The Cost of Adherence Mismeasurement in Serious Mental Illness: A Claims-Based Analysis

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ABSTRACT

OBJECTIVES: To quantify how adherence mismeasurement affects the estimated impact of adherence on inpatient costs among patients with serious mental illness (SMI).

STUDY DESIGN: Proportion of days covered (PDC) is a common claims-based measure of medication adherence. Because PDC does not measure medication ingestion, however, it may inaccurately measure adherence. We derived a formula to correct the bias that occurs in adherence-utilization studies resulting from errors in claims-based measures of adherence.

METHODS: We conducted a literature review to identify the correlation between gold-standard and claims-based adherence measures. We derived a bias-correction methodology to address claims-based medication adherence measurement error. We then applied this methodology to a case study of patients with SMI who initiated atypical antipsychotics in 2 large claims databases.

RESULTS: Our literature review identified 6 studies of interest. The 4 most relevant ones measured correlations between 0.38 and 0.91. Our preferred estimate implies that the effect of adherence on inpatient spending estimated from claims data would understate the true effect by a factor of 5.3, if there were no other sources of bias. Although our procedure corrects for measurement error, such error also may amplify or mitigate other potential biases. For instance, if adherent patients are healthier than nonadherent ones, measurement error makes the resulting bias worse. On the other hand, if adherent patients are sicker, measurement error mitigates the other bias.

CONCLUSIONS: Measurement error due to claims-based adherence measures is worth addressing, alongside other more widely emphasized sources of bias in inference.

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Nonadherence to medication is a prevalent and burdensome problem among patients with serious mental illness (SMI).[1] Estimates of adherence to antipsychotics among patients with schizophrenia-spectrum disorders, for instance, range from 47% to 95%.[2] The consequences of poor adherence include suboptimal health outcomes and higher avoidable healthcare costs.[3,4] In patients with schizophrenia, medication nonadherence impedes recovery,[5-7] increases the risk of hospitalization,[6,8-12] and extends the length of in-hospital stays.[6,11] Overall, hospitalizations due to medication nonadherence have been estimated to cost more than $100 billion annually in the United States,[13] and hospitalization costs due to antipsychotic nonadherence specifically have been estimated at $1.5 billion annually.[14]

CMS includes medication adherence as a rating measure when determining healthcare quality.[15] A common method to indirectly assess adherence is the proportion of days covered (PDC),[16] which typically uses prescription claims data and is calculated as the proportion of days in the measurement period, usually 1 year, for which the patient has medication on hand. The International Society for Pharmacoeconomics and Outcomes Research (ISPOR) has determined that PDC is one of the preferred methods to calculate medication adherence.[17] PDC also is used to measure adherence to antipsychotic medications as part of the Healthcare Effectiveness Data and Information Set quality measures.[18]

Although PDC is widely used, it suffers from 2 key shortcomings. First, PDC underestimates adherence when patients pay cash for medication or use other coverage options that fail to result in a recorded insurance claim. Second, PDC overstates adherence when patients purchase but do not take a given medication. New technologies, such as electronic pillboxes, smart caps, or ingestible sensors, may provide more accurate adherence measurements, but currently, payers and providers rarely use these technologies to monitor adherence.

Neither the magnitude nor the direction of the bias associated with PDC adherence estimates are widely discussed or incorporat-

ed into adherence analyses. This study aimed to quantify how adherence mismeasurement affects the estimated impact of adherence on inpatient costs among patients with SMI.

TAKEAWAY POINTS

Using pharmacy claims data on patients with serious mental illness (SMI), this study demonstrates that increased medication adherence correlates with lower inpatient costs. A bias-correction formula was used to show that measurement error in claims-based adherence measures results in the effects of adherence being underestimated by a factor of 5.3.

- Medication nonadherence is a burdensome problem in SMI, substantially contributing to healthcare costs.
- Few studies address errors in adherence measurement, which can introduce bias when estimating the impact of adherence on inpatient costs.
- Using a reliable estimate of the correlation between true adherence and claims-based adherence can identify the effects of measurement error on the estimated relationship between adherence and cost.

METHODS

Our methodology relies on a 3-step approach to estimate the potential impact of measurement error on inpatient spending. We mathematically derived a formula for a bias-correction factor. As this factor depends principally on the link between true and measured adherence, we next conducted a review of the literature to identify studies that measured the relationship between a "gold standard" measure of adherence (eg, Medication Event Monitoring System [MEMS] caps, electronic pill counts) and adherence measured in claims data. Finally, we applied the bias-correction factor to a case study of patients with SMI who initiated therapy with an atypical antipsychotic.

Bias Derivation

Consider the case where a researcher wants to measure the relationship between patient adherence and inpatient spending. One commonly used approach is an ordinary least squares (OLS) regression, such as the following:

$$Y_i=\beta_0+\beta_1 PDC_i+\mathrm{W}_i'\,\gamma+u$$

In this case, the dependent variable Y_i represents inpatient spending for patient i, PDC_i represents patient adherence to atypical antipsychotics, and the vector W_i' contains other patient covariates of interest. The coefficient on adherence, β_1, is the primary parameter of interest.

Mismeasurement in PDC biases the estimated effect of adherence on inpatient spending (ie, $\widehat{\beta_1}$) toward 0. However, the true effect of adherence on inpatient costs can be derived if the relationship between measured adherence in claims data and true adherence is known. As shown in **eAppendix 1** (eAppendices available at **ajmc.com**), one can correct for measurement error bias using the following formulation:

$$\beta_1 = \widehat{\beta_1}\ \frac{1\text{-}R^2_{PDC_i,\mathrm{W_i}}}{\rho^2\text{-}R^2_{PDC_i,\mathrm{W_i}}}$$

where β_1 is the true effect of adherence on inpatient spending after adjusting for adherence mismeasurement, $\widehat{\beta_1}$ is the OLS estimator from the regression in equation 1, and $(1\text{-}R^2_{PDC_i,\mathrm{W_i}})/(\rho^2\text{-}R^2_{PDC_i,\mathrm{W_i}})$ is the correction factor for the mismeasurement in PDC_i. The term $R^2_{PDC_i,\mathrm{X_i}}$ is the R-squared value of linear regression of measured adherence (PDC_i) on all other patient covariates (W_i), and ρ^2 is the square of the correlation between measured and true adherence.

