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ORIGINAL ARTICLE

Good and poor adherence: optimal cut-point for adherence measures using administrative claims data

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ABSTRACT

Objective: To identify the adherence value cut-off point that optimally stratifies good versus poor compliers using administratively derived adherence measures, the medication possession ratio (MPR) and the proportion of days covered (PDC) using hospitalization episode as the primary outcome among Medicaid eligible persons diagnosed with schizophrenia, diabetes, hypertension, congestive heart failure (CHF), or hyperlipidemia.

Research design and methods: This was a retrospective analysis of Arkansas Medicaid administrative claims data. Patients $\geq$18 years old had to have at least one ICD-9-CM code for the study diseases during the recruitment period July 2000 through April 2004 and be continuously eligible for 6 months prior and 24 months after their first prescription for the target condition. Adherence rates to disease-specific drug therapy were assessed during 1 year using MPR and PDC.

Main outcome measure and analysis scheme: The primary outcome measure was any-cause and disease-related hospitalization. Univariate logistic regression models were used to predict hospitalizations. The optimum adherence value was based on the adherence value that corresponded to the upper most left point of the ROC curve corresponding to the maximum specificity and sensitivity.

Results: The optimal cut-off adherence value for the MPR and PDC in predicting any-cause hospitalization varied between 0.63 and 0.89 across the five cohorts. In predicting disease-specific hospitalization across the five cohorts, the optimal cut-off adherence values ranged from 0.58 to 0.85.

Conclusions: This study provided an initial empirical basis for selecting 0.80 as a reasonable cut-off point that stratifies adherent and non-adherent patients based on predicting subsequent hospitalization across several highly prevalent chronic diseases. This cut-off point has been widely used in previous research and our findings suggest that it may be valid in these conditions; it is based on a single outcome measure, and additional research using these methods to identify adherence thresholds using other outcome metrics such as laboratory or physiologic measures, which may be more strongly related to adherence, is warranted.

Introduction

In recent years, administrative claims data has emerged as an important resource in calculating medication adherence. The International Society for Pharmacoeconomics and Outcomes Research (ISPOR) 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]. The significance of administrative claims data becomes apparent on account of its easy accessibility and the ability to provide information on large populations in a real-world setting. Medication adherence measured using claims data has been used for a variety of purposes such as in developing

interventions to improve prescribing quality, to inform clinicians about high-risk patient groups, and to study the impact of medication non-adherence on clinical outcomes such as blood pressure control, hemoglobin A_{1c}, and LDL cholesterol[2–6]. For example, a recent study by Woltmann and colleagues evaluated the importance of a commonly used adherence measure, the medication possession ratio (MPR) as a screening tool to identify at-risk patients with severe mental illness[3]. The authors concluded that the MPR can be a useful screening tool to identify patients in need of assistance with medication adherence and design interventions accordingly. In addition, medication adherence studied using administrative claims data has been commonly used to predict healthcare costs and utilization[7–13]. Thus there exist a multitude of applications of medication adherence measured using administrative claims.

Even though medication adherence has a broad scope, researchers are often faced with the dilemma regarding the optimum level of adherence required to achieve their treatment objective. Traditionally, medication adherence is dichotomized using a cut-off value (e.g., >80%). This dichotomy results in patients being classified into adherent and non-adherent groups. For example in chronic conditions such as diabetes, schizophrenia, hypertension, hyperlipidemia, it has often been reported that a therapy adherence rate of 80% or greater is associated with lower healthcare utilization and cost[3,7,10,14]. This dichotomization of a continuous measure to identify good and poor compliers should be undertaken cautiously unless the cut-off point has been validated[2,15]. It also needs to be recognized that in some conditions, consumption of less than the recommended amount of medication is sufficient to attain the goals of treatment[14]. Similarly, the ISPOR checklist recommends that, during calculation of medication adherence using a retrospective database, continuous data should not be converted into categorical unless empirical evidence exists for such a cut-off point[16]. In a few cases, such cut-off values have been derived empirically. For example, in hypertension it has been observed that consumption of at least 80% of antihypertensive medication was associated with adequate blood pressure control[14]. Such threshold values are not available for other chronic disease conditions of clinical importance and thus there exists a need to identify an optimal adherence cut-off point that has been empirically validated.

