs who initiated atypical antipsychotic therapy between January 1, 2001, and December 31, 2003. Pharmacy claims were used to define days with gaps in medication availability. We tested the association of gaps in medication availability with all-cause, mental health, and schizophrenia-specific hospitalization using a Cox regression model.

Results: Compared to individuals with available medication, individuals in the first 10 days following a missed prescription refill had a hazard ratio of 1.54 (95% CI = 1.02 to 2.32) for mental health hospitalization and 1.77 (95% CI = 1.16 to 2.71) for schizophrenia hospitalization. Similarly, medication gaps of more than 30 days were associated with 50% increased hazard for all 3 hospitalization outcomes. Switching and augmenting therapy, previous hospitalization, and clinical severity measures were also associated with substantially increased hazard of hospitalization.

Conclusion: Our findings indicate that patients may be at significantly increased risk for hospitalization as early as the first 10 days following a missed medication refill. Patients who switched or augmented medications or were previously hospitalized also demonstrated increased hospitalization risk. Clinicians and Medicaid programs should consider using pharmacy claims to monitor medication use and target adherence interventions to reduce relapses in this vulnerable population.

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While antipsychotic medications are effective at reducing symptoms and preventing relapse, adherence to therapy remains a significant concern.[1,2] Clinical guidelines suggest benefits to maintaining regular medication use through both acute and stable phases of schizophrenia.[3] However, estimates suggest that only 50% to 60% of individuals with schizophrenia adhere to medication protocols.[2] Nonadherence is of particular concern among Medicaid patients, as only an estimated 12% of Medicaid patients with schizophrenia complete a full year of uninterrupted treatment.[4]

Medication nonadherence is associated with serious clinical consequences. Several studies have used pharmaceutical claims data to assess the relationship between medication nonadherence and adverse outcomes such as hospitalization. A study of California Medicaid recipients found nonadhering patients to have 21% higher odds of hospitalization.[5] Using a similar population, Weiden et al.[6] found that patients with a gap as short as 10 days (38% of their sample) had a 2-fold increase in the odds of

hospitalization compared with patients with no gaps in treatment. Similar findings have been shown in studies using various definitions of adherence.[7–10] An earlier meta-analysis suggested that relapse rates for nonadherent individuals were approximately double the rates of those who are adherent.[11]

The clinical and policy implications of these cross-sectional relationships between adherence averaged over long time periods and hospitalization are somewhat unclear because they fail to capture the temporal relationship between changes in adherence and risk of hospitalization over time. Yet there is no reason to expect that an individual consistently adheres to medication over time. Therefore, it is important to assess how different patterns of adherence over time affect subsequent hospitalization risk. Further, many studies measure adherence and hospitalization over the same time period, raising 2 important methodological issues affecting the validity of the findings. First, measures of adherence include time periods following hospitalization, so the causal order of events may be reversed. Second, because measures of adherence are typically based on outpatient pharmacy claims, having a long hospitalization may itself lower adherence estimates if it causes individuals to "miss" 1 or more medication refills while they were receiving in-hospital medications. Few studies are explicit about if and how they have accounted for hospitalization in their adherence calculations.[8] Moreover, concern over confounding in previous analyses has led to debate over whether results correlating adherence to poor health outcomes are simply a result of a "healthy adherer" effect and not adherence itself.[12,13]

This study addressed these issues by using longitudinal data and survival analysis to examine patterns of adherence over time. Our primary aim was to examine whether gaps in availability of medicine were associated with hospitalization risk among Medicaid enrollees. In addition, we examined the association between hospital admission and 2 likely indicators of clinical severity, namely, switching and augmenting medications.