The true effect of adherence is feasible to estimate, but problematic. First, one must assume that there cannot be any unobserved patient characteristics that affect both medication adherence and inpatient spending. For instance, patients with less severe forms of SMI may be more likely to be adherent to their medication and have lower inpatient costs.[19,20] To address this, we derived the bias that would remain in the case where medication adherence was an endogenous variable in **eAppendix 1**. The formula we derived fully addresses the bias due to measurement error, even when adherence is endogenous, so that researchers will recover the same parameter that would have been estimated if they had had access to correctly measured adherence. To be clear, our approach does not simultaneously address the endogeneity itself; rather, it represents a full solution to the problem of measurement error in adherence due to the use of claims data.

Second, one needs a reliable estimate of the correlation between true medication adherence and claims-based adherence. The following section describes our review of the literature that was used to identify this parameter.

Literature Review

A targeted literature review was conducted in Google Scholar and PubMed to identify estimates of the relationship between gold-standard adherence measures and claims-based adherence measures. The search combined free text and medical subject headings (MeSHs; in PubMed only) that describe various measures of adherence (MEMS caps, direct observation, PDC, medication possession ration, self-report, prescription claims, lab tests, pill count, and physician estimate) and the search term "adherence accuracy." Searches were conducted without disease specification, with the term "schizophrenia," and with the term "serious mental illness." After reviewing the results of this initial search, the search was conducted again with other central nervous system diseases, specifically multiple sclerosis, Alzheimer's disease, and Parkinson's disease. A maximum of 50 titles were screened

in each search or until titles were no longer generally relevant to the research questions.

Abstracts were screened from relevant titles, which were defined as papers that discussed or compared multiple measures of medication adherence. Titles were not relevant if they indicated an intervention to improve adherence, factors influencing adherence, or outcomes associated with adherence or nonadherence, without language suggesting relevance. Titles that were non-English, nonhuman, and did not focus on schizophrenia or another SMI were also not investigated. Full texts were assessed if their abstracts included adherence measures collected using different methodologies and these data were explicitly compared in the results or conclusions sections. Abstracts and full texts were not identified or screened more than once if they appeared as results from multiple searches or were duplicated in databases. Additional citations were identified through previous literature searches, forward reference searches of each manuscript, and the references used in each manuscript. A complete description of the search terms used, number of full texts, abstracts, and articles reviewed is contained in **eAppendix 2**.

Empirical Analysis Case Study

We used the Truven Health Analytics MarketScan (MarketScan) Commercial Claims and Encounters Database and the Medicaid Multi-State Database from October 1, 2007 through December 31, 2013 to identify patients with SMI. The commercial database included medical and pharmacy claims for individuals and their dependents who were covered by employer-sponsored private health insurance. The Medicaid database included medical and pharmacy claims of Medicaid beneficiaries from 11 deidentified but geographically dispersed states. We limited the sample to individuals aged 18 or older who had at least 1 inpatient or 2 outpatient claims with a diagnosis code for schizophrenia (*International Classification of Diseases, Ninth Revision, Clinical Modification* [*ICD-9-CM*] diagnosis code: 295.x), bipolar disorder (*ICD-9-CM* diagnosis code: 296.0x–296.1x, 296.4x–296.8x), or major depressive disorder (*ICD-9-CM* diagnosis code: 296.2x–296.3x, 311.x).

To measure adherence and healthcare utilization among patients initiating therapy, patients were required to have a new prescription for an antipsychotic and to be continuously enrolled for 6 or more months before and 12 or more months after the date they filled the new prescription. We required that a patient have an SMI diagnosis and no antipsychotic prescriptions during the 6-month "clean" period before the medication initiation date. Both atypical (eg, aripiprazole, asenapine, iloperidone, lurasidone, olanzapine, paliperidone, quetiapine, risperidone, ziprasidone) and typical (eg, chlorpromazine, fluphenazine haloperidol, perphenazine) oral antipsychotics were included in the analysis. Patients using clozapine were excluded from the sample, as clozapine is typically used only for patients who do not respond to at least 2 other antipsychotic medications.[21] Also excluded were patients missing data on age or patients who received antipsychotics via mail order.

We applied an OLS regression to measure the effect of medication adherence on inpatient cost measured over the 365 days following the initiation of the antipsychotic medication regimen. Costs included payments made by primary payers (ie, commercial insurers or Medicaid), patient out-of-pocket payments, and other third-party payments. All costs were inflated to 2015 US dollars using the Consumer Price Index.[22] The primary independent variable of interest was a patient's PDC, which was calculated as the total days covered by all antipsychotics supplied across all claims in the 365 days after the initial medication fill divided by 365. As this study focused on nonadherence rather than overuse, PDC values were capped at 100%.

To account for compositional differences between the populations of adherent and nonadherent patients, we included patient demographics and health status as explanatory variables in our regression analysis. The Charlson Comorbidity Index[23] was used to measure patients' overall health status.[24] Mental health status was measured based on the presence of comorbid SMI conditions (ie, schizophrenia, bipolar disorder, or major depressive disorder), a diagnosis of alcoholism (*ICD-9-CM*: 265.2, 291.1-291.3, 291.5-291.9, 303.0, 303.9, 305.0, 357.5, 425.5, 535.3, 571.0-571.3, 980.x, V11.3), or drug dependence or abuse (*ICD-9-CM*: 292.x, 304.x, 305.2–305.9, V65.42).[24,25] We also included an indicator for whether the patient was commercially insured or covered by Medicaid and a measure of inpatient spending levels during the 6 months before antipsychotic initiation, as a measure of disease severity. In addition to our baseline specification, we included interaction terms of PDC with indicator terms for specific SMI diagnoses (ie, schizophrenia, bipolar disorder, and major depressive disorder) to estimate the effect of adherence for patients with a specific type of SMI.

All statistical analyses were performed using Stata-MP version 13.0 (StataCorp LP, College Station, Texas).