The authors have previously identified the adherence measures that were the best predictors of subsequent hospitalization among five chronic disease states: schizophrenia, diabetes, hypertension, hyperlipidemia and congestive heart failure (CHF)[17–19]. Of the eight adherence measures studied, medication possession ratio (MPR) and proportion of days covered (PDC) were identified as the most predictive of a hospitalization episode. Thus, the objective of this study is to identify the ideal threshold adherence value for the adherence measures MPR and PDC that best stratifies adherers and non-adherers using subsequent hospitalization as the outcome measure. The availability of such a cut-off adherence value should enable clinicians to determine the optimum medication consumption necessary to meaningfully classify adherent and non-adherent patients based on future hospitalization risk which is often desired in clinical and research settings.

Methods

This study was a retrospective analysis of the Arkansas Medicaid administrative claims data. Patients were included in the study by first identifying persons diagnosed with the target conditions (identified using the ICD-9-CM codes recorded in the medical and inpatient claims file – Table 1) during the 'enrollment period' July 1, 2000 through April 30, 2004. An 'index date' was defined as the date on which the first prescription for the target condition was filled by the patient in the enrollment period occurring on or after a code for the target conditions were recorded. This study utilized a longitudinal prospective design, where adherence rates were computed in the 1-year period starting from the index date (i.e., 'index period') and hospitalization rates were assessed the following year (i.e., 'post-index period'). C-statistics were used to evaluate predictive performance of the adherence measures. For the preferred adherence measures (i.e., MPR and PDC), the optimum adherence value was determined by identifying the adherence value that corresponded to the upper most left point of the receiver operating characteristic (ROC) curve which is associated with optimum specificity and sensitivity.

Table 1. *ICD-9-CM codes considered for patient identification*

Target condition	ICD-9-CM codes for patient identification[11,26–30]
Schizophrenia	295.xx
Diabetes	250.0x – 250.9x, where x = 0 or 2
Hypertension	401.xx– 405.xx
Hyperlipidemia	272.x
Congestive heart failure (CHF)	398.91, 402.01, 402.11, 402.91, 404.01, 404.03, 404.11, 404.13, 404.91, 404.93, 428.xx

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Subjects

The following inclusion and exclusion criteria were used to select the study cohorts. Subjects could enter into more than one disease cohort if they met all the inclusion and exclusion criteria for each condition.

Inclusion criteria

- Diagnosis for target conditions based on their respective ICD-9-CM code(s) recorded in the medical and inpatient claims file during the period July 1, 2000 through April 30, 2004
- At least two paid claims for a medication prescribed for the target condition in a 1-year period between July 1, 2000 through April 30, 2004 (Table 2)
- Age 18 years or older at the index date
- Continuous eligibility for the 6 months before and 24 months after the index date
- 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.

Exclusion criteria

- Patients identified as qualified Medicare beneficiaries
- Patients taking two different drug products (within each drug class) simultaneously
- Excluding patients with a nursing home claim during the index period

Medication adherence was measured in terms of adherence to monotherapy within a class of drugs prescribed for treating the target condition although, patients were allowed to be on two different strengths of the same drug and were permitted to switch drugs within the target condition medications, however, the switching could not be overlapping. This was done with a rationale that the patient should be on some drug that controls the disease, but we were not interested in describing the adherence to any one drug. Drug classes outside the target condition were not considered in the adherence calculations. For example, diabetic agents were not considered when calculating adherence to CHF medications. In order to have tractable adherence calculations, this study focused on monotherapy patients and excluded patients simultaneously on two or more different drug products. This study was approved by the institutional review board at the University of Arkansas for Medical Sciences.

