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Prospective Validation of Eight Different Adherence Measures for Use with Administrative Claims Data among Patients with Schizophrenia

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ABSTRACT

Objective: The aim of this study was to compare the predictive validity of eight different adherence measures by studying the variability explained between each measure and hospitalization episodes among Medicaid-eligible persons diagnosed with schizophrenia on antipsychotic monotherapy.

Methods: This study was a retrospective analysis of the Arkansas Medicaid administrative claims data. Continuously eligible adult schizophrenia (ICD-9-CM = 295.**) patients on antipsychotic monotherapy were identified in the recruitment period from July 2000 through April 2004. Adherence rates to antipsychotic therapy in year 1 were calculated using eight different measures identified from the literature. Univariate and multivariable logistic regression models were used to prospectively predict all-cause and mental health-related hospitalizations in the follow-up year.

Results: Adherence rates were computed for 3395 schizophrenic patients with a mean age of 42.9 years, of which 52.5% (n = 1782) were females, and 52.8% (n = 1793) were white. The proportion of days covered (PDC) and continuous measure of medication gaps measures of adherence had equal C-statistics of 0.571 in predicting both all-cause and mental health-related hospitalizations. The medication possession ratio (MPR) continuous multiple interval measure of oversupply were the second best measures with equal C-statistics of 0.568 and 0.567 for any-cause and mental health-related hospitalizations. The multivariate adjusted models had higher C-statistics but provided the same rank order results.

Conclusions: MPR and PDC were among the best predictors of any-cause and mental health-related hospitalization, and are recommended as the preferred adherence measures when a single measure is sought for use with administrative claims data for patients not on polypharmacy.

Keywords: adherence, pharmacy claims, schizophrenia, validation.

Introduction

The International Society for Pharmacoeconomics and Outcomes Research Medication Compliance and Persistence Work Group defines medication adherence as "the extent to which a patient acts in accordance with the prescribed interval and dose of a dosing regimen" [1]. Medication nonadherence is commonly associated with adverse health conditions and increased economic burden to the health-care system [2–6], and is a critical issue especially in case of chronic therapies such as schizophrenia. Adherence measures include direct and indirect techniques. Direct methods include biological assays, whereas indirect methods consist of pill counts, electronic monitors, and use of administrative database claims [7]. Indirect methods and, in particular, use of administrative data are becoming increasingly popular because they afford ease of use and are considered economical; however, there are no clear standards for measuring or calculating adherence with these indirect approaches.

Medication nonadherence rates in patients suffering from schizophrenia range from 20% to 89% based on the adherence definition used [8]. Adherence measures using pharmacy claims data have been used to predict health-care cost and utilization [9–11]. Svarstad et al. found that persons with schizophrenia with poorer adherence had higher hospitalization rates than their more adherent counterparts. Additional studies have reported similar findings in persons with schizophrenia [5,6]. Nonadherence to the prescribed treatment may account for 40% of the rehospitalizations associated with schizophrenia [8]. Thieda et al. conducted a literature review for the years 1995 through 2002 evaluating the relationship between compliance and the economic costs of schizophrenia [4]. The authors concluded that lower compliance was associated with adverse outcomes such as increased relapse rates with associated costs ranging from $10,000 to $26,000. Bearing in mind the economic outcomes associated with medication nonadherence, schizophrenia serves as a favorable condition to determine the predictive validity of various adherence measures.

Because of their usefulness in recent years, administrative claims data have been one of the most commonly used sources for calculating medication adherence. Medication adherence measured using pharmacy claims has been validated using other adherence measures such as patient reports, pill counts, questionnaires, and interviews [12–17]. Despite these validation studies, there are no standards for the mathematical calculation of adherence using claims data. A systematic review by Andrade et al. [18] identified 136 studies that employed administrative claims

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to calculate medication adherence and persistence. About 57% of the studies considered medication possession ratio (MPR) and related measures,10% used medication gaps, and 43% used switching and discontinuation in calculating medication adherence and persistence. Even among the 57% that considered MPR and related measures, the follow-up period definitions varied, ranging from a specified follow-up period (e.g., 1 year) to the period between the first and last refill. This study emphasized the lack of consensus among definitions and methods used to calculate adherence using administrative claims. Hess et al. published a study that identified 11 different adherence measures calculated using administrative claims data, and initiated the idea of standardizing adherence measures [19]. This study, however, did not empirically validate these measures.

