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Predictors of First-Fill Adherence for Patients With Hypertension

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Abstract

BACKGROUND—Between the promise of evidence-based medicine and the reality of inadequate patient outcomes lies patient adherence. Studies of prescription adherence have been hampered by methodologic problems. Most rely on patient self-report of adherence or cross-sectional data of plan-wide prescription fills to estimate patient-level adherence.

METHODS—We conducted a retrospective cohort study and linked individual patient data for incident prescriptions for antihypertensive medications from electronic health records (EHRs) to claims data obtained from the patient's insurance plan. Clinical data were obtained from the Geisinger Clinic, a 41 site group practice serving central and northeastern Pennsylvania with an EHR in use since 2001. Adherence was defined as a prescription claim generated for the first-fill prescription within 30 days of the prescribing date.

RESULTS—Of the 3,240 patients written a new, first-time prescription for an antihypertensive medication, 2,685 (83%) generated a corresponding claim within 30 days. Sex, age, therapeutic class, number of other medications prescribed within 10 days of the antihypertensive prescription, number of refills, co-pay, comorbidity score, baseline blood pressure (BP), and change in BP were significantly associated with first-fill rates ($P < 0.05$).

CONCLUSIONS—Patients who are older, female, have multiple comorbidities, and/or have relatively lower BPs may be less likely to fill a first prescription for antihypertensive medications and may be potential candidates for interventions to improve adherence to first-fill prescriptions.

Hypertension is a chronic disease affecting approximately 70 million adults in the United States.1 Untreated hypertension significantly increases the risk of renal disease, stroke, coronary heart disease, and congestive heart failure. Despite these consequences, blood pressure (BP) control is achieved in less than 31% of hypertensive patients,2,3 and it cannot be fully explained by insufficient treatment intensification.4 Poor medication adherence may explain much of the unacceptably low rates of uncontrolled BP.4–6

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Although numerous studies have identified a variety of reasons for nonadherence in hypertensive patients, ranging from an individual's beliefs to treatment costs and side effects,7 most studies have been hampered by methodological problems, relying on patient self-report of adherence or cross-sectional data of plan-wide prescription fills to estimate patient-level adherence.8,9 While the latter method of assessment provides a more objective view of patient's level of prescription adherence than self-report, much of the evidence to date is based on follow-up studies of patients who have filled their first prescription. That is, most strategies are confined to individuals who fill at least one prescription in the therapeutic class of interest.10 This constraint is inherent to systems that measure adherence using prescription claims data. Thus, little is known about the percent of prescriptions that are written by a physician yet never filled. In addition, the factors that contribute to first-fill nonadherence and the resulting impact on health outcomes are unknown.

Access to electronic health record (EHR) data provides a means of identifying patients who were prescribed a medication, whether or not a claim was processed. In this study, we used EHR data from clinics and prescription claims data to evaluate first-fill rates for hypertension. Specifically, we used a retrospective cohort design to assess the proportion of patients with incident hypertension who filled a naïve prescription for antihypertensive medications and to understand characteristics associated with first-fill rates.

METHODS

Setting and patients

Geisinger Clinic's EHR and Geisinger Health Plan's (GHP) claims database were the primary sources of data for this study. Geisinger is a diversified health care system encompassing the Geisinger Clinic, a multispecialty practice that has 57 clinic sites and 730 employed physicians and physician's assistants. The Epic Systems Corporation EHR system, which has been in use in all Geisinger Clinic community practice sites and specialty clinics since 1996, contains information on almost three million patients. This system allows for the integration of clinical information across diverse settings of care and makes all patient information available in digital form. Geisinger Clinic patients are represented by a diverse group of payers, including GHP, which accounts for 30% of the Clinic patients. Though GHP shares its name with Geisinger, it is an independent entity and one of the nation's largest rural health maintenance organizations. Prescription claims data were obtained from GHP.

The Geisinger Clinic patient population includes residents from central and northeastern Pennsylvania, a predominantly white population (96% Caucasian). Patients were eligible for this study if they (i) were ≥18 years of age, (ii) sought care from the Geisinger Clinic, (iii) had GHP pharmacy benefits, and (iv) were prescribed their first antihypertensive medication between January 2002 and September 2006. To be considered hypertensive, patients had to meet at least one of the following three criteria in the EHR: (i) prescribed at least one antihypertensive medication linked to the primary indication of hypertension, (ii) systolic BP >130 or diastolic BP (DBP) >80 for at least two clinical encounters, (iii) diagnosis of hypertension (International Classification of Diseases, Ninth Revision code of 401.*) linked to at least two clinical encounters or listed as an active problem on the problem list. Eligible medications fell into the following subclasses: angiotensin-converting enzyme inhibitors, angiotensin II receptor antagonists (ARBs), antiadrenergic antihypertensives, antihypertensive combinations, β-blockers (cardioselective), β-blockers (nonselective), calcium channel blockers, diuretic combinations, loop diuretics, or thiazide diuretics. Patients were eligible if they had been in the Geisinger system for at least 1 year prior to the date of the index medication, to ensure incident cases of hypertension were captured (and not prevalent disease). Finally, to eliminate patients who utilized spousal pharmacy benefits,

the analysis was limited to those who had used their GHP pharmacy benefit at any time prior to the date of the index medication.