Variables

Measures of medication adherence

The medication possession ratio (MPR) was defined as the cumulative number of days supplied in the index year divided by the number of days the patient is ambulatory (not hospitalized) in the index year.

Table 2. *ICD-9-CM codes used for identifying disease specific hospitalizations and drug classes used for patient identification*

Target condition	Target condition related hospitalization ICD-9-CM codes[11,30,31]	Drug classes
Schizophrenia	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.	Atypical and Conventional Antipsychotics
Diabetes	250.xx, 357.2, 362.0x, 366.41, 648.0	Thiazolidinedione, sulfonylureas, meglitinides, biguanides, α-glucosidase inhibitors
Hypertension	401.xx–405.xx, 272.x, 410.xx–417.xx, 425.x, 428.xx, 429.0–429.3, 433.xx–438.xx, 440.x, 444.xx	β-Blockers, ACE inhibitors, calcium channel blockers, angiotensin receptor blockers, diuretics, central α_2-agonist, adrenergic antagonist, vasodilators, aldosterone receptor antagonists
Hyperlipidemia	272.x, 401.xx–405.xx, 410.xx–417.xx, 425.x, 428.xx, 429.0–429.3, 433.xx–438.xx, 440.x, 444.xx	HMG CoA reductase inhibitors (statins) fibrates, niacin bile salt sequestrants
Congestive heart failure (CHF)	398.91, 402.01, 401.91, 402.11, 402.91, 404.01, 404.03, 404.11, 404.13, 404.91, 404.93, 428.0, 428.1, 428.9, 4251, 4254, 4255, 4257	ACE inhibitors, aldosterone receptor antagonists, vasodilators, β-blockers, diuretics, digitalis glycosides, angiotensin receptor blockers

The proportion of days covered (PDC) was defined using the definition published by Hess *et al.*[20] and shares the same formula as the MPR except values greater than 1.0 were capped or truncated at 1.0.

Dependent variable

Two different hospitalization measures were used: any-cause hospitalization and disease-specific hospitalization. Hospitalization in the 'post-index period' (1-year period after the index period) was defined as any inpatient admission regardless of the primary diagnosis. Target condition related inpatient admissions were defined by inpatient admissions with an ICD-9-CM code for the target conditions (Table 2) coded as the primary diagnosis.

Analysis

To explore the relationship between the adherence measures and subsequent hospitalization, single variable logistic regression models were estimated that only included the individual adherence values as the covariate. A multivariable logistic model was used to identify the ideal adherence measure and these methods and results are described elsewhere[17–19]. Selection of the most predictive adherence measure was based on C-statistic and the strength of the odds ratio. The C-statistic is defined as the area under receiver operating characteristic (ROC) curve and its value ranges from 0.5 (no predictive power) to 1 (perfect prediction)[21,22].

For each of the adherence measures, a cut-off value was determined based on a ROC curve plot[23] for the outcome hospitalization. The cut-off value signifies an adherence value associated with the minimum distance from the ROC curve to the upper left-hand corner of the sensitivity axis. This is the point of optimum sensitivity and specificity. This point will result in the lowest number of overall errors, i.e. minimum false negatives and false positives. The adherence value associated with the minimum distance was termed the 'cut-off value'. All the statistical analyses were conducted using SAS 9.1 (SAS Institute Inc., Cary, NC, USA) hosted on the server or the Windows platform. Stata 9.1 was used to obtain the cut-off values.

Results

The number of subjects in each cohort was: schizophrenia ($n = 3395$), diabetes ($n = 4943$), hypertension ($n = 16\,398$), hyperlipidemia ($n = 7925$), CHF ($n = 5251$). The mean ages of the five cohorts varied from 42.8 to 68.3 years (Table 3). The study sample comprised over 73% females for the diabetes, hypertension, hyperlipidemia and CHF cohorts and over 50% were whites across all five cohorts. Any-cause hospitalization rates during the index and post-index period were in the range of 23–29% for the schizophrenia, diabetes, hypertension, and hyperlipidemia cohort. For the CHF cohort, hospitalization rates were considerably higher for the index (41.0%, $n = 2154$) and post-index (48.3%, $n = 2537$) period. The adherence rates for the study cohorts are presented in Table 4.