The primary aim of this study was to prospectively validate administrative claims-based adherence measures using hospitalization as the end point for persons with schizophrenia. Medication adherence was measured in terms of adherence to monotherapy within a class of drugs prescribed for treating schizophrenia. This study sought to identify adherence measures which had the best predictive validity, in an effort to offer practitioners and researchers an empirical basis for selecting an adherence measure among eight unique measures based on administrative claims data.

Methods

To assess the predictive validity of each adherence measure, the adherence rates among schizophrenia patients were compared with hospitalization rates. Our primary hypothesis is that an increase in adherence will be associated with lower hospitalization rates. This was a prospective study where adherence was assessed in year 1 following an index prescription, and hospitalization rates were determined in the subsequent year.

The study used patient-linked administrative claims data for the Arkansas Medicaid population representing adjudicated paid claims for services rendered from January 1, 2000 through April 30, 2005. A schematic representation of the study periods is shown in Figure 1. Patients with schizophrenia were identified using the ICD-9-CM code of 295.xx (recorded in the medical and inpatient claims file) during the "enrollment period" July 1, 2000 through April 30, 2004. An "index date" defined as the date on which the first prescription for oral antipsychotic medication (conventional: fluphenazine, haloperidol, loxapine, pimozide, perphenazine, trifluoperazine, chlorpromazine, thioridazine, molindone, thiothixene; atypical: risperidone, quetiapine, olanzapine, aripiprazole, clozapine, ziprasidone) was filled by the patient in the enrollment period. Adherence rates, defined below, were computed using eight different adherence definitions for the 1-year period starting from the index date.

Subjects

The following inclusion and exclusion criteria were used to select study subjects:

1. Primary diagnosis for schizophrenia (ICD-9-CM = 295.**) [6,20] recorded in the medical and inpatient claims file during the period July 1, 2000 through April 30, 2004 (starting cohort size N = 11,587);
2. Patients with at least one prescription for oral antipsychotic medication in a 1-year period between July 1, 2000 and April 30, 2004 (N = 9025; patients excluded N = 2562);
3. Excluded patients less than 18 years of age at the index date and Qualified Medicare Beneficiaries (N = 7552; patients excluded N = 1473);
4. Continuous eligibility for the 6 months before and 24 months after the index date (N = 6344; patients excluded N = 1208);
5. At least two paid claims for an oral antipsychotic medication in a 1-year period during the period July 1, 2000 through April 30, 2004 (N = 5936; patients excluded N = 408);
6. Excluding patients taking two different oral antipsychotic medications simultaneously (N = 3971; patients excluded N = 1965);
7. Patients were required to have at least one inpatient, outpatient, pharmacy, or nursing home claim during the post-index period. This inclusion criterion was imposed to verify that patients were utilizing Medicaid benefits in the post-index period (N = 3957; patients excluded N = 14);
8. Excluding patients with a nursing home claim during the index period (final cohort size N = 3395; patients excluded = 562).

This study was approved by the Institutional Review Board at the University of Arkansas for Medical Sciences.

Variables

Measures of Medication Adherence

Medication adherence was measured in terms of adherence to monotherapy within a class of drugs prescribed for treating

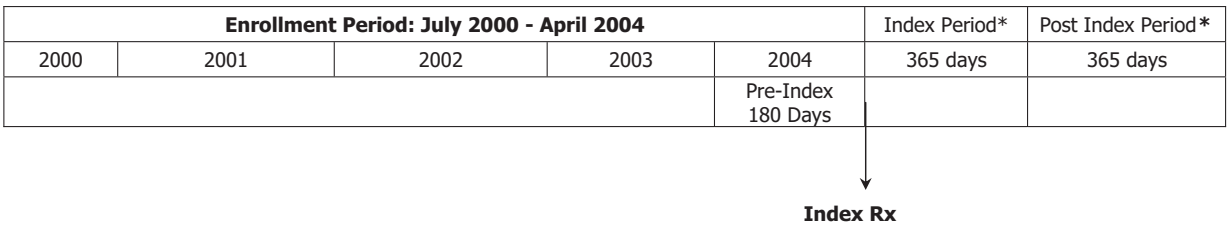

Figure 1 Description of study periods for a person diagnosed with schizophrenia.

