Development and Evaluation of an Improved Methodology for Assessing Adherence to Evidence-Based Drug Therapy Guidelines Using Claims Data

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ABSTRACT

Non-adherence to evidence-based pharmacotherapy is associated with increased morbidity and mortality. Claims data can be used to detect and intervene on such non-adherence, but existing claims-based approaches for measuring adherence to pharmacotherapy guidelines have significant limitations. In this manuscript, we describe a methodology for assessing adherence to pharmacotherapy guidelines that overcomes many of these limitations. To develop this methodology, we first reviewed the literature to identify prior work on potential strategies for overcoming these limitations. We then assembled a team of relevant domain experts to iteratively develop an improved methodology. This development process was informed by the use of the proposed methodology to assess adherence levels for 14 pharmacotherapy guidelines related to seven common diseases among approximately 36,000 Medicaid beneficiaries. Finally, we evaluated the ability of the methodology to overcome the targeted limitations. Based on this evaluation, we conclude that the proposed methodology overcomes many of the limitations associated with existing approaches.

INTRODUCTION

Evidence-based (EB) pharmacotherapy may significantly decrease the morbidity and mortality associated with many diseases. For example, the use of beta-blockers after a myocardial infarction reduces mortality by 23%;¹ the use of angiotensin converting enzyme (ACE) inhibitors among patients with left ventricular systolic dysfunction reduces mortality by 20%;² and the use of statins among patients with diabetes reduces cardiac mortality by 20%.³ These and other drug therapies represent an integral component of many EB clinical guidelines.⁴ Despite these proven benefits, clinicians do not always follow EB pharmacotherapy guidelines. For example, among Medicare patients suffering acute myocardial infarctions in 1998 and 1999, only 70.7% of patients without a contraindication were prescribed a beta-blocker at the time of discharge, and only 70.8% of patients with left ventricular systolic dysfunction were prescribed an ACE inhibitor.⁵ Even when clinicians prescribe the appropriate EB medications, patients oftentimes do not take the medications as prescribed. In general, patients are only about 50% adherent to medication regimens for chronic conditions.⁵ For example, one study found the mean adherence rate to statin therapy to be only 50% during the first year of therapy.⁷

Whether due to clinicians not prescribing the appropriate medications (clinician non-adherence) or patients not taking the prescribed medications (patient non-adherence), the lack of adherence to EB pharmacotherapy guidelines results in significant morbidity and mortality.⁸⁻¹⁰ The associated financial costs are also significant. Within the United States, the yearly cost for hospitalizations due to medication non-adherence is estimated at $100 billion a year.⁹

Claims data are widely available and can be used to assess patient and clinician adherence to EB pharmacotherapy.⁸⁻¹² Such adherence assessments could in turn be used to drive decision support interventions designed to improve adherence to EB pharmacotherapy. However, as described in two recent systematic reviews,¹¹,¹² existing claims-based methods for measuring medication adherence vary widely in their approach and are associated with one or more important limitations.

First, many existing methods can only assess patient adherence to medications for which the patient has filled a prescription.¹¹ This approach is problematic in that clinicians may prescribe a contraindicated drug or fail to prescribe an indicated drug, and patients may fail to fill an appropriately prescribed drug. Secondly, many methods lack a mechanism for handling incomplete data (e.g., patients who were not continuously enrolled in the insurance program serving as the source of claims data).¹¹,¹² Eliminating incomplete data may result in less generalizable interpretation of the data and limit development of effective interventions for the broader population. Third, some methods do not appropriately adjust for early prescription refills¹⁰ and/or medication adjustments within a drug class (e.g., dose adjustment or drug switching).¹¹,¹² Fourth, most methods assess for patient eligibility for pharmacotherapy at a single point in time rather than over the entire assessment period.¹² Fifth, many methods use an arbitrary adherence level (usually 80%) to classify patients as being adherent or non-adherent, even though the level of adherence required
for efficacy is likely to be drug and disease-dependent.\textsuperscript{11,12} Finally, when using claims data to identify patients eligible for EB pharmacotherapy, existing approaches generally fail to systematically consider the tradeoffs between sensitivity and specificity associated with alternate algorithms for disease identification. Subtle differences in claims-based disease identification algorithms can have important impacts on these algorithms’ sensitivity and specificity.\textsuperscript{14} Consequently, it is important that patients are identified as requiring therapy using disease identification algorithms that have been systematically developed and validated.

In this manuscript, we describe an improved methodology for assessing adherence to EB pharmacotherapy guidelines that overcomes these limitations. To develop this methodology, we first conducted a literature review to identify relevant prior work. We then assembled a team of relevant domain experts to iteratively develop the methodology. To assess the feasibility of the methodology and to identify areas for potential improvement, we used a draft of the methodology to assess adherence to 14 EB pharmacotherapy guidelines using Medicaid claims data. We then evaluated the ability of the methodology to overcome the limitations of existing approaches.