For all five cohorts, the C-statistic and cut-off values, for the preferred adherence measures predicting subsequent hospitalizations are described in Tables 5 and 6. The C-statistics for the all cause and disease-specific hospitalizations ranged from 0.511 to 0.574 and sensitivity and specificity values ranged from 0.489 to 0.634. The optimal cut-off adherence value in predicting any-cause hospitalization varied between 0.63 and 0.89 across the five cohorts for the MPR and PDC. In predicting disease-specific hospitalization across the five cohorts, the cut-off adherence values for the MPR and PDC ranged from 0.58 to 0.85.

Discussion

To the knowledge of the authors, this was the first study that identified an empirically derived cut-off adherence value across a broad array of disease states treated with chronic therapy using administrative claims data. These cut-off values will assist in classifying patients into adherent and non-adherent groups and predicting their subsequent risk of hospitalization. For example, in predicting any-cause hospitalization within the schizophrenia cohort, the cut-off value for the preferred measure MPR and PDC was found to be 0.80. Thus, a patient with an adherence value below 0.80 can be classified into the non-adherent group and is at an increased risk of hospitalization. The results of this research find application in identifying patients in need of interventions to improve adherence. The cut-off adherence values can be considered as a preliminary screening tool to identify patients with a higher risk of hospitalization based on the adherence rates.

For the five disease states under consideration, it has been commonly cited in the literature that adherence rates above 80% are associated with lower rates of hospitalization[3,7–10,12]. There exists some empirical evidence in hypertension, that consumption of at least 80% of antihypertensive medication was associated with adequate blood pressure control[14]. But for the other disease states under consideration, the authors did not find any empirical evidence that suggest 80% to be the ideal cut-off adherence value – even so,

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Table 3. *Baseline characteristic of study population*

	Schizophrenia $n=3395$		Diabetes $n=4943$		Hypertension $n=16398$		Hyperlipidemia $n=7925$		CHF* $n=5251$	
	Mean (*n*)	SD (%)	Mean (*n*)	SD (%)	Mean (*n*)	SD (%)	Mean (*n*)	SD (%)	Mean (*n*)	SD (%)
Age	42.9	13.2	60.9	15.9	59.62	17.5	59.6	14.0	68.4	15.7
Age 18–30	643	18.9	159	3.2	815	5.0	173	2.2	67	1.3
Age 31–40	977	28.8	423	8.6	1805	11.0	584	7.4	199	3.8
Age 41–50	928	27.3	831	16.8	2917	17.8	1463	18.5	528	10.1
Age 51–64	637	18.8	1444	29.2	4355	26.6	2832	35.7	1282	24.4
Age 65 and above	210	6.2	2086	42.2	6506	39.7	2873	36.3	3175	60.5
Sex										
Female	1782	52.5	3744	75.7	12207	74.4	5851	73.8	4161	79.2
Male	1613	47.5	1199	24.3	4191	25.6	2074	26.2	1090	20.8
Race										
White	1793	52.8	2611	52.8	8450	51.5	4912	61.9	2907	55.4
Black	1327	39.1	1693	34.3	5963	36.4	1940	24.5	1661	31.6
Other/unknown	275	8.1	639	12.9	1985	12.1	1073	13.5	683	13.0
Medicare eligible	1619	47.7	3307	66.9	10672	65.1	5008	63.2	4204	80.1
Comorbidity score	2.1	1.2	2.1	1.4	1.8	1.4	1.9	1.4	2.6	2.0
Index period hospitalization	788	23.2	1190	24.1	3757	22.9	1995	25.2	2154	41.0
Post-index period hospitalization										
Any-cause hospitalization	979	28.8	1362	27.6	4414	26.9	2140	27.0	2537	48.3
Disease-related hospitalization	616	18.1	295	5.9	1336	8.2	847	10.7	665	12.7