Table 1 Mathematical formulas for the various adherence measures under evaluation

Adherence measure*	Formula
Medication possession ratio†	Number of days supply in index period/number of days in the study period (365 days)
Medication refill adherence†	[Number of days supply in index period/number of days in the study period (365)] × 100
Continuous measure of medication acquisition†	Number of days supply/total days to next fill or end of observation period (365 days)
Proportion of days covered (PDC)	[Number of days supply in index period/number of days in the study period (365)] × 100 capped at 1
Refill compliance rate†	(Number of days supply/last claim date – index date) × 100
Days-between-fills adherence rate†	1 – [(Last claim date – index date) – total days supply/last claim date – index date] × 100
Compliance ratio	Number of days supply in the index period – last days supply/last claim date – index date
Medication possession ratio, modified	[Number of days supply/(last claim date – index date + last days supply)] × 100
Continuous measure of medication gaps	Total days of treatment gaps/total days to next fill or end of observation period (365 days)
Continuous multiple interval measure of oversupply	Total days of treatment gaps (+) or surplus (–)/total days to next fill or end of observation period (365 days)
Continuous, single interval measure of medication acquisition	Days supply obtained at the beginning of the interval/days in interval

*Hess et al. Ann Pharmacotherapy 2006.
†Mathematically similar formulas for calculating adherence.

schizophrenia. Patients on two different strengths of the same drug were included in the study. Second, we allowed for non-overlapping switching based on a rationale that the patient should be on some drug that controls schizophrenia. Thus, by excluding patients on multiple antipsychotic drugs, we reduced the complexity of adherence calculations.

The 11 adherence measures that were the initial bases of adherence measures are reported in Table 1 [19]. Three of these measures—MPR, medication refill adherence, and continuous measure of medication acquisition (CMA)—have mathematically equivalent formulas, and only MPR was considered for evaluation. Similarly, days-between-fills adherence rate and refill compliance rate (RCR) yield the same adherence values, and hence, only RCR was considered for evaluation. Thus, in our study, we compared eight unique measures that have been used to measure adherence using administrative prescription claims data.

The patients were assumed to be 100% adherent to their schizophrenia medications during hospitalization admissions in the 1-year index period. Hence, we subtracted the corresponding number of days a patient was hospitalized during the index period from the denominator for all the eight adherence measures. To check if there was variation in the results, we conducted a sensitivity analysis where we calculated adherence rates without adjusting for the time patient was hospitalized in the 1-year, post-index period.

Dependent Variable

Hospitalization in the "postindex period" was defined as any inpatient admission regardless of the primary diagnosis. Mental health-related inpatient admissions were defined as any inpatient admission with a primary diagnosis with the following ICD-9-CM codes: 295.xx, 296.2x, 296.3x, 296.9x, 300.4x, 309.0x, 311.xx, 300.0x, 300.2x, 300.3x, 306.9x, 308.xx, 309.2x, 309.4x, 309.9x, 297.xx, 298.xx, 299.xx, 300.1x, 302.8x, 307.9x, 290.xx, 291.2x, 310.9x, 331.0. These ICD-9-CM diagnosis codes were adapted from a previously published study by Weiden et al. [6].

Other Covariates

Demographics. Age (calculated based on the date of birth and the index date), gender, race (whites, blacks, and others) were based on the Medicaid recipient summary file.

Previous hospitalization. A marker variable "previous hospitalization" was created and defined as any inpatient stay by the patient during the "index period."

Comorbidity assessment. A measure of comorbidity was based on the Chronic Illness and Disability Payment System developed specifically for Medicaid programs [21]. Inpatient and outpatient claims during the index period were used in calculating comorbidity scores for the patients.

Prior Cost

Prior cost which included inpatient and outpatient nondrug costs was computed by summing the cost for each patient in the 1-year index period.

Admission to rehabilitation center during the index period: covariate indicating patients admitted to rehabilitation center during the index period.

Analysis

To determine if the adherence measures are statistically different from each other, Tukey's and Bonferroni's multiple comparisons tests were used. To access the association between the adherence measures and hospitalization, we estimated Spearman's correlation coefficients and logistic regression models for each of the eight adherence measures. Reduced models including only the adherence measures and multivariable models including all the covariates were estimated. Second, we inspected odds ratios (ORs) and confidence intervals (CIs) to check if the adherence measure was of the right direction (i.e., as adherence rates increased, hospitalization rates decreased). We used C-statistics to select adherence measure that explains the most variability in hospitalization rates. The C-statistic is defined as the area under receiver operating characteristic curve [22], and the model with the highest C-statistic was considered to be the most predictive of hospitalization. C-statistics for the eight adherence measures were estimated using the univariate and multivariable logistic regression models. Second, we also inspected the ORs to identify those adherence measures most strongly associated with hospitalization rates.