METHOD

Data Sources

The study analyzed a retrospective cohort of 1191 patients from the Maine and New Hampshire Medicaid programs. The research was appraised and granted an exemption from review by the Harvard Pilgrim Health Care Human Studies Committee. We identified individuals with schizophrenia aged 18 to 64 years for the entire study period who initiated atypical antipsychotic therapy between January 1, 2001, and December 31, 2003. We used a previously validated algorithm to define schizophrenia as 1 inpatient or 2 outpatient diagnoses of schizophrenia or schizoaffective disorder (ICD-9 codes 295.xx) in either Medicaid or Medicare claims data.[14,15] Continuous Medicaid enrollment was required from 90 days prior to therapy initiation until either a hospital event or censoring at the study end date. Patients enrolled in a health maintenance organization (HMO) at any point during the study time period (N = 3) were excluded as their utilization data would be incomplete.

Initiation of therapy was defined as receipt of any atypical antipsychotic medication following a 90-day period of no atypical antipsychotic availability. We required that individuals refill their index atypical antipsychotic at least once during the first 60 days following initiation of therapy to demonstrate recurring medication use. The therapy initiation date was used as the starting date for all subsequent survival analyses. Follow-up for each eligible individual started from his or her initial 90-day medication-free period during our study window. We excluded patients who received clozapine at any point over the study period (N = 150), as they very likely received more intensive medicine administration, monitoring, and practitioner follow-up.

Adherence Profiling

Our primary study aim was to assess the relationship between specific longitudinal patterns of medication-taking behavior—namely, gaps, switching, and augmentation—and the risk of hospitalization. All 3 medication patterns were defined at the day level using the days supply field from Medicaid drug claims records. To investigate the reliability of this field, we examined the lengths of prescriptions received to ensure they were common supplies in clinical practice. Over 90% of the claims had days supplied of 7, 14, or 30, and 98% were 30 days or less. These values suggest realistic prescription lengths, particularly given 30-day supply limits in both states. Moreover, adherence measurement using claims data has been previously validated against other adherence

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measures, including self-report, pill counts, and biologic fluid concentrations.[16]

To define gaps, prescriptions for atypical agents were spanned over the duration of their dispensed days supply, identifying days when medication would have been available if used as indicated. Any supply available from previous claims was added to the dispensed days supply. When an individual's drug supply had run out according to this convention, a gap was started and continued until a subsequent refill was obtained. On the basis of methods used in previous work, we divided gaps into 3 segments (1–10 days, 11–30 days, and > 30 days) to assess whether the hazard of hospitalization varied within gap periods.[6] For each follow-up day, 3 binary variables indicated whether an individual was in the first 10 days of a gap, in day 11 through 30, or in a gap longer than 30 days. An individual with available antipsychotic medication would have had all 3 variables set to zero.

Switching and augmentation were defined using 2 time-varying covariates. Switching was defined as initiation of a second atypical agent followed by discontinuation (fewer than 2 refills) of the index agent. For example, if a patient was followed for 100 days and switched medications on day 50, he or she would be coded as a switcher for days 50 through 100. If an individual initiated a second atypical agent without discontinuing the index atypical, he or she was considered to have augmented therapy.

Outcomes

The primary outcome for the analysis was an inpatient hospital admission, including admissions identified in either Medicaid or Medicare claims. We examined 3 different types of admissions: all-cause hospitalization, excluding obstetric claims related to pregnancy (ICD-9 codes 630–677); mental health hospitalization as defined by Weiden et al.,[6] including schizophrenia (295.xx), depression (296.2x, 296.3x, 296.9x, 300.4x, 309.0x, 311.xx), anxiety (300.0x, 300.2x, 300.3x, 306.9x, 308.xx, 309.2x, 309.4x, 309.9x), other psychoses (297.xx, 298.xx, 299.xx, 300.1x, 302.8x, 307.9x), and dementia (290.xx, 291.2x, 310.9x, 331.0); and schizophrenia-specific hospitalization (primary diagnosis with 295.xx). Medicaid eligibility was assessed separately for each outcome, as some individuals continuously eligible until an all-cause hospitalization lost eligibility before one of our other outcomes or the study end date (N = 36 for mental health and N = 43 for schizophrenia-specific).