RESULTS

Literature Review

Estimates of the correlation between gold-standard medication adherence and other adherence measures varied widely in the literature. As shown in **Table 1**, only 2 studies measured the correlation between electronic monitoring systems and prescription refill records, with correlation values of 0.32 and 0.48, respectively.[26,27] Two additional studies calculated the correlation between electronic monitoring systems and non-claims measures.[20,28] When we broadened our definition of gold standard to include pill counts, we found 2 additional studies.[29,30] Ignoring the relationship between adherence and patient characteristics, these figures indicate that the effect of adherence on inpatient spending could

TABLE 1. Studies Measuring the Correlation Between "Gold Standard" and Other Forms of Medication Adherence

Adherence Measures Compared						
Publication	**Disease**	**Medication of Interest**	**Gold Standard**	**Comparison Method**	**Correlation**	**Ratio of True and Observed Adherence Effect[a]**
Choo et al (1999)[26]	Hypertension	Antihypertensive monotherapy	Electronic pill counts	Pharmacy dispensing records	0.32[b]	9.8
Hansen et al (2009)[27]	Hypertension or heart failure	ACE inhibitor, beta-blocker, diuretic, digoxin, spironolactone, calcium channel blockers	MEMS 5 TrackCap	Prescription refill records	0.48[c]	4.3
Bruce, Hancock, Lynch (2009)[28]	Relapsing remitting multiple sclerosis	Glatiramer acetate, interferon beta-1a and 1b	Needle disposal bottle fitted with MEMS cap	Patient self-report (prospective, retrospective), calendar-style adherence diary	0.70[b] 0.84[b] 0.91[b]	2.0 1.4 1.2
Remington et al (2007)[20]	Schizophrenia or schizoaffective disorder	Antipsychotic	MEMS cap	Pill count	0.46[b]	4.7
Elm et al (2007)[30]	Parkinson's disease	Creatine, minocycline, or placebo (study arm 1); CoQ_{10}, GPI-1485, or placebo (study arm 2)	Pill count	Morisky medication adherence questionnaire	0.38[c]	6.9
Grymonpre et al (2006)[29]	Adults ≥65 years taking ≥2 medications daily	ACE inhibitors	Pill count, conducted by pharmacist	CMA	0.79[c]	1.6

ACE indicates angiotensin-converting enzyme; CMA, cumulative medication adherence; MEMS, Medication Event Monitoring System.
[a] The ratio of the true compared with the observed effect is calculated as 1 over the square of the correlation ($1/\rho^2$). This simple calculation assumes that medication adherence is exogenous to the dependent variable (inpatient spending) and ignores the correlation between medication adherence and patient covariates included in the regression model ($R^2_{PDC_i,W_i}$). When these assumptions hold, one can calculate the share of the adherence effect observed as ρ^2.
[b] Pearson correlation coefficient.
[c] Spearman's rank correlation.

be underestimated by a factor ranging from 1.2 to 9.8, due to measurement error alone.

Empirical Case Study

In our empirical case study, 145,235 patients in the commercially insured population and 86,321 patients in the Medicaid population had an SMI and initiated an antipsychotic medication regimen (**Figure 1**). Descriptive statistics for patient characteristics are shown in **Table 2**. Patient age was concentrated between 28 and 55 years, and 65.3% of patients in our sample were women. Of these patients, 17.7% had an alcohol dependence problem and 9.8% suffered from drug abuse. Among patients with an SMI, 16.4%, 47.8%, and 75.6% had schizophrenia, bipolar disorder, or major depressive disorder, respectively. The average patient had a PDC of 48.0%.

Results from the regression analysis indicated that patients with higher adherence had lower levels of inpatient spending (**Table 3**). In our baseline approach (model 1), a 10-percentage-point increase in PDC was correlated with a change in annual inpatient cost of –$41 (95% confidence interval [CI], –$65 to –$16; $P = .001$) per patient with an SMI. When allowing for PDC to interact with each of the 3 SMIs of interest (model 2), schizophrenia patients with a 10-percentage-point higher PDC had a higher inpatient cost of $86 (95% CI, –$152 to –$20; $P = .011$). The corresponding amounts for major depressive disorder and bipolar disorder were $67 (95% CI, –$106 to –$27; $P = .001$) and $10 (95% CI, –$45 to $26; $P = .596$), respectively.

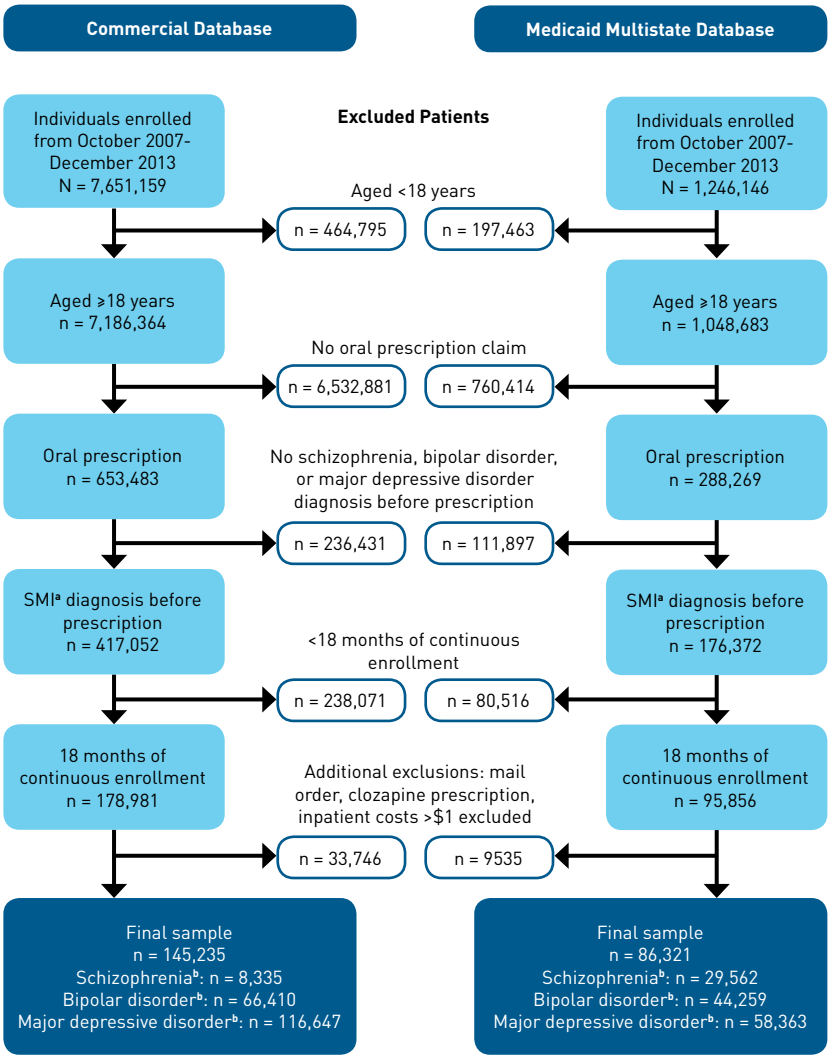
When we corrected for adherence mismeasurement using the bias-correction formula above and our preferred estimate for the correlation between claims-based and true adherence, the impact of medication on inpatient spending increased by a factor of 5.3. This estimate is calculated from the correlation from Hansen et al[32] and empirically estimated the R^2 between the PDC and patient covariates:

$$5.3 = \frac{1\text{-}R^2_{PDC_i,W_i}}{\rho^2\text{-}R^2_{PDC_i,W_i}} = \frac{1\text{-}0.0514}{(0.48)^2\text{-}0.0514}$$

When we applied this bias-correction factor to our case study, patients with a 10-percentage-point greater PDC had $217 (95% CI, –$347 to –$87) higher inpatient cost per patient (**Figure 2**). Even if we applied the most conservative adjustment factor from Bruce et al,[28] that would still inflate the relationship by 20%:

$$\text{(ie, } 1.2 = \frac{1\text{-}0.0514}{(0.91)^2\text{-}0.0514}\text{).}$$

FIGURE 1. CONSORT Diagram Identifying Patients With SMI Who Initiated Antipsychotic Therapy



M indicates million; SMI, serious mental illness.
[a]Schizophrenia, bipolar disorder, and major depressive disorder.
[b]Diagnoses are not mutually exclusive.

DISCUSSION

Patients with better medication adherence had lower inpatient costs, but the magnitude of this relationship is underestimated when adherence is measured using claims-based metrics. Failure to adjust for measurement error in this context understates the impact of adherence on inpatient costs by a factor of 5.3 using our preferred estimate. This study provides a practical strategy for eliminating the bias due specifically to mismeasured adherence, quantitatively demonstrates that this bias is quite substantial, and calls for the development of newer, more accurate measures of adherence. Finally, we show that measurement error has significantly decreased the estimated size of the impact of adherence; thus, medication adherence might be even more important than currently shown.

To our knowledge, this is the first study to propose a concrete adherence mismeasurement adjustment factor. Although the errors-in-variables measurement error bias is well known in the statistical literature, correcting for this bias requires a valid estimate of the correlation between true and measured adherence. By conducting a literature review between gold-standard and measured adherence, researchers and practitioners can now determine the true effect of medication adherence for any outcome of interest.

Limitations

One key limitation of this approach is that the measurement error adjustment may not, in itself, address other potential forms of bias, like endogeneity bias. Specifically, our approach does not solve problems with the linear regression identification strategy, but—conditional on having a robust identification strategy—does correct for errors-in-variables measurement error bias. Indeed, if the effect of adherence on health care costs is overstated in a regression of health care costs on true adherence, correcting for measurement error could move us farther away from the truth, and vice-versa. Although the measurement error correction accurately and fully accounts for the errors-in-variables measurement error, it does not, in itself, address other possible forms of bias, such as the potential endogeneity of adherence.

For observational claims-based data analyses, such as our case study, there are a number of reasons why identification of the effect of true adherence on healthcare costs could suffer from endogeneity bias, but the sign of this bias is likely unknown. For instance, patients with recently diagnosed schizophrenia may have less insight into their disease than patients who have experienced the condition for longer,[32] but these new patients also typically have less severe, earlier-stage forms of the disease.[33] Prior research suggests patients with more limited disease insight have lower medication adherence.[34] By this logic, patients who are more adherent would have a more serious form of SMI and the

effect of adherence on spending would be understated due to this problem of endogeneity of true adherence. Measurement error would exacerbate this problem, but even correcting for it would not remove the endogeneity bias. On the other hand, some studies have found that less severe forms of schizophrenia are associated with higher rates of medication compliance.[35,36] This would lead to the opposite scenario, in which measurement error actually mitigates the endogeneity bias. Other studies have found no statistically significant relationship between adherence and baseline disease severity.[37] In short, although our case study is observational in nature, both the magnitude and size of the bias from this observational study is unknown.

There are a number of other limitations of this study. First, our model assumed that adherence measured by MEMS caps in the literature represented true adherence. However, MEMS caps only measure the opening of a pill bottle, not actual ingestion of a pill, and thus, adherence measured with MEMS caps is also imperfect..

Second, we assumed that the relationship between adherence and inpatient spending is linear. In practice, a 10-percentage point adherence increase from 0% to 10% PDC may have a larger or smaller impact on inpatient spending then increasing adherence from 90% to 100%. However, measurement error in nonlinear

TABLE 2. Patient Characteristics

Variable	Mean	SD (Min-Max)
Age, years	41.6	13.3 (1890)
Commercially insured, %	62.7	
Female, %	65.3	
Alcoholism, %	17.7	
Drug abuse, %	9.8	
Charlson Comorbidity Index	0.390	0.673 (0-2)
PDC, %	48.0	34.9 (0-100)
Inpatient spending, US$		
6 months before initiating antipsychotic	2226	17,103 (0-918,722)
12 months after initiating antipsychotic	3384	20,400 (0-948,400)
Schizophrenia, %[a]	16.4	
Bipolar disorder, %[a]	47.8	
Major depressive disorder, %[a]	75.6	
N	231,556	