A sensitivity analysis was conducted excluding patients dually eligible for Medicare benefits. This was done as a check to guard against possible hospital claims that might be missing from the Medicaid files for these dually eligible recipients. All the statistical analyses were conducted using SAS 9.1 (SAS Institute Inc., Cary, NC, USA) hosted on the server or the Windows platform.

Results

Baseline Characteristics

The baseline characteristics of the schizophrenia cohort are described in Table 2. The study cohort consisted of 3395 patients

Table 2 Baseline characteristics of schizophrenia cohort (N = 3395)

	Mean (N)	SD (%)
Age (years)	42.9	13.2
18–30	643	18.9
31–40	977	28.8
41–50	928	27.3
51–64	637	18.8
65 and above	210	6.2
Sex		
Female	1782	52.5
Male	1613	47.5
Race		
White	1793	52.8
Black	1327	39.1
Other/unknown	275	8.1
Medicare eligible	1619	47.7
Comorbidity score	2.1	1.2
Index period hospitalization	788	23.2
Post-index period hospitalization		
Any-cause hospitalization	979	28.8
Mental health–related hospitalization	616	18.1

with mean age of 42.8 years of which 52.5% (n = 1782) were female, 52.8% (n = 1793) were white, and 39% (n = 1327) were black. Approximately 47.7% (n = 1619) were also Medicare eligible; 23.2% (n = 788) of the patients had an inpatient admission during the index period. During the post-index period, 28.8% (n = 979) had an inpatient admission, and 18.1% (n = 616) had inpatient admission related to a mental health condition.

Adherence Rates

The adherence rates for the schizophrenia cohort are described in Table 3. Adherence rates were observed to be slightly higher after excluding the number of days hospitalized from the denominator in the adherence calculation. The adherence rates varied between a low of 0.724 for proportion of days covered (PDC) and a high of 0.909 for RCR for the adherence measures where higher values correspond to better adherence. The adherence values were significantly different ($P < 0.05$) from each other for all the nongap-based possible pair-wise comparisons except RCR–continuous, single interval measure of medication acquisition (CSA), compliance ratio (CR)–medication possession ratio, modified (MPRm), and PDC–MPR (data not shown). The values for the gap measures, continuous measure of medication gaps (CMG) and continuous multiple interval measure of oversupply (CMOS), were 0.276 and 0.262, respectively, and values closer to zero correspond to better adherence. MPR, PDC, CMG, and CMOS, which use the entire index period in the denominator, tended to have lower adherence values than RCR, CR, and MPRm which only consider the period between the first and last prescription in the index period.

All eight adherence measures were found to be significantly correlated with hospitalization rates. The six adherence measures MPR (–0.107, $P \leq 0.001$), PDC (–0.113, $P \leq 0.001$), RCR (–0.048, $P \leq 0.006$), CR (–0.07, $P \leq 0.001$), MPRm (–0.066, $P \leq 0.001$), and CSA (–0.040, $P \leq 0.021$) were negatively correlated with any-cause hospitalization. Whereas, the two gap-based adherence measures CMG (0.113, $P \leq 0.001$) and CMOS (0.107, $P \leq 0.001$), are positively correlated with any-cause hospitalization.

The OR estimates and C-statistics for the full and reduced models for each of the eight adherence measures considering any-cause inpatient admission and mental health-related inpatient admission are presented in Tables 4 and 5.

All adherence measures other than CSA (OR = 0.941 95% CI: 0.797–1.113) and RCR (OR = 0.833, 95% CI: 0.678–1.024) were statistically significant predictors of any-cause hospitalization in the reduced models. The reduced model OR estimates varied between 0.417 (PDC) and 0.553 (CR) for the nongap measures indicating that as the adherence rates increase, the chances of hospitalization decrease. The two gap-based measures, CMG and CMOS, had ORs of 2.398 and 2.253, respectively, which also demonstrate that improved adherence decreases the probability of hospitalization. The reduced models with PDC and CMG as adherence measures had the highest univariate C-statistics of 0.571. Mathematically, (PDC and CMG) and (MPR and CMOS) are the inverse of each other; hence, numerically similar C-statistics should be observed for these two pairs of measures. Similarly, CMG and PDC had the highest C-statistics of 0.687 in the full model; however, MPR and CMOS had slightly lower C-statistics of 0.686. Adherence measures PDC (OR = 0.498), MPR (OR = 0.519), CMG (OR = 2.007), and CMOS (OR = 1.927) had ORs farthest from 1. Similar relationships were observed for the models on mental health hospitalization where PDC and CMG had the highest C-statistics in both the reduced and full models.