Statistical Analysis

We determined the relationship between patterns of adherence over time and hospitalization using an extended Cox model.[17] Our key variables of interest included the 3 time-varying indicators for the gap periods discussed above; patients who were not experiencing a gap in medication use at the time of a given event served as the reference group. Similarly, we included time-varying indicators to denote switching and augmentation and compared these patients to those remaining on their index therapy. We expected to observe the largest effect sizes for the relationship between adherence and schizophrenia-specific hospitalization.

We included several additional baseline covariates, including gender, age in 3 groups (18–34, 35–54, and 55–64 years), and an indicator for Medicare dual eligibility. Three baseline measures of comorbidity were also included. First, we used prescription claims for the 90-day period up to atypical initiation to construct a count of Chronic Disease Score categories, a previously validated measure of comorbidity constructed from pharmacy claims.[18,19] We added an indicator variable for the depression category in the Chronic Disease Score, as past research has shown that depressive symptoms are related to treatment adherence and thus may represent an important confounder.[20] Finally, we included an indicator for any inpatient hospitalization during the 90-day preinitiation period in the model.

RESULTS

Descriptive Statistics

Descriptive statistics for the sample of 1191 individuals that met the cohort eligibility criteria are presented in Table 1. The sample was largely middle-aged (i.e., 35–54 years) with a slightly higher prevalence of men. In terms of severity of illness, just over 30% had been hospitalized in the 90 days preceding their initiation of an atypical medication, and the majority had 1 or more identified chronic conditions based on the Chronic Disease Score. The main agents being used as both first- and second-line therapy were olanzapine, risperidone, and quetiapine. Augmentation of therapy occurred among 22% of patients, while switching occurred for 13% during their follow-up period. For our outcomes, 552 of the 1191 individuals (46%) had an inpatient hospitalization. Of the 1155 individuals continuously eligible for mental health hospitalization, 371 (32%) had a mental health hospitalization. Finally, of 1148 individuals continuously eligible for schizophrenia-specific hospitalization, 315 (27%) had a schizophrenia-specific admission. Patients experienced substantial gaps in adherence to therapy, consistent with past studies.[4] During follow-up, 79% of patients experienced at least 1 gap in therapy, and patients did not have medication available for 27% of follow-up days (not shown).

Figure 1 shows the cumulative proportion of patients reaching their first gap period of each length (1–10 days, 11–30 days, and > 30 days) during follow-up. It demonstrates widespread nonadherence, with many first gaps occurring during the several months following therapy initiation. Median follow-up times were 315 days for all-cause hospitalization, 414 days for mental health hospitalization,

Table 1. Descriptive Statistics of the Cohort of Medicaid Patients Initiating Atypical Antipsychotic Therapy in Maine and New Hampshire From January 2001 to December 2003

Variable	N	Percent of Total
Age category		
18–34 y	329	27.62
35–54 y	690	57.93
55–64 y	172	14.44
Gender		
Male	649	54.49
Female	542	45.51
Previous hospitalization		
No	826	69.35
Yes	365	30.65
Medicare eligible		
No	535	44.92
Yes	656	55.08
Chronic Disease Score		
0	37	3.11
1	189	15.87
2	242	20.32
3	217	18.22
4	149	12.51
5	132	11.08
6	87	7.30
7+	138	11.59
Chronic Disease Score-depression		
No	622	52.23
Yes	569	47.77
Start drug		
Aripiprazole	48	4.03
Olanzapine	379	31.82
Quetiapine	287	24.10
Risperidone	372	31.23
Ziprasidone	105	8.82
Second drug		
Aripiprazole	80	6.72
Olanzapine	122	10.24
Quetiapine	147	12.34
Risperidone	112	9.40
Ziprasidone	78	6.55
None	652	54.74
Augmenter		
No	934	78.42
Yes	257	21.58
Switcher		
No	1036	86.99
Yes	155	13.01
Inpatient hospitalization		
No	639	53.65
Yes	552	46.35
Mental health hospitalization[a]		
No	784	67.88
Yes	371	32.12
Schizophrenia-specific hospitalization[a]		
No	833	72.56
Yes	315	27.44

[a]Numbers do not total to 1191 as some individuals are not continuously eligible.