METHODS

Definition of Medication Adherence. In accordance with the prevalent methodologies used in the literature,\textsuperscript{11,12} we determined medication adherence by the number of eligible days within a given timeframe that were covered by an appropriate drug, divided by the number of eligible days. The contribution of this work lies in how the proposed methodology classifies a given day as being eligible for pharmacotherapy and as being covered by an appropriate therapy.

Design Objectives. In developing the assessment methodology, we sought to overcome the six limitations of existing approaches described earlier. In addition, we sought to design our methodology so that electronic data in addition to claims data (e.g., data from electronic health record [EHR] systems) could be leveraged where available.

Literature Review. In order to develop the adherence assessment methodology, we began by reviewing the assessment methodologies described in two systematic reviews from 2006 regarding the use of claims data to measure medication adherence.\textsuperscript{11,12} To augment the findings in these reviews, we searched MEDLINE for English-language articles published between January 2004 and March 2007 with the following search terms, which were derived from a previous systematic review\textsuperscript{12}: ([persistence OR adherence OR patient compliance (MeSH)] and drug and [claims OR records]). Studies evaluating medication adherence using claims data were reviewed for strategies to improve the measurement of adherence to EB pharmacotherapy guidelines.

Methodology Development. To develop the assessment methodology, we assembled a team of relevant domain experts, including a pharmacist with expertise in medication adherence research (NAL); medical informatics researchers with significant experience providing clinical decision support using claims data (KK and DL); a senior software engineer with significant experience working with claims data (GS); and a statistician (KA) and health economist (EE) with significant experience using claims data for analytic purposes. These team members iteratively developed the methodology over three months.

Trial Use of Draft Methodology. To assess the feasibility of the methodology and to identify areas for potential improvement, we used a mature draft of the methodology to assess adherence to 14 EB drug therapy guidelines for asthma, diabetes, heart failure, chronic obstructive pulmonary disease, hypertension, ischemic heart disease, and stroke. Table 1 outlines the guidelines for one of these diseases (diabetes). The population evaluated was 36,000 North Carolina Medicaid beneficiaries, the data source was Medicaid claims data, and the analysis time frame was calendar year 2005. The National Drug Codes (NDCs) of relevant drugs were identified using First DataBank’s Drug Information Framework.\textsuperscript{16}

As a component of this trial implementation, we conducted a limited number of chart audits to identify areas for potential improvement. The methodology was refined to its final form based on this experience.

Methodology Evaluation. To evaluate the final methodology, we assessed whether the methodology was able to fulfill the original design objectives and thereby overcome the limitations of existing methods. When appropriate, descriptive examples are provided to illustrate how the design objectives are fulfilled.

RESULTS

Literature Review Results. The MEDLINE search identified 280 potentially relevant articles. Each article was reviewed for strategies to improve the measurement of adherence to EB drug therapy guidelines. However, no additional information was found beyond what had already been described in recent systematic reviews on methods for measuring medication adherence using claims data.\textsuperscript{11,12}

Methodology Description. Figure 1 outlines the methodology we developed for assessing adherence.
to EB pharmacotherapy guidelines. The ten steps of this methodology are described below.

**Step 1: Specification of analysis timeframe.** As the first step, the analysis timeframe is specified (e.g., a 1 year interval). If adherence is being calculated as part of an intervention such as point-of-care decision support, the ending date of the analysis timeframe should be set to the latest date for which data are available in the pharmaceutical claims database.

**Step 2: Enumeration of guideline parameters.** Next, the EB pharmacotherapy guideline is analyzed to identify inclusion criteria, exclusion criteria, and indicated drug class(es). Contraindications such as drug allergies are treated as exclusion criteria. If key criteria or the use of indicated drugs cannot be determined from available data, adherence cannot be accurately calculated for this guideline.

**Step 3: Definition of algorithms for inclusion and exclusion criteria.** In this step, algorithms are developed for determining the dates when patients met individual inclusion and/or exclusion criteria. For example, if diabetes is a criterion, a patient might be categorized as having diabetes for three years following any billing diagnosis for diabetes. Similarly, a patient might be categorized as being pregnant for 10 months following an initial billing diagnosis related to pregnancy, unless the period can be limited due to data indicating a birth or an abortive outcome. Our experience indicates that most, if not all, inclusion and exclusion criteria can be assigned an applicable time interval in this manner.

In designing these algorithms, the tradeoffs between sensitivity and specificity should be considered explicitly and systematically. Ideally, this process will involve the iterative refinement of the algorithm based on its performance against a gold standard such as chart audits. At a minimum, the anticipated sensitivity and specificity of the algorithm should be explicitly considered and documented.