Sensitivity Analysis

In predicting any-cause and mental health-related hospitalization, PDC and CMG were found to have the highest C-statistics of 0.584 and 0.579, respectively. Even after adjusting for other covariates, models containing these two measures (PDC and CMG) had the highest C-statistics of 0.686 and 0.671 in predicting any-cause and mental health-related hospitalization. Models with MPR and CMOS remained the second best predictors of any-cause and mental health-related hospitalization after adjusting for covariates. The same four measures had ORs farthest from 1.0.

Table 3 Adherence rates for the schizophrenia cohort (N = 3395)

	Adherence rates without accounting for hospitalization days		Adherence rates after excluding days hospitalized	
Adherence measure	Mean	SD	Mean	SD
Medication possession ratio	0.733	0.309	0.738	0.310
Proportion of days covered	0.720	0.295	0.724	0.295
Refill compliance rate	0.902	0.384	0.909	0.386
Compliance ratio	0.766	0.287	0.772	0.288
Medication possession ratio, modified	0.789	0.246	0.794	0.247
Continuous measure of medication gaps (CMG)*	0.280	0.295	0.276	0.295
Continuous multiple interval measure of oversupply (CMOS)*	0.267	0.309	0.262	0.310
Continuous, single interval measure of medication acquisition	0.880	0.444	0.893	0.464

*CMG and CMOS are gap measure; lower values represent better compliance.

Table 4 Comparison of odds ratios (ORs), full model, and reduced model* (any-cause hospitalization)

	Full multivariate model					Reduced univariate model				
Adherence measure	OR	95% Wald CI		Pr > chi-square	C-statistics	OR	95% Wald CI		Pr > chi-square	C-statistics
Medication possession ratio	0.519	0.398	0.677	<0.001	0.686	0.444	0.350	0.562	<0.001	0.568
Proportion of days covered	0.498	0.377	0.659	<0.001	0.687	0.417	0.326	0.534	<0.001	0.571
Refill compliance rate	0.911	0.738	1.124	0.383	0.677	0.833	0.678	1.024	0.083	0.530
Compliance ratio	0.653	0.492	0.868	0.003	0.681	0.553	0.427	0.717	<0.001	0.544
Medication possession ratio, modified	0.617	0.445	0.856	0.004	0.681	0.508	0.378	0.683	<0.001	0.542
Continuous measure of medication gaps (CMG)†	2.007	1.518	2.653	<0.001	0.687	2.398	1.873	3.071	<0.001	0.571
Continuous multiple interval measure of oversupply (CMOS)†	1.927	1.478	2.513	<0.001	0.686	2.253	1.778	2.854	<0.001	0.568
Continuous, single interval measure of medication acquisition	0.897	0.756	1.064	0.212	0.677	0.941	0.797	1.113	0.479	0.525

*Full multivariate model includes covariates—adherence measure, comorbidity score, age, gender, race, prior hospitalization, and prior cost. Reduced univariate model includes only the adherence measure.
†CMG and CMOS are gap measure; lower values represent better compliance.

Discussion

With the availability of different adherence measures that can be computed using claims data, researchers often face a dilemma in selecting an adherence measure. Our study compared the predictive validity of eight different adherence measures computed using administrative claims data for any-cause and disease-related inpatient episodes. To the knowledge of the researchers, the present study was the first of its kind to prospectively validate adherence calculated using pharmacy claims among schizophrenia patients, and provides an empirical basis for selecting adherence measures based on administrative claims.