Study variables

EHR data—Patient age, sex, race, number of refills written on the index prescription, number of prescriptions for all conditions ordered within 10 days of the index prescription, drug class, number of common comorbid conditions (other than HIV) for a calculated Charlson index,11 number of office visits 6 months prior to index prescription, BP values pre- and postindex prescription were extracted from the EHR. The Charlson index includes 19 disease categories, weighted by 1-year adjusted relative risks for mortality, to provide an indicator of disease burden. For patients in the antihypertensive medication sample, the number of medications ordered to treat hypertension on the date of the index prescription was extracted.

Pharmacy data—Data on drug class, co-pay amount, date of order for particular medication, whether the prescription was filled, and if so, the fill date were collected from the pharmacy claims database. Identifiers from the EHR record were linked to GHP pharmacy data files. Co-pay amounts for patients who did not fill their antihypertensive prescriptions were imputed from their benefit design information.

Analysis

Because fewer than 1% of prescriptions were filled beyond 30 days, a patient was designated as being adherent to the first-fill if a prescription claim was generated within 30 days of the EHR order date. Kaplan–Meier analysis was used to examine time until prescription first fill and to stratify estimates by patient characteristics (log-rank test). The primary outcome of adherence was based on patients who were classified as either fillers or nonfillers. Bivariate analysis was conducted to determine which characteristics were related to first fill. Categorical variables were analyzed using chi-square tests, Fisher's exact test, and Cochran–Armitage trend tests. Continuous variables were assessed using *t*-tests and Wilcoxon Rank Sum tests, where appropriate. A multiple logistic regression model was conducted to determine those variables that independently predicted first-fill adherence. Variables were considered for inclusion in the model when bivariate *P* values were less than 0.15 and were selected for inclusion in the model based on scientific plausibility rather than focusing on individual *P* values. All analyses were conducted with the SAS statistical software package version 9.1 (SAS Institute, Cary, NC). This study was approved by the Geisinger Institutional Review Board.

RESULTS

A total of 3,240 patients met all inclusion criteria. Of this sample, 50% (1,626) were women, 96% (3,099) were Caucasian, with a mean age of 47 years (Table 1). Prior to the index prescription, the mean systolic BP and DBP were 133 mm Hg and 88 mm Hg, respectively.

Characteristics associated with first-fill rate

In all, 83% (2,685) of naïve prescriptions were filled within a 30-day period, with most within 5 days. Age, sex, and number of medical comorbidities were associated with first-fill rate. Males were more likely to fill a first prescription than females (85% vs. 81%) and the adherent group had a mean age of 47 as compared to 49 in the nonadherent group ($P < 0.05$). Alternatively, patients with a Charlson index score of 2+ were less likely to fill their naïve prescription within 30 days than those with lower scores.

Therapeutic class and number of medications prescribed were associated with first-fill adherence rates (see Table 2). Patients prescribed ARBs (69% adherent) and loop diuretics (66% adherent) were less likely to fill their prescriptions than those prescribed other therapeutic classes such as angiotensin-converting enzyme inhibitors (84% adherent), although the finding for the ARB group was most likely confounded by a step therapy edit in place at GHP for ARB that required patients to try an angiotensin-converting enzyme inhibitor before filling an ARB prescription. Therefore, many of the ARB patients may have filled prescriptions for angiotensin-converting enzyme inhibitors or other antihypertensives. Patients prescribed an antihypertensive medication with five or more refills (84% adherent) were more likely to fill their prescriptions than patients prescribed one to four refills (80% adherent) or zero refills (79% adherent). Number of other medications prescribed within 10 days of the index prescription and co-pay were also associated with adherence rates. Patients with co-pay under $10.00 (87% adherent) were more likely to fill their prescription than patients who had to pay more than $10.00 (72% adherent, $P < 0.001$). Number of other antihypertensive medications ordered and number of office visits within 6 months prior to the prescription were not associated with adherence. Finally, BP prior to the prescription was associated with subsequent first-fill adherence (adherent: 146/89, not adherent: 140/84, $P < 0.001$, Table 3). Change in BP values were also associated with first-fill adherence rates (adherent: −14/−8, not adherent: −8/−4, $P < 0.001$). This change in BP likely resulted in postprescription BP values not being associated with adherence.