**Step 4: Use of algorithms to determine dates when patient met guideline criteria.** In this step, the algorithms from step 3 are used to identify the dates within the analysis timeframe when the patient met individual inclusion and exclusion criteria.

**Step 5: Identification of periods of missing prescription data.** Next, periods when prescription data are likely to be missing are identified. Data may be missing, for example, because a patient lost insurance coverage or was hospitalized and received medications from the inpatient pharmacy.

**Step 6: Identification of dates eligible for therapy.** The dates on which the patient was eligible for therapy are identified using set operations. A patient is eligible for therapy on a given date if the patient met all inclusion criteria on that date, did not meet any exclusion criteria, and prescription data available. For example, for the use of ACE inhibitors and angiotensin II receptor blockers for diabetes (Table 1), a patient would be eligible on a given date if the following held true: 

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\text{[diabetes]} \land \text{[hypertension]} \land \text{[age > 55]} \land \text{[ischemic heart disease or dyslipidemia]} \land \text{NOT [pregnant]} \land \text{NOT [uninsured]} \land \text{NOT [hospitalized]}. 
\]

**Step 7: Determine if eligible for minimum required period.** At this point, if the patient was not eligible for a minimum required period (e.g., 6 months), the patient is excluded due to guideline ineligibility and/or the lack of sufficient data to make a meaningful assessment. The minimum required timeframe may depend on such factors as the purpose of the assessment (e.g., intervention vs. evaluation) and the frequency with which patients must refill a prescription (e.g., every 30, 60, or 90 days). For intervention purposes, patients will typically also be required to be currently eligible for the therapy.

**Step 8: Identify dates within analysis timeframe when patient was covered by indicated drug class(es) (see Figure 2).**

**Step 9: Calculate adherence as % of eligible days covered by appropriate pharmacotherapy.**

**Step 10: Interpret adherence as categorical value if needed.** Determine thresholds via empirical data or expert opinion.

**Table 1. Sample Evidence-Based Pharmacotherapy Guidelines Used for Trial Implementation of Adherence Assessment Methodology.**

<table>
<thead>
<tr>
<th>Condition</th>
<th>Guideline</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetes</td>
<td>Use of insulin or oral hypoglycemic agents by patients with diabetes and hemoglobin A1c &gt; 7%17</td>
</tr>
<tr>
<td>Diabetes</td>
<td>Use of angiotensin converting enzyme inhibitors (ACEIs) or angiotensin II receptor blockers (ARBs) by patients with diabetes who are not pregnant and (i) have hypertension, (ii) are aged &gt; 55 years old and have ischemic heart disease or dyslipidemia, or (iii) have microalbuminuria or macroalbuminuria17</td>
</tr>
<tr>
<td>Diabetes</td>
<td>Use of statins by patients with diabetes and ischemic heart disease17</td>
</tr>
<tr>
<td>Diabetes</td>
<td>Use of insulin or oral hypoglycemic agents by patients with diabetes and hemoglobin A1c &gt; 7%17</td>
</tr>
<tr>
<td>Diabetes</td>
<td>Use of angiotensin converting enzyme inhibitors (ACEIs) or angiotensin II receptor blockers (ARBs) by patients with diabetes who are not pregnant and (i) have hypertension, (ii) are aged &gt; 55 years old and have ischemic heart disease or dyslipidemia, or (iii) have microalbuminuria or macroalbuminuria17</td>
</tr>
<tr>
<td>Diabetes</td>
<td>Use of statins by patients with diabetes and ischemic heart disease17</td>
</tr>
</tbody>
</table>

**Figure 1. Overview of Adherence Assessment Methodology.**

**Step 1:** Specify analysis timeframe (e.g., a 12 month interval).

**Step 2:** Enumerate EB drug therapy guideline in terms of inclusion and exclusion criteria and indicated drug class(es). Key criteria and drug usage must be identifiable by available data.

**Step 3:** Develop algorithms for determining points in time in which patient met individual inclusion and/or exclusion criteria. Adjust systematically considering specificity and sensitivity.

**Step 4:** Use algorithms to determine dates within analysis timeframe when patient met individual guideline criteria.

**Step 5:** Identify periods when prescription data are missing.

**Step 6:** Perform set operations to determine dates when patient was eligible for therapy (met inclusion criteria, did not meet exclusion criteria, and prescription data available).

**Step 7:** Determine if patient was eligible for therapy for minimum required period. If not, stop (ineligible &/or insufficient data).

**Step 8:** Identify dates within analysis timeframe when patient was covered by indicated drug class(es) (see Figure 2).