All but three of all the possible adherence pair-wise comparisons yielded statistically different adherence values than each other, and there is a 25% difference between the most conservative measure, PDC = 0.720, and the most optimistic, RCR = 0.902, so the selection of an adherence metric can yield fairly meaningful differences. All the adherence measures (except RCR and CSA) were found to be significant predictors of inpatient admission even after adjusting for covariates such as demographic factors, prior hospitalization, comorbidity, and prior cost. Among the eight adherence measures, PDC and CMG had the highest C-statistics and OR farthest from 1, and were the best predictors of future hospitalization (any cause and mental health related). MPR and CMOS had very similar C-statistics and were the two second best predictors of any-cause and mental health-related hospitalization. Because the formula employed in calculating PDC is similar to that of MPR, the only difference being that for PDC the adherence is capped at 1; these findings are expected. Our findings suggest that oversupply or drug stockpiling has a minor impact on hospitalization. These findings were robust as PDC remained the best predictor after excluding patients eligible for Medicare benefits. Researchers can select between PDC, MPR, CMG, and CMOS in estimating adherence as the differences in discriminatory power among these four adherence measures remain relatively small. Nevertheless, we recommend using MPR or PDC for a couple of reasons. Both MPR and PDC have formulas in which better compliance corresponds to higher values, thus these two may be preferred because they provide more intuitive values. Moreover, in our previous research, we found MPR and PDC to be most predictive of hospitalizations among diabetes patients [23]. Researchers should, however, consider MPR as their primary choice in calculating adherence as it has been widely used in many pharmacy claims-based studies.

In our study, we found that adherence measures using the entire study period (365 days) as the denominators (MPR, PDC, CMG, and CMOS) were better predictors of hospitalization (univariate C-statistic range: 0.567–0.571) as compared to the adherence measures that only considered the period between first and last refill (RCR, CR, MPRm: univariate C-statistic range: 0.525–0.549). The primary reason for this might be because of the fact that if we only consider the period between first and last refills, then it does not account for early discontinuation and would overestimate adherence for persons that completely stop taking their medications. Consider a hypothetical scenario wherein a person fills three consecutive prescriptions of each 30-day supply and has a 90-day period between the first and last refills, then the RCR value will be 1.0 (RCR = 90/90), indicating perfect adherence. The MPR or PDC value for the same person would be 0.25 (MPR = 90/365). For patients with chronic conditions such as schizophrenia, it is important for these adherence

Table 5 Comparison of odds ratios (ORs), and full multivariate and reduced univariate model* (mental health hospitalization)

	Full multivariate model*					Reduced univariate model				
Adherence measure	OR	95% Wald CI		Pr > chi-square	C-statistics	OR	95% Wald CI		Pr > chi-square	C-statistics
Medication possession ratio	0.544	0.402	0.736	<0.001	0.665	0.456	0.347	0.600	<0.001	0.567
Proportion of days covered	0.522	0.380	0.717	<0.001	0.666	0.430	0.323	0.572	<0.001	0.571
Refill compliance rate	0.789	0.611	1.017	0.068	0.657	0.711	0.548	0.923	0.011	0.536
Compliance ratio	0.622	0.451	0.858	0.004	0.660	0.522	0.387	0.706	<0.001	0.549
Medication possession ratio, modified	0.594	0.411	0.859	0.006	0.660	0.484	0.344	0.681	<0.001	0.547
Continuous measure of medication gaps (CMG)†	1.916	1.396	2.632	<0.001	0.666	2.328	1.749	3.099	<0.001	0.571
Continuous multiple interval measure of oversupply (CMOS)†	1.838	1.359	2.486	<0.001	0.665	2.191	1.665	2.883	<0.001	0.567
Continuous, single interval measure of medication acquisition	0.919	0.758	1.115	0.394	0.655	0.957	0.787	1.165	0.663	0.528

*Full multivariate model includes covariates—adherence measure, comorbidity score, age, gender, race, prior hospitalization, and prior cost. Reduced univariate model includes only the adherence measure.
†CMG and CMOS are gap measure; lower values represent better compliance.

measures to account for early discontinuations, and our data support this fact. This study also affirms the importance of medication adherence in preventing future hospital utilization [3,5,8,24]. It should also be noted that MPR and PDC were not statistically different from each other and yielded similar results which reflect the same manner in which these are calculated for all values less than 1.0.