Predictors of first-fills: logistic regression model

Age, BP, and co-pay were considered in logistic regression models to determine their independent effects on first-fill rates. Odds ratio and 95% confidence intervals for each predictor retained in the model are displayed in Table 4. Patients with co-pays ≤$10.00 were more than two times as likely to fill their prescriptions than patients with co-pays of more than $10.00 (odds ratio = 2.49, 95% confidence intervals 2.03–3.06, $P < 0.0001$). Older patients were less likely to fill their prescription than patients 10 years younger (odds ratio = 0.91, 95% confidence intervals 0.84–0.98, $P = 0.016$). Patients with higher DBP prior to the index prescriptions were more likely to fill their medications than patients with DBP 10 mm Hg lower (odds ratio = 1.36, 95% confidence intervals 1.26–1.47, $P < 0.001$).

DISCUSSION

To the best of our knowledge, this is the first study to empirically measure nonadherence rates for first-fill antihypertensive prescriptions. Overall, we found that 17% of prescriptions that are written for antihypertensives go unfilled. Several factors were also observed to be associated with unfilled prescriptions including older age, female sex, lower preprescription BP, and more than two medical comorbidities. Patients prescribed ARBs, loop diuretics, given less than five refills, or with co-pay greater than $10.00 were also less likely to fill their prescriptions (ARB finding may have been confounded by ARB step-therapy edit in place at the time of the study, and loop diuretics are usually part of a multidrug treatment). This is also the first study to quantify first-fill adherence utilizing an integrated EHR, prescription claims methodology. By using established electronic databases, including EHR and pharmacy claims data and carefully excluding patients who had not used their pharmacy benefits in the past, we avoided biases associated with patient self-report. More importantly, we were able to characterize and estimate adherence rates for first fill, not just adherence among persons who filled at least one prescription, as is the case with most other studies that employ only administrative claims data.[12–15]

Our findings with regards to the characteristics of the medication regimen are consistent with those in the literature.[7] For instance, it has been noted that co-pay increases of even $2.00 can significantly reduce adherence rates.[16] Larger co-pay amounts may lead to poor

outcomes in asymptomatic patients who may elect to forgo needed medications,17 and Pharmacy and Therapeutics committees should give careful thought to medication price as a barrier to treatment. In addition, having a more complex medication regimen to manage multiple medical comorbidities is regarded as a significant barrier to adherence to antihypertensive medications.7 Finally, it is important to note that patients who filled their first prescription within 30 days of the index date experienced a greater change in BP (i.e., taking into account their higher preorder BP, Table 3) as compared to those who did not fill their prescription within the 30 days. While more longitudinal research is needed to determine whether this relationship is maintained over time, it reinforces the need to implement adherence-enhancing interventions at the inception of treatment to improve health outcomes.

A limitation of this study is that a majority of our patient population was Caucasian and only included GHP members. While our population has considerable variability in socioeconomic status, age, and comorbidity, we have limited generalizability of our findings to other racial/ethnic patient populations or those with no or limited health insurance. In addition, patients were categorized as adherent based on first-fill rates. Knowing first-fill rates alone, however, does not reveal whether a patient actually took the medication as prescribed, only that the patient filled the prescription. While we did show an association between first-fill adherence and patient cost sharing, the impact of other benefit designs and formulary controls such as prior authorizations and step-therapy edits were not evaluated in this study.

The lower threshold chosen for definition of hypertension may have overestimated the proportion of patients with diagnosis of hypertension in our sample (especially in those patients without comorbid diabetes or chronic kidney disease). That said, all eligible patients were required to have an International Classification of Diseases code for diagnosis of hypertension, which may mitigate the effect of any misclassification noted above. We purposefully restricted our analyses to use of BP control rather than by systolic BP or DBP, as per national quality reporting guidelines (i.e., Healthcare Effectiveness Data and Information Set measures required as part of the National Committee for Quality Assurance accreditation process).18

Despite these limitations, this study identified several modifiable determinants of first-fill prescription adherence to antihypertensive medications that can provide insight into the development of strategies for early intervention. When prescribing treatment for hypertension, physicians should consider not only the effectiveness of therapy but also the cost as well as characteristics of the patient that may influence overall adherence.