Figure 1. Cumulative Proportion of Schizophrenia Patients Experiencing a Prescription Gap

Figure 2. Hospital Event Survivor Curves

and 435 days for schizophrenia-specific hospitalization. Survival curves showing time-to-event for the 3 outcomes are shown in Figure 2.

Model Results

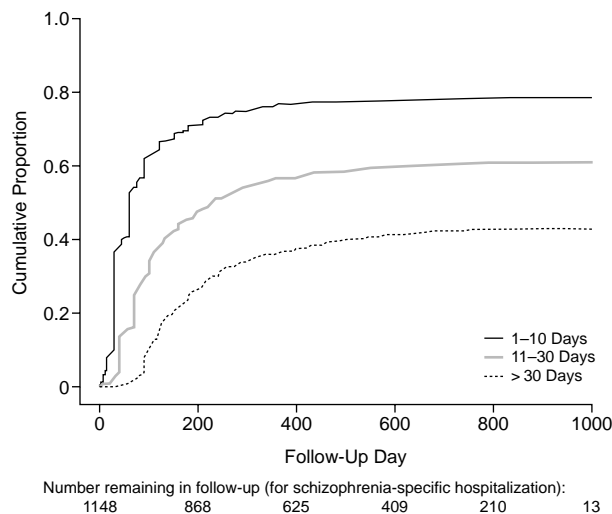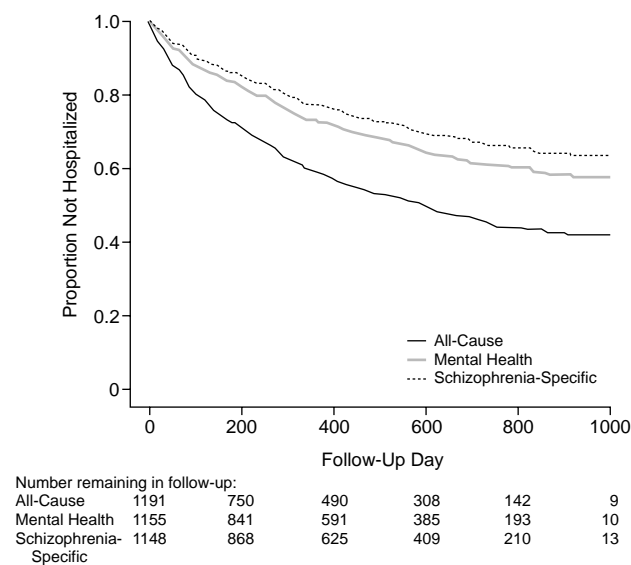The model results for all 3 hospitalization outcomes, shown in Table 2, suggest that disruptions in atypical antipsychotic adherence were strongly associated with increased hospitalization, particularly during the first 10 days without therapy. In comparison to enrollees not experiencing a gap, individuals in the first 10 days of a gap in medication use had estimated hazard ratios of 1.54 and 1.77 for mental health and schizophrenia-specific hospitalizations, respectively (p = .04 and p < .01, respectively). The estimate for all-cause hospitalization, 1.40, bordered on statistical significance (p = .06). Similarly, gaps longer than 30 days were associated with an