Certain limitations of this study need to be acknowledged. We calculated medication adherence using claims data, and thus the actual consumption of the medication was not estimated although medication possession is imperative for its consumption. We measured medication adherence in terms of adherence to monotherapy within a class of drugs prescribed for treating schizophrenia, but we allowed for patients taking different strengths of the same drug simultaneously and for switches between antipsychotics. Focusing on persons taking one antipsychotic at a time limits the generalizability, and the findings may not be applicable to patients on more than one concomitant therapy, which may be presumed to have greater disease severity and/or lack perceived efficacy. Unfortunately, the adherence measures we investigated do not have standardized methods for incorporating multiple concurrent medication use in the calculations, and we believe that this is an important next step in advancing adherence measures to handle these complex situations. Depending on the scope of studies, some analyses consider medication switches as new therapy starts. Our analysis adopted the perspective of measuring adherence to antipsychotics in general, but not to any one particular antipsychotic and ignored medication switches within the antipsychotic class. This perspective will yield different adherence values than those that focus on adherence to a particular antipsychotic, although the relationship between the adherence values and subsequent hospitalizations may not be greatly different. Additionally, our study design allowed for patients taking different strengths of the same drug simultaneously, thus, adherence rates may be overestimated in such patients. Several other factors, such as severity of the illness, side effects, occupational status, education level, patient support system, and side effects may affect medication adherence as well as hospitalization, were not available in the data set and were not included in the multivariable models, and if included, these additional variables may alter the adjusted relationships we report. Lastly, the C-statistics reported in the univariate models were low; none of the adherence measures alone had a C-statistic >0.60, which indicates that adherence by itself, although statistically significant, is a relatively modest factor influencing subsequent hospitalization. The full models which included prior hospitalization, comorbidity burden, and patient demographics in addition to the adherence measures had higher C-statistics greater than 0.60, but less than 0.70 which indicate that subsequent hospitalization can only be modestly predicted given the confines of an administrative data source.

In our study, we initially considered two outcome measures, hospitalization and total nonpharmacy costs for discriminating between adherence measures based on past empirical evidence which has consistently demonstrated a relationship between adherence and these two outcome measures. After our initial analysis, we found a positive correlation between the adherence measures and nonpharmacy costs, indicating that an increase in adherence was associated with increased costs which is in contrast to several studies that have found a negative correlation indicating that lower adherence was associated with increased health-care expenditures and utilization [3–6,8,25]. The positive correlation observed in our data may be because of the fact that approximately 83% of our study sample was in a rehabilitation center during the index or the postindex period. These rehabilitation centers are expensive and monitor adherence which may drive up adherence resulting in the positive association between nonpharmacy costs and adherence we observed. Given the likely endogeneity between cost and adherence in these rehabilitation centers and the fact that a very high percentage of our sample accessed these centers, we chose to not use nonpharmacy cost to discriminate between these different adherence measures. Lastly, there are other possible dependent measures such as medication augmentation or switching that may also have the potential to discriminate between adherence measures, and we encourage future research in this area.

In our literature review, we came across nonconsistent nomenclature used for adherence measures where the same term might have two different mathematical expressions or definitions [18]. For example, adherence measures such as continuous multiple refill interval measure of medication availability (CMA), medication-total (MED_TOT), are used synonymously with MPR [18,19,26,27]. Conversely, we also found that different terms have the same mathematical expression or definition [18,28–33]. Because the objective of our study was to validate the measures, we adopted the nomenclature and formulas used by Hess et al. in their study [19]. Secondly, our adherence definitions were based on the most recent published literature [19] at the time this study was undertaken, and we acknowledge that newer adherence definitions may have evolved. One of the adherence measures, PDC, has been defined differently than defined in this report, and the alternative definition for PDC should be considered [34]. The PDC definition in our paper may alternatively be described as a "capped" MPR or MPR modified measure. Because our study provides the precise formulas for the adherence measures, we suggest that future researchers and practitioners consider using these definitions, except for PDC, and names when describing adherence measures in the future.

Conclusion

Significant associations were observed between six different measures of medication adherence any-cause and disease-specific hospitalization rates among patients with schizophrenia. Among schizophrenia patients not prescribed polypharmacy, we found that the PDC, MPR, CMOS, and CMG were the best predictors of any-cause and mental health-related hospitalization as compared to other adherence measures. Overall adherence measures considering an index period of 365 days as the denominator were better predictors of subsequent hospitalization as compared to adherence measures that only considered the period between the first and last refills. The MPR and PDC provide similar intuitively appealing adherence values, where better adherence corresponds to higher values, and had the highest predictive validity for subsequent hospitalizations. Ideally, persons should explore a range of possible metrics to measure adherence, but in instances when only a single adherence calculation is sought, persons should first consider these measures when calculating adherence from administrative claims data for persons with schizophrenia. Our recommendations are based on the ability of the adherence measures to predict one outcome—hospitalization. Additional studies are warranted to measure the predictive ability of adherence measures on other potential outcomes.

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