*CHF, congestive heart failure

Table 4. *Adherence rates for the study cohorts*

Adherence measure	Schizophrenia		Diabetes		Hypertension		Hyperlipidemia		CHF*	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Medication possession ratio (MPR)	0.738	0.310	0.763	0.279	0.712	0.304	0.731	0.295	0.619	0.304
Proportion of days covered (PDC)	0.724	0.295	0.751	0.266	0.702	0.293	0.722	0.284	0.612	0.295

*CHF, congestive heart failure

Table 5. *Preferred adherence measures in predicting any-cause hospitalization*

Disease state	Preferred adherence measures	C-statistic	Cut-off value*	Specificity	Sensitivity	Distance†	Odds ratio‡	*p*-value
Schizophrenia	MPR	0.568	0.80	0.592	0.529	0.623	0.444	<0.001
	PDC	0.571	0.80	0.592	0.529	0.623	0.417	<0.001
Diabetes	MPR	0.542	0.89	0.493	0.586	0.655	0.590	<0.001
	PDC	0.544	0.89	0.493	0.586	0.655	0.581	<0.001
Hypertension	MPR	0.542	0.82	0.521	0.555	0.654	0.607	<0.001
	PDC	0.541	0.82	0.521	0.555	0.654	0.600	<0.001
Hyperlipidemia	MPR	0.518	0.81	0.539	0.497	0.682	0.785	0.005
	PDC	0.518	0.81	0.539	0.497	0.682	0.777	0.004
CHF¶	MPR	0.531	0.63	0.514	0.544	0.666	0.681	<0.001
	PDC	0.530	0.63	0.514	0.544	0.666	0.678	<0.001

MPR, medication possession ratio; PDC, proportion of days covered; CHF, congestive heart failure
*The cut-off value signifies an adherence value associated with the minimum distance
†Minimum distance from the receiver operating characteristic curve to the upper left-hand corner of the sensitivity axis
‡Odds ratio estimates (and corresponding *p*-values) for the outcome measure any-cause hospitalization

Table 6. *Preferred adherence measures in predicting disease-related hospitalization*

Disease state	Preferred adherence measures	C-statistic	Cut-off value*	Specificity	Sensitivity	Distance†	Odds ratio‡	*p*-value
Schizophrenia	MPR	0.567	0.76	0.573	0.541	0.627	0.456	<0.001
	PDC	0.571	0.76	0.573	0.541	0.627	0.430	<0.001
Diabetes	MPR	0.570	0.85	0.489	0.634	0.629	0.449	<0.001
	PDC	0.574	0.85	0.489	0.634	0.629	0.434	<0.001
Hypertension	MPR	0.528	0.82	0.505	0.546	0.672	0.712	<0.001
	PDC	0.526	0.82	0.505	0.546	0.672	0.708	<0.001
Hyperlipidemia	MPR	0.543	0.81	0.538	0.543	0.650	0.591	<0.001
	PDC	0.543	0.81	0.538	0.543	0.650	0.581	<0.001
CHF¶	MPR	0.511	0.58	0.527	0.522	0.672	0.856	0.254
	PDC	0.512	0.58	0.527	0.522	0.672	0.855	0.265

MPR, medication possession ratio; PDC: proportion of days covered; CHF, congestive heart failure
*The cut-off value signifies an adherence value associated with the minimum distance
†Minimum distance from the receiver operating characteristic curve to the upper left-hand corner of the sensitivity axis
‡Odds ratio estimates (and corresponding *p*-values) for the outcome measure disease-related hospitalization

researchers often cite this value. Excluding the cut-off adherence values for the CHF cohort, the cut-off values varied from 76% to 89% in predicting any-cause and disease-specific hospitalizations. These findings are in accordance with the commonly cited cut-off adherence value of 80%, thus validating it in monotherapy for schizophrenia, hypertension, or hyperlipidemia. Slightly higher cut-points of 0.89 and 0.84 were observed for diabetes patients and it is unclear exactly how much loss in precision would be made rounding

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the cut-point to 0.80, but the rounding would unlikely to have profound effect on the sensitivity/specificity reported.