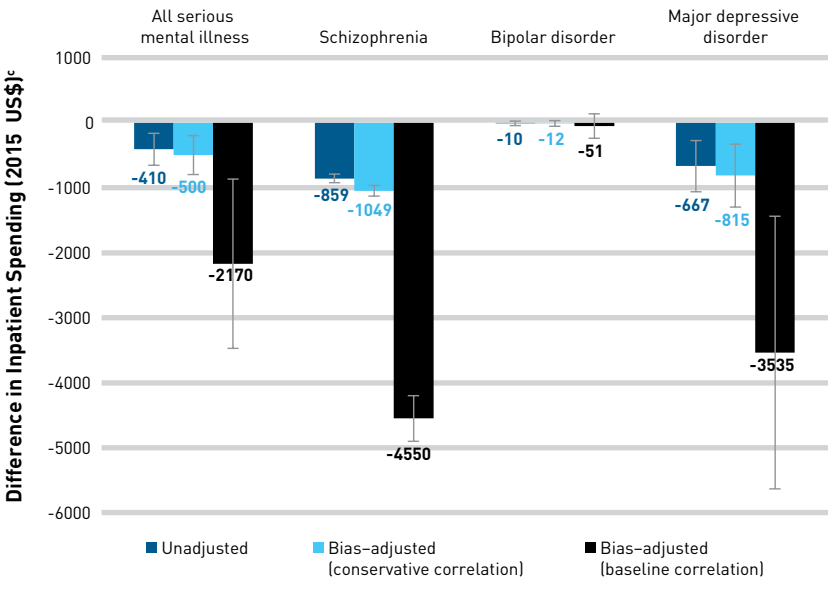
PDC indicates proportion of days covered; SD, standard deviation.
[a]Patients can have multiple serious mental illnesses, and disease diagnoses are based on diagnosis codes in health insurance claims data.

TABLE 3. Effect of an Increase of PDC on Annual Inpatient Cost

	Model 1			Model 2		
	Coefficient	SE	95% CI	Coefficient	SE	95% CI
PDC[a]	−40.95*	12.52	−65.50 to −16.41	−66.71*	20.18	−106.27 to −27.16
Bipolar disorder	–	–		−383.2**	157.3	−691.4 to −74.9
Schizophrenia	–	–		564.3***	292.9	−9.9 to 1138.5
Bipolar disorder × PDC[a]	–	–		57.08**	26.89	4.38-109.77
Schizophrenia × PDC[a]	–	–		−19.14	39.35	−96.27 to 58.00
Age, years						
25 to 34	315.7*	123.3	74.0 to 557.3	319.7*	123.3	77.9-561.4
35 to 49	960.1*	120.2	724.4 to 1195.8	947.2*	120.5	711.1-1183.4
50 to 64	2185.4*	144.5	1902.1to 2468.6	2157.4*	144.4	1874.5-2440.4
65 to 80	1006.2***	572.4	−115.8 to 2128.2	928.5	572.8	−194.2 to 2051.2
>80	−1723.8*	384.4	−2477.2 to −970.3	−1735.7*	386.0	−2492.3 to −979.0
Commercial	−393.3*	100.0	−589.2 to −197.3	−276.5*	105.8	−483.8 to −69.2
Female	136.0	96.4	−52.9 to 325.0	185.0***	98.3	−7.6 to 377.7
Alcoholism	722.5*	148.0	432.4 to 1012.7	733.1*	148.1	442.9-1023.4
Drug abuse	1708.7*	209.9	1297.3 to 2120.0	1694.0*	210.3	1281.8-2106.1
Charlson Comorbidity Index						
1	1566.7*	120.0	1331.5 to 1801.9	1576.8*	119.9	1341.8-1811.8
>1	6935.7*	270.0	6406.5 to 7465.0	6951.4*	270.5	6421.4-7481.5
Prior inpatient spending	0.264*	0.018	0.229 to 0.298	0.264	0.018	0.229-0.298
Constant	1054.3*	149.8	760.7 to 1347.9	1054.6*	177.6	706.5-1402.6

CI indicates confidence interval; PDC, proportion of days covered; SE, standard error.
[a]PDC measured in increments of 10 percentage points.
"*" indicates P <.01; "**" indicates P <.05; "***" indicates P <.10.

FIGURE 2. Effect of a 10-Percentage-Point Increase in PDC on Inpatient Spending, Unadjusted and Bias-Adjusted Results[a,b]



PDC, proportion of days covered; SMI, serious mental illness; US$, US dollars.

[a]Results obtained from standard regression methodology were corrected for adherence mismeasurement using the bias-correction formula. Without correction, the impact of adherence on inpatient spending per patient with SMI was underestimated by a factor of about 5.3.

[b]The whiskers represent the 95% confidence interval.

[c]Difference in inpatient spending between patients with a 10-percentage-point higher PDC.

models depends heavily on the model's functional form and thus cannot be derived in a general case.[38,39]

Third, the data used in the case study represent a convenience sample from health insurers and large employers, from Medicare patients with a Medicare supplemental plan, and patients with Medicaid coverage in 11 states. Nevertheless, average patient characteristics in our sample (eg, age, sex, substance abuse, adherence) were fairly representative of the national patient population with SMI.[40,41] Likewise, the average PDC in our study (48%) was in line with estimates reported in recent systematic reviews of antipsychotic adherence for patients with SMI.[2,18,42]

Future research should explore the costs and benefits of using more accurate adherence measures to inform patients, providers, payers, and other stakeholders. Med-eMonitor (InforMedix; Rockville, Maryland), for example, stores a patient's medication and can measure the time and date the patient opens the container.[27] Another example is a digital health feedback system that uses an ingestible sensor embedded within a tablet to track adherence through patient ingestion.[43] However, the most appropriate adherence measurement collection approach depends on both the accuracy of the technology and other factors, such as the cost of data collection, the burden on patients and providers, and the ability to standardize data collection, among others.

CONCLUSIONS

Patients with SMI who had higher levels of medication adherence had lower inpatient costs, but the magnitude of this relationship is underestimated when adherence is measured using claims-based metrics. We derived a bias-correction formula to show that measurement error in claims-based adherence measures results in the effects of adherence being underestimated by a factor of 5.3. In part due to the size of this bias, we believe that measurement error due to claims-based adherence measures is worth addressing, alongside other more widely emphasized sources of bias in inference. ■

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Authorship Information: Concept and design (JS, FF, DL); acquisition of data (JS, FF); analysis and interpretation of data (JS, FF, AH, DL, ES); drafting of the manuscript (JS, FF, AH, DL, ES); critical revision of the manuscript for important intellectual content (JS, FF, AH, EV, DL); statistical analysis (JS, EV, ES); provision of patients or study materials (); obtaining funding (FF); administrative, technical, or logistic support (JS, FF); and supervision (JS, FF, DL).