Table 2. Results of the Extended Cox Models of Time to First All-Cause, Mental Health, and Schizophrenia Hospitalization Among Maine and New Hampshire Medicaid Patients From January 2001 to December 2003

| | Hospitalization Type | | | | | |
| | All-Cause | | Mental Health | | Schizophrenia | |
Variable	Hazard Ratio	95% CI	Hazard Ratio	95% CI	Hazard Ratio	95% CI
Gap[a]						
≤ 10 days	1.40	0.99 to 1.98	1.54	1.02 to 2.32	1.77	1.16 to 2.71
11–30 days	1.30	0.87 to 1.93	1.06	0.64 to 1.77	1.23	0.74 to 2.06
> 30 days	1.57	1.23 to 2.01	1.60	1.21 to 2.13	1.49	1.09 to 2.02
Adherence[a]						
Switcher	1.34	0.88 to 2.05	1.59	1.02 to 2.47	1.64	1.03 to 2.61
Augmenter	1.26	0.96 to 1.65	1.57	1.18 to 2.11	1.68	1.24 to 2.29
Medicare eligible	1.31	1.10 to 1.57	1.44	1.15 to 1.79	1.53	1.20 to 1.94
Previous hospitalization	2.35	1.98 to 2.79	2.30	1.87 to 2.83	2.27	1.81 to 2.85
Number of CDS categories	1.11	1.06 to 1.15	1.05	1.00 to 1.11	1.04	0.99 to 1.10
CDS-depression	1.27	1.05 to 1.53	1.30	1.04 to 1.64	1.04	0.81 to 1.34
Male	0.82	0.69 to 0.98	0.91	0.73 to 1.12	1.09	0.86 to 1.37
Age						
35–54 y	0.78	0.64 to 0.97	0.68	0.53 to 0.86	0.74	0.57 to 0.96
55–64 y	0.68	0.50 to 0.91	0.56	0.38 to 0.81	0.67	0.45 to 0.99

[a]All hazard ratio estimates are relative to individuals not in a gap, who have not switched or augmented antipsychotic.
Abbreviation: CDS = Chronic Disease Score.

increased hazard ratio of 1.57 for all-cause, 1.60 for mental health, and 1.49 for schizophrenia-specific hospitalization (p ≤ .01 for all estimates). While the point estimates for gap days 11–30 were all greater than 1, none of these were statistically significant predictors of hospitalization. This may result from our sample having limited power due to a smaller number of follow-up days in this gap period.

The indicators for switching and augmentation were associated with an increased hazard of both mental health and schizophrenia-specific hospitalization. The time period following a switch was associated with an increased hazard ratio of hospitalization of 1.59 for mental health (p = .04) and 1.64 for schizophrenia-specific inpatient admissions (p = .04). Augmentation displayed a similar pattern, with estimates of 1.57 (p < .01) and 1.68 (p < .01), respectively. Neither switching nor augmenting were statistically significant in the all-cause model (p = .18 and .09, respectively). As hypothesized, the hazard ratios became larger as the outcome became more specific to schizophrenia, which the medication is intended to treat.

Among the covariates included in the models, the health status variables were highly correlated with hospitalization. Having a previous hospitalization was related to a more than 2-fold increase in the hazard of hospitalization across all 3 outcomes. Similarly, being dually enrolled in both Medicaid and Medicare at baseline was associated with an increase in hazard ranging from 1.31 for all-cause to 1.53 for schizophrenia-specific hospitalization. The count of Chronic Disease Score comorbidities was only related to a higher hazard of all-cause hospitalization, while the depression indicator was related to higher hazard of mental health hospitalization.

DISCUSSION

This study suggests that disruptions in medication adherence are associated with higher risk of hospitalization. The results show a clinically meaningful link between patient adherence during particular time periods—in this case as short as 10 days past a missed prescription refill—and hospitalization risk. This finding is consistent with a pharmacologic study of atypical antipsychotics demonstrating short half-lives and quick effects of treatment cessation.[21] For example, one pharmacokinetic profiling study of olanzapine suggests a mean half-life of just 33 hours in healthy individuals.[22] Thus, even short deviations in medication adherence might result in biologic responses. It is important to note that refills are likely an inexact measure of clinical adherence. For example, a missed refill might represent the first sign of a longer period of nonadherence if individuals did not finish their previous prescriptions. However, this method might be the first opportunity to observe such a change with regularly collected clinical data.