**Step 9:** Calculate adherence as % of eligible days covered by appropriate pharmacotherapy.

**Step 10:** Interpret adherence as categorical value if needed. Determine thresholds via empirical data or expert opinion.
Step 8: Identify dates of drug coverage. Next, the dates on which the patient was covered by the indicated therapy are determined. This assessment is made using the approach defined in Figure 2. Of note, this process is simplified if a drug database is available to (i) identify the NDCs of individual drugs in the indicated therapeutic classes and to (ii) identify identical drugs with different NDCs. First DataBank, and Cerner Multum offer drug databases that can be used for this purpose.

Step 9: Calculate adherence. Using the outputs from steps 6 and 8, adherence to the EB drug therapy is calculated as the proportion of eligible days covered by the appropriate pharmacotherapy. Differences in the lengths of eligibility periods among patients can be adjusted for using standard statistical methods such as inverse probability weighted estimation.

Step 10: Interpret adherence as categorical value if needed. Medication adherence should generally be analyzed as a continuous variable. However, a categorical assessment is sometimes needed, for example to determine if a clinician should be alerted regarding a patient’s adherence level. Ideally, the appropriate threshold(s) for classification are determined via empirical data on the impacts of differing levels of adherence on the drug therapy in question. If such data cannot be obtained, the thresholds are determined by obtaining expert opinion on the level of adherence required for the specific pharmacotherapy to be effective.

Results of Trial Use of Methodology. The trial use of the draft methodology validated the feasibility of the approach. A sample distribution of adherence for one of the guidelines is provided in Figure 3.

The methodology was modified in two ways as a result of this trial implementation. First, patient eligibility is assessed throughout the analysis period rather than at a single point in time. Second, prescription data from before the analysis timeframe are included, so that drugs obtained prior to the analysis timeframe can be counted towards drug coverage (Figure 2, step A).

Methodology Evaluation. The methodology described in this manuscript fulfills all seven of our design objectives and overcomes the identified limitations of existing approaches. First, the methodology does not rely on whether a patient filled a prescription in order to determine whether the patient should be prescribed the medication. For example, a patient who never filled an indicated prescription will be correctly identified as being completely non-adherent, rather than as being ineligible for the therapy. Second, our approach enables adherence assessments to be made when incomplete but useful data are available. For example, a patient who lost insurance coverage during a portion of the analysis period can still be analyzed. Third, the methodology appropriately adjusts for early prescription refills and for medication adjustments (Figure 2). Fourth, a therapy-specific manner. For example, the binary adherence threshold for HIV pharmacotherapy may be set at 95% given the need for high adherence to prevent viral replication and drug resistance. Sixth, the methodology requires a systematic consideration of the tradeoffs between sensitivity and specificity associated with alternate algorithms for disease identification. Finally, the methodology allows relevant electronic data in addition to claims data to be used for calculating adherence, as such data can inform the points in time for which a patient is considered to meet inclusion or exclusion criteria for the drug therapy. For example, echocardiogram results from an EHR could be used to inform when a patient had left ventricular systolic dysfunction and was therefore in need of ACE inhibitor therapy.
DISCUSSION

In this manuscript, we have described an improved methodology for assessing adherence to EB pharmacotherapy guidelines using claims data. This methodology was designed to overcome the limitations associated with existing approaches.

Strengths and limitations. The central strength of our methodology is that it overcomes six significant limitations associated with existing approaches for measuring medication adherence using claims data. In addition, the methodology is feasible to implement, and it allows non-claims data such as EHR data to be utilized when available.

One limitation of our methodology is that it is more complex to implement than many existing approaches. Also, as with any claims-driven method, it assumes that patients appropriately consume medications that are dispensed. Furthermore, the methodology cannot assess adherence for over-the-counter medications (e.g., aspirin) are critical to EB pharmacotherapy guidelines. Additionally, if only claims data are available, it may not be possible to properly account for important contraindications such as allergies.

Finally, the methodology cannot differentiate between clinicians not prescribing indicated medications and patients not filling prescribed medications. Making this distinction would require the availability of prescribing data obtained from such sources as e-Prescribing systems or EHR systems. If such data were available, clinician adherence could be assessed using our approach by substituting periods in which the medication was prescribed for the periods in which the medication was available (step 8 in Figure 1). Also, patient adherence could be assessed by making the prescription of an appropriate drug an inclusion criterion in steps 2 and 3 of the methodology.

Implications. Given the significant morbidity, mortality, and cost associated with non-adherence to EB pharmacotherapy, we anticipate that there will be increased efforts aimed at measuring adherence to such therapy and at intervening when appropriate. We speculate that our methodology will inform future efforts aimed at assessing and impacting adherence to EB pharmacotherapy.

Future directions. Currently, we are in the process of using the methodology described in this manuscript to characterize adherence levels across multiple EB pharmacotherapy guidelines within a population of Medicaid beneficiaries residing in North Carolina. We then plan to leverage this methodology to implement and evaluate a point-of-care clinical decision support intervention designed to improve the use of appropriate pharmacotherapy within this vulnerable patient population.

REFERENCES