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eAppendix 1: Bias Derivation

Derivation of Bias Correction Assuming Medication Adherence is Exogenous

Suppose that the "true" model is given by:

$Y_i = \beta X^* + \boldsymbol{W_i'}\boldsymbol{\gamma} + \epsilon_i$

where

Y_i Inpatient spending

X_i^* True adherence

X_i Adherence measured in claims data

ν_i Measurement error

ϵ_i The residual

The dependent variable is inpatient cost Y_i. Independent variables are X^*, the adherence measure, and $\boldsymbol{W_i'}$, a vector of covariates consisting of age, insurance type (commercial or Medicaid), sex, alcoholism indicator, drug abuse indicator, Charlson Comorbidity Index, comorbid SMI conditions, and inpatient spending during the 6 months before medication initiation.

Suppose that instead of directly observing X_i^* (eg, the MEMS caps), we instead observe an imperfect measure of adherence, such as PDC from claims data. Thus, instead of X_i^* we observe X_i which is defined the following way:

$$X_i = X_i^* + \nu \quad (1)$$

Where ν represents measurement error in X_i^*. We then make the following assumptions:

A-1 $E(X_i^*\epsilon_i) = 0$

A-2 $E(\boldsymbol{W_i'}\epsilon_i) = 0$

A-3 $E(\nu_i) = 0$

A-4 $E(X_i^*\nu_i) = 0$

A-5 $E(\boldsymbol{W_i'}\nu_i,) = 0$

A-6 $E(\epsilon_i\nu_i) = 0$

Assumptions A-1 and A-2 are standard assumptions for regression analysis, that OLS regression will give a consistent estimator if we measure X_i^* without error. Assumption A-3 indicates that the measurement error has a mean of zero. Assumptions A-4 and A-5 indicate that the error is uncorrelated with the true adherence measure, X_i^*, as well as the other covariates in the model. Finally, assumption A-6 indicates that the error is uncorrelated with the error term in the equation (1). Using these assumptions, Wooldridge[44] shows that we can rewrite the estimate for $\hat{\beta}$ to be:

$$plim(\hat{\beta}) = \beta\left(\frac{\sigma_r^2}{\sigma_r^2 + \sigma_v^2}\right) \quad (1)$$

where *plim* is the probability limit as the sample size trends to infinity and σ_r^2 is the variance of the residual from the regression of X_i^*, on $\boldsymbol{W_i}$. Now solving for β, we have:

$$\beta = plim(\hat{\beta})\left(\frac{\sigma_r^2 + \sigma_v^2}{\sigma_r^2}\right) \quad (2)$$

Now let $\sigma_{\hat{r}}^2$ denote the variance of the residual from the regression of X_i on $\boldsymbol{W_i}$. If we assume that ν_i is uncorrelated with both X_i^* and $\boldsymbol{W_i}$ (eg, A-4 and A-5), then $\sigma_{\hat{r}}^2 = \sigma_r^2 + \sigma_v^2$. Next, our assumption that ν_i and X_i^* are uncorrelated (A-4) implies that $\sigma_X^2 - \sigma_{X^*}^2 = \sigma_v^2$, where σ_X^2 and $\sigma_{X^*}^2$

are the variances of $X_i$and X_i^*, respectively. Using these 2 pieces, we can now rewrite expression (4) as:

$$\beta = plim(\hat{\beta})\left(\frac{\sigma_{\hat{r}}^2}{\sigma_{\hat{r}}^2 - (\sigma_X^2 - \sigma_{X^*}^2)}\right) \quad (3)$$

Finally, let $R_{X,W}^2$denote the $R^2$from a linear projection of X_i on $\boldsymbol{W}_i$ (the probability limit of the R^2 from the linear regression of X_i on $\boldsymbol{W}_i$). Furthermore, note that $R_{X,W}^2$ can be expressed as:

$$R_{X,W}^2 = 1 - \frac{\sigma_{\hat{r}}^2}{\sigma_X^2} \quad (4)$$

Now plugging this expression into equation (5) and simplifying terms we get:

$$\beta = plim(\hat{\beta})\left(\frac{\sigma_X^2(1 - R_{X,W}^2)}{\sigma_X^2(1 - R_{X,W}^2) - (\sigma_X^2 - \sigma_{X^*}^2)}\right)$$

$$= plim(\hat{\beta})\left(\frac{\left(1 - R_{X,W}^2\right)}{\frac{\sigma_{X^*}^2}{\sigma_X^2} - R_{X,W}^2}\right) \quad (5)$$

$$= plim(\hat{\beta})\left(\frac{(1 - R_{X,W}^2)}{\rho^2 - R_{X,W}^2}\right)$$

Where ρ^2denotes the squared correlation between $\hat{X}$ and X because we are using the assumption that X and ε are uncorrelated to imply that $\rho^2 = \frac{\sigma_{X^*}^2}{\sigma_X^2}$.

Derivation of Bias Correction Assuming Adherence is Endogenous

Now consider the case where adherence is endogenous. For simplicity, we ignore the presence of all other covariates besides adherence. Consider the case where we again aim to estimate the following equation:

$Y_i = \beta_0 + \beta_1 X_i^* + \epsilon_i$

$Y_i = \beta_0 + \beta_1(X_i - \nu_i) + \epsilon_i$

$Y_i = \beta_0 + \beta_1 X_i + (\epsilon_i - \beta_1 \nu_i)$

In practice, we do not observe X_i^*, so the OLS estimator from regressing Y_i on measured adherence X_i is

$$plim(\hat{\beta}_1) = \beta_1 + \frac{Cov(X_i, \epsilon_i)}{Var(X_i)} - \beta_1 \frac{Cov(X_i, \nu_i)}{Var(X_i)}$$

$$plim(\hat{\beta}_1) = \beta_1 + \frac{\sigma_{X^*,\epsilon}}{\sigma_{X^*}^2 + \sigma_\nu^2} + \frac{\sigma_{\nu,\epsilon}}{\sigma_{X^*}^2 + \sigma_\nu^2} - \beta_1 \frac{\sigma_\nu^2}{\sigma_{X^*}^2 + \sigma_\nu^2}$$

$$plim(\hat{\beta}_1) = \beta_1 + \frac{\sigma_{X^*}^2}{\sigma_{X^*}^2 + \sigma_\nu^2} B_1 + B_2 - \beta_1 B_3$$

(The terms $B_1, B_2,$ and B_3 are defined as one would expect by comparing the second equation with the third.) Thus, the bias from regressing Y_i on measured adherence is given by the sum of 3 terms. The first bias term is $\frac{\sigma_{X^*}^2}{\sigma_{X^*}^2 + \sigma_\nu^2} B_1$, the bias from endogeneity of true adherence. The term B_1 is the bias that would remain if you regressed the Y_i on true adherence X_i. If true adherence is

exogenous, then this term will equal zero. If true adherence is endogenous, then $B_1 \neq 0$ and this term will be nonzero. B_2 is the bias from the endogeneity of the measurement error. If the measurement error is exogenous (unrelated to ϵ_i; eg, unrelated to mental illness), then this term will equal zero. B_3 is the proportional bias due to measurement error.