With increased awareness of prescription nonfill rates and identification of factors that influence nonfill, physicians can optimize therapy early in the treatment of patients with hypertension. Maximizing patient acceptance and adherence to prescribed medications will lead to better health outcomes. More research is needed to prospectively examine the relationship between first-fill rates, future prescription refills, and BP control to determine whether the characteristics identified in this study continue to predict adherence and persistence behaviors.

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Table 1

Patient characteristics

	Number adherent/total	Adherent %	*P* value
Overall	2,685/3,240	83%	
Sex			0.014[a]
Male	1,364/1,614	85%	
Female	1,321/1,626	81%	
Ethnicity/race			0.12[a]
Caucasian	2,575/3,099	83%	
Other	110/141	78%	
Charlson index[b]			<0.0001[c]
0	1,818/2,137	85%	
1	553/700	79%	
2+	314/403	78%	

Adherence was defined as prescription fill for an antihypertensive medication within 30 days of initial order.

[a] Chi-square test.

[b] HIV was not included in the score due to Institutional Review Board restrictions.

[c] Cochran–Armitage trend test.

Table 2

Characteristics of medication regimen

	Number adherent/ total	Adherent (%)	*P* value
Overall	2,685/3,240	83%	
First prescribed any use of[a]			
ACE inhibitors	1,089/1,292	84%	0.081[b]
Angiotensin II receptor antagonists (ARBs)	79/115	69%	<0.001[b]
Antiadrenergic antihypertensive	193/238	81%	0.45[b]
Antihypertensive combinations	456/542	84%	0.39[b]
β-Blockers cardioselective	1,116/1,340	83%	0.60[b]
β-Blockers nonselective	136/164	83%	0.98[b]
Calcium channel blockers	286/360	79%	0.067[b]
Diuretic combinations	105/126	83%	0.89[b]
Loop diuretics	83/126	66%	<0.001[b]
Thiazides and thiazide-like diuretics	503/605	83%	0.85[b]
Other[c]	30/42	71%	0.061[d]
Number of antihypertensive drugs ordered		83%	0.25[e]
1	1,697/2,041	83%	
2	692/828	84%	
3+	296/371	80%	
Total number of drugs ordered (±10 days)			0.014[e]
1	940/1,107	85%	
2–3	1,206/1,462	82%	
4–7	496/618	80%	
8+	43/53	81%	
Number of refills			0.0025[e]
0	194/247	79%	
1–4	440/553	80%	
5+	2,051/2,440	84%	
Co-pay amount			<0.001[b]
$0–$10.00	2,068/2,383	87%	
$10.01+	617/857	72%	
Office visits in prior 6 months			0.080[e]
0	9/10	90%	
1–4	2,273/2,730	83%	
5–9	337/414	81%	
10+	66/86	77%	

ACE, angiotensin-converting enzyme.

[a] Because a single patient can have multiple prescriptions, the totals will not add up to 100%.

[b] χ^2 test.

[c] Other hypertension medications include the following: agents for pheochromocytoma, αβ-blockers, selective aldosterone receptor antagonist, and vasodilators.

[d] Fisher's exact test.

[e] Cochran–Armitage trend test.

Table 3

Blood pressure changes and medication adherence

		Adherent (*N* = 2,685)	Not adherent (*N* = 555)	*P* value
Age	Mean (s.d.)	47 (12)	49 (13)	0.036[a]
Preorder BP[b]	Mean (s.d.)	146/89 (21/13)	140/84 (21/13)	<0.001[a]/<0.001[a]
Postorder BP[b]	Mean (s.d.)	133/81 (18/11)	132/80 (20/11)	0.39[a]/0.10[a]
Change in BP[b]	Mean (s.d.)	$-13/-8$ (20/12)	$-8/-4$ (20/12)	<0.001[a]/<0.001[a]
Co-pay amount	Median (Q1–Q3)	$8.00 ($4.68–$10.00)	$10.00 ($6.00–$13.50)	<0.001[c]

BP, blood pressure.

[a] Two-sample *t*-test.

[b] Preorder BP is the BP occurring on the day of the order (if available) or the most recent BP occurring within 180 days prior to the order. Postorder BP is the first BP occurring 10 to 365 days after the order. Change in BP is postorder BP minus preorder BP.

[c] Wilcoxon Rank Sum test.

Table 4

Multiple logistic regression model for predicting 30-day adherence to filling antihypertensive medication

	Odds ratio[a]	95% CI	*P* value
10 year increase in age	0.91	0.84–0.98	0.016
10 mm Hg increase in baseline diastolic blood pressure	1.36	1.26–1.47	<0.001
Co-pay amount < $10.00	2.49	2.03–3.06	<0.0001

CI, confidence interval.

[a] An odds ratio greater than 1 indicates a greater likelihood of a patient filling a naïve prescription.