Certain limitations of this study need to be mentioned. We identified the cut-off adherence value based on the outcome hospitalization, thus, this value may differ for other outcome measures. The adherence measures were all significantly related to subsequent hospitalization, however, the C-statistics and sensitivity and specificity measures for these univariate models were all less than 0.60, indicating that adherence, by itself, is only a modest predictor of subsequent hospitalizations. Clearly there are many factors that influence an individual's likelihood of requiring subsequent hospitalization and adherence is only one small factor and, correspondingly, these univariate adherence models could not be used to reliably predict subsequent hospitalization, however, they do provide insights as to at which cut-point sensitivity and specificity are maximized. This work represents an important first step and not an end in identifying the ideal thresholds for classifying adherent and non-adherent patients. We encourage future work to explore the relationships between adherence, the ideal cut-point(s), and other outcome metrics that may be more tightly correlated with adherence, such as laboratory or physiological markers, which were not available to us with these data.

The strategy adopted for this analysis was to measure adherence to a class of drugs used in treating the target condition and not to any one drug in particular. In addition, medication switches within a particular drug class were ignored and patients taking more than one target medication (polypharmacy) concurrently excluded. By excluding persons on multiple target medications concurrently, the generalizability of these findings was limited to those patients who can manage their chronic condition with singled therapy which likely reflects a less severe population. Also, the cut-off values are for adherence to a class of medications, not to any particular medication and these values may change when adherence to any one specific drug is considered. In this study the adherence cut-off value for the CHF cohort was relatively low compared to other disease conditions studied which suggests patients may require lower adherence to these medications than the other chronic disease states; however, one should be extremely cautious adopting this potential finding. The reasons for this are unclear but it should be noted that adherence was a less influential predictor of hospitalization than for nearly all the other conditions studied which decreases the confidence one might have in using this value as a cut-point. Lastly, as a point of nomenclature, the PDC definition used in this study was published by Hess *et al*. in 2006[20] (Table 7); however, there are alternative definitions for the PDC[24]. Also, others have referred to the definition of the PDC used in this study as the truncated MPR[25].

Table 7. *Mathematical formulas for the two adherence measures considered for the study*

Adherence measure[20]	Formula
Medication possession ratio (MPR)	No. of days supply in index period/No. of days in the study period (365 days)
Proportion of days covered(PDC)	[No. of days supply in index period/No. of days in the study period (365)] × 100 capped at 1

Conclusion

This study provided an empirical basis for selecting 0.80 as a reasonable cut-off value that stratifies adherent and non-adherent patients based on predicting subsequent hospitalization in patients treated with monotherapy for schizophrenia, hypertension, or hyperlipidemia. Slightly higher cut-off values of 0.84 and 0.89 were observed for the anti-diabetic agents and lower cut-points were observed for CHF treatments. The 0.80 cut-off value has been widely used in previous research and our findings suggest that this cut-off value may be a valid one based on the risk of subsequent hospitalizations across a broad array of chronic diseases. However additional research using these methods to identify adherence thresholds using other outcome metrics, such as laboratory or physiologic measures which may be more strongly related to adherence, is warranted. Availability of such a cut-off adherence value would be useful for researchers and clinicians, to categorize adherent and non-adherent persons, and in estimating their risk of hospitalization.

Transparency

Declaration of funding
This study was not funded by any source.

Declaration of financial/other relationships
S.K. has disclosed that he is now an employee of RTI Health Solutions, Research Triangle Park, NC, USA. This study was not supported by RTI, and S.K. was not an employee at the time the study was conducted. The other authors have disclosed that they have no relevant financial relationships.

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