We assume that measurement error is exogenous, and thus $B_2 = 0$, but the 2 bias terms $\frac{\sigma_{X^*}^2}{\sigma_{X^*}^2+\sigma_v^2} B_1$ from the endogeneity of true adherence and the bias term B_3 from measurement error may remain. Observe that this exogeneity assumption allows us to express the percentage bias as:

$$\frac{plim(\hat{\beta}_1)}{\beta_1} - 1 = \frac{\sigma_{X^*}^2}{\sigma_{X^*}^2 + \sigma_v^2}\frac{B_1}{\beta_1} - B_3$$

The assumption of an exogenous measurement error also leads to the following simplification:

$$plim(\hat{\beta}_1) = \beta_1\left(1 - \frac{\sigma_v^2}{\sigma_{X^*}^2 + \sigma_v^2}\right) + \frac{\sigma_{X^*}^2}{\sigma_{X^*}^2 + \sigma_v^2} B_1$$

$$plim(\hat{\beta}_1) = \frac{\sigma_{X^*}^2}{\sigma_{X^*}^2 + \sigma_v^2}[\beta_1 + B_1]$$

Assuming that measurement error is uncorrelated with true adherence, then:

$$\rho^2 \equiv \left(Corr(X_i, X_i^*)\right)^2 = \frac{\sigma_{X^*}^2}{\sigma_X^2} = \left(\frac{\sigma_{X^*}^2}{\sigma_{X^*}^2 + \sigma_v^2}\right)$$

Using the correlation between true and measured adherence to rescale the OLS estimate to adjust for the measurement error, we obtain:

$$plim(\hat{\beta}_1)/\rho^2 = \beta_1 + B_1$$

If true adherence is exogenous (ie, $B_1 = 0$), then dividing the coefficient of interest by the square of the correlation between true and measured adherence produces an unbiased estimate of the effect of adherence on inpatient spending. If true adherence is endogenous, we obtain the same parameter that would be obtained if we were to regress on true adherence, with the same endogeneity bias we would have if we were to regress on true adherence.

eAppendix 2. Literature Search

Table A1. Literature Search for the Correlation Between "Gold Standard" and Claim-Based Adherence Measures

Search Terms	Yield	Titles Screened	Unique Abstracts Screened	Unique Relevant Full Texts Identified
Serious Mental Illness Search (Google Scholar)				
Medication adherence accuracy	187,000	30	6	4
MEMS caps adherence accuracy	4520	40	3	2
Direct observation adherence accuracy	219,000	50	1	1
PDC adherence accuracy	5320	50	0	0
MPR adherence accuracy	5760	50	5	1
Self-report adherence accuracy	234,000	50	0	0
Prescription claims adherence accuracy	42,000	40	2	0
Lab tests adherence accuracy	72,100	50	1	0
Pill count adherence accuracy	24,400	40	2	1
Physician estimate medication adherence accuracy	58,900	50	1	1
Medication adherence accuracy schizophrenia	28,900	50	4	1
MEMS caps adherence accuracy schizophrenia	1040	50	5	1
Direct observation adherence accuracy schizophrenia	22,600	40	0	0
PDC adherence accuracy schizophrenia	303	30	0	0
MPR adherence accuracy schizophrenia	1080	40	1	0
Self-report adherence accuracy schizophrenia	26,600	45	1	0
Prescription claims adherence accuracy schizophrenia	17,300	50	4	2
Lab tests adherence accuracy schizophrenia	19,100	40	0	0
Pill count adherence accuracy schizophrenia	16,400	50	2	2
Physician estimate medication adherence accuracy schizophrenia	19,300	40	0	0
Medication adherence accuracy serious mental illness	38,600	35	0	0
MEMS caps adherence accuracy serious mental illness	5520	40	0	0
Direct observation adherence accuracy serious mental illness	38,300	30	0	0
PDC adherence accuracy serious mental	1330	30	0	0

Search Terms	Yield	Titles Screened	Unique Abstracts Screened	Unique Relevant Full Texts Identified
illness				
MPR adherence accuracy serious mental illness	5170	25	0	0
Self-report adherence accuracy serious mental illness	51,400	30	1	0
Prescription claims adherence accuracy serious mental illness	25,300	35	0	0
Lab tests adherence accuracy serious mental illness	25,000	30	0	0
Pill count adherence accuracy serious mental illness	19,600	30	0	0
Physician estimate medication adherence accuracy serious mental illness	26,400	40	0	0
Serious Mental Illness Search (PubMed)				
Medication adherence accuracy	171	50	0	0
MEMS caps adherence accuracy	3	3	0	0
Direct observation adherence accuracy	12	12	0	0
PDC adherence accuracy	5	5	0	0
MPR adherence accuracy	5	5	0	0
Self-report adherence accuracy	62	50	0	0
Prescription claims adherence accuracy	9	9	0	0
Lab tests adherence accuracy	1	1	0	0
Pill count adherence accuracy	10	10	0	0
Physician estimate medication adherence accuracy	2	2	0	0
Medication adherence accuracy schizophrenia	4	4	0	0
MEMS caps adherence accuracy schizophrenia	0	0	0	0
MEMS schizophrenia	13	13	2	0
Direct observation adherence accuracy schizophrenia	0	0	0	0
PDC adherence accuracy schizophrenia	1	1	0	0
PDC schizophrenia	12	12	0	0
MPR adherence accuracy schizophrenia	1	1	0	0
MPR schizophrenia	21	21	1	0
Self-report adherence accuracy schizophrenia	2	2	0	0
Prescription claims adherence accuracy schizophrenia	0	0	0	0