While the results are consistent across the outcomes examined, some potential limitations of our analysis should be highlighted. First, we had access to only a limited range of demographic and disease severity measures. There may be other factors which predict relapse that do not regularly appear in administrative data, such as the involvement of family members in treatment or geographic proximity to services.[23] Second, this study does not account for the role that typical antipsychotics may play in treatment adherence. However, atypical antipsychotics were much more frequently used during this period. Third, the study only follows individuals for up to 3 years, so it provides no evidence on the long-term effects of gaps in medication adherence or discontinuation.

Finally, the findings do not confirm a causal effect; in other words, we cannot conclude that these 3 adherence behaviors cause relapse. It is possible that a clinical change unrelated to adherence could both cause a failure to obtain a prescription refill and increase the hazard of subsequent hospitalization. However, there are 2 reasons to believe our findings are strongly suggestive of a causal effect. First, clinical trials provide strong evidence for the efficacy of atypical antipsychotics in preventing relapse.[24] Second, our results suggest a temporal relationship between specific predictable periods of adherence and subsequent hospitalization. This approach is an advance over previous studies, which tended to assess hospitalization and average adherence over the same period of time,[5,6] thereby violating a necessary condition for causality (i.e., that a lapse in adherence precede hospitalization). Further, our methods of tying specific periods of nonadherence to subsequent hospitalization reduced the potential influence of unmeasured confounders, such as the "healthy adherer" effect, as these would have to vary in time with adherence in order to confound the relationship of interest.[12]

The results for switching and augmentation are more likely a proxy for poor symptom control and a resulting clinical decision to change the therapeutic approach. Therefore, these findings may just signal a high-risk period related to an underlying factor such as disease severity or recent medication nonadherence. Similarly, our measure of drug-taking behavior, the days supply indicated in prescription claims, may produce misclassification. If clinicians instruct a patient to change dose or an individual skips doses, then a gap as we define it may not actually be specific enough. However, any such misclassification would most likely bias our results in the direction of no effect, as patients would appear to be in a gap when in fact they were not. Moreover, except in specific, unusual circumstances, such as when electronic treatment monitors are used to monitor patterns of therapy, data on actual medicine taking would typically be unavailable for targeting adherence interventions.[16]

Drug claims data have been suggested as a comparatively inexpensive, unobtrusive, and readily available mechanism for monitoring adherence.[5,8,25] Our findings of a strong link between short-term adherence and risk of relapse in schizophrenia suggest the possibility of testing interventions that intervene with patients at the first sign of nonadherence. In particular, Medicaid programs should consider such interventions. The benefit of this approach would hold even if the relationship between adherence and hospitalization is not fully causal, as it could potentially alert caregivers to periods of increased hospitalization risk. Additionally, adherence profiles derived from drug claims might be used by clinicians as a tool for discussing medication use with their patients.[26–29] Daily adherence measures such as those used in this study could be used to mimic the close personal attention found in community models of care credited with increasing patient adherence.[28] However, simple provision of adherence information to clinicians is insufficient to effect change. In a previous study, we found that a fax-based physician reminder at 10 days after patients failed to refill prescriptions for antidepressant medication showed no discernable impact on patient adherence.[30] The effectiveness of such monitoring in multifaceted adherence inventions remains unknown.

Relapse is very distressing to patients and families and is very expensive to the health system.[9,31] This study suggests that nonadherence to medication is related to higher risk of hospitalization in as short a period as 10 days after a missed prescription refill. Immediate action to support reinitiation of treatment early in a possible gap in therapy could potentially aid in preventing hospitalization.[32,33] The results reported here suggest that automated prescription refill data can profile medication adherence and identify periods associated with a higher hazard of hospitalization. Future research should use similar methods to assess whether these patterns of increased risk during gaps in therapy hold up for other medical conditions and should evaluate the impact of using real-time monitoring and outreach to increase patient adherence.

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