Search Terms	Yield	Titles Screened	Unique Abstracts Screened	Unique Relevant Full Texts Identified
Lab tests adherence accuracy schizophrenia	0	0	0	0
Pill count adherence accuracy schizophrenia	0	0	0	0
Physician estimate medication adherence accuracy schizophrenia	0	0	0	0
Medication adherence accuracy serious mental illness	2	2	0	0
MEMS caps adherence accuracy serious mental illness	0	0	0	0
MEMS serious mental illness	3	3	0	0
Direct observation adherence accuracy serious mental illness	0	0	0	0
PDC adherence accuracy serious mental illness	0	0	0	0
MPR adherence accuracy serious mental illness	0	0	0	0
Self-report adherence accuracy serious mental illness	2	2	0	0
Prescription claims adherence accuracy serious mental illness	0	0	0	0
Prescription claims adherence serious mental illness	1	1	0	0
Lab tests adherence accuracy serious mental illness	0	0	0	0
Pill count adherence accuracy serious mental illness	0	0	0	0
Pill count adherence serious mental illness	1	1	0	0
Physician estimate medication adherence accuracy serious mental illness	0	0	0	0
Other central nervous system diseases (Google Scholar)				
Medication adherence accuracy multiple sclerosis	24,500	50	1	1
MEMS caps adherence accuracy multiple sclerosis	772	40	0	0
Direct observation adherence accuracy multiple sclerosis	20,500	40	0	0
PDC adherence accuracy multiple sclerosis	598	30	2	0

Search Terms	Yield	Titles Screened	Unique Abstracts Screened	Unique Relevant Full Texts Identified
MPR adherence accuracy multiple sclerosis	567	35	0	0
Self-report adherence accuracy multiple sclerosis	7290	30	0	0
Prescription claims adherence accuracy multiple sclerosis	10,500	50	1	0
Lab tests adherence accuracy multiple sclerosis	19,400	40	0	0
Pill count adherence accuracy multiple sclerosis	15,500	40	2	1
Physician estimate medication adherence accuracy multiple sclerosis	18,700	30	0	0
Medication adherence accuracy Alzheimer's	20,000	40	1	0
MEMS caps adherence accuracy Alzheimer's	714	50	0	0
Direct observation adherence accuracy Alzheimer's	18,100	40	0	0
PDC adherence accuracy Alzheimer's	302	30	1	0
MPR adherence accuracy Alzheimer's	602	30	1	1
Self-report adherence accuracy Alzheimer's	8320	40	0	0
Prescription claims adherence accuracy Alzheimer's	12,300	40	0	0
Lab tests adherence accuracy Alzheimer's	17,800	40	0	0
Pill count adherence accuracy Alzheimer's	13,200	40	0	0
Physician estimate medication adherence accuracy Alzheimer's	17,800	40	0	0
Medication adherence accuracy Parkinson's	19,900	50	3	2
MEMS caps adherence accuracy Parkinson's	793	40	1	1
Direct observation adherence accuracy Parkinson's	17,900	50	1	0
PDC adherence accuracy Parkinson's	354	35	0	0
MPR adherence accuracy Parkinson's	504	50	1	0
Self-report adherence accuracy Parkinson's	7760	30	0	0
Prescription claims adherence accuracy Parkinson's	11,600	35	0	0

Search Terms	Yield	Titles Screened	Unique Abstracts Screened	Unique Relevant Full Texts Identified
Lab tests adherence accuracy Parkinson's	17,600	40	0	0
Pill count adherence accuracy Parkinson's	12,000	30	0	0
Physician estimate medication adherence accuracy Parkinson's	17,400	50	0	0
Other central nervous system diseases (PubMed)				
Medication adherence accuracy multiple sclerosis	0	0	0	0
MEMS caps adherence accuracy multiple sclerosis	0	0	0	0
Direct observation adherence accuracy multiple sclerosis	0	0	0	0
PDC adherence accuracy multiple sclerosis	0	0	0	0
PDC multiple sclerosis	26	26	0	0
MPR adherence accuracy multiple sclerosis	0	0	0	0
MPR multiple sclerosis	21	21	0	0
Self-report adherence accuracy multiple sclerosis	0	0	0	0
Prescription claims adherence accuracy multiple sclerosis	0	0	0	0
Lab tests adherence accuracy multiple sclerosis	0	0	0	0
Pill count adherence accuracy multiple sclerosis	0	0	0	0
Physician estimate medication adherence accuracy multiple sclerosis	0	0	0	0
Medication adherence accuracy Alzheimer's	0	0	0	0
MEMS caps adherence accuracy Alzheimer's	0	0	0	0
Direct observation adherence accuracy Alzheimer's	0	0	0	0
PDC adherence accuracy Alzheimer's	0	0	0	0
PDC Alzheimer's	63	50	0	0
MPR adherence accuracy Alzheimer's	0	0	0	0
MPR Alzheimer's	7	7	0	0
Self-report adherence accuracy Alzheimer's	0	0	0	0

Search Terms	Yield	Titles Screened	Unique Abstracts Screened	Unique Relevant Full Texts Identified
Prescription claims adherence accuracy Alzheimer's	0	0	0	0
Lab tests adherence accuracy Alzheimer's	0	0	0	0
Pill count adherence accuracy Alzheimer's	0	0	0	0
Physician estimate medication adherence accuracy Alzheimer's	0	0	0	0
Medication adherence accuracy Parkinson's	0	0	0	0
MEMS caps adherence accuracy Parkinson's	0	0	0	0
Direct observation adherence accuracy Parkinson's	0	0	0	0
PDC adherence accuracy Parkinson's	0	0	0	0
PDC Parkinson's	80	40	0	0
MPR adherence accuracy Parkinson's	0	0	0	0
MPR Parkinson's	6	6	1	0
Self-report adherence accuracy Parkinson's	0	0	0	0
Prescription claims adherence accuracy Parkinson's	0	0	0	0
Lab tests adherence accuracy Parkinson's	0	0	0	0
Pill count adherence accuracy Parkinson's	0	0	0	0
Physician estimate medication adherence accuracy Parkinson's	0	0	0	0