Pharmacy-based Interventions to Reduce Primary Medication Nonadherence to Cardiovascular Medications

Michael A. Fischer, MD, MS, Niteesh K. Choudhry, MD, PhD,* Katsiaryna Bykov, PharmD, MS,* Gregory Brill, BA,* Gregory Bopp, MS,† Aaron M. Wurst, BS,† and William H. Shrank, MD, MSHS*†*

Background: Primary medication nonadherence (PMN) occurs when patients do not fill new prescriptions. Interventions to reduce PMN have not been well described.

Objectives: To determine whether 2 pharmacy-based interventions could decrease PMN.

Design: Two sequential interventions with a control group were evaluated after completion. The automated intervention began in 2007 and consisted of phone calls to patients on the third and seventh days after a prescription was processed but remained unpurchased. The live intervention began in 2009 and used calls from a pharmacist or technician to patients who still had not picked up their prescriptions after 8 days.

Subjects: Patients with newly prescribed cardiovascular medications received at CVS community pharmacies. Patients with randomly selected birthdays served as the control population.

Measures: Patient abandonment of new prescription, defined as not picking up medications within 30 days of initial processing at the pharmacy.

Results: The automated intervention included 852,612 patients and 1.2 million prescriptions, with a control group of 9282 patients and 13,178 prescriptions. The live intervention included 121,155 patients and 139,502 prescriptions with a control group of 2976 patients and 3407 prescriptions. The groups were balanced by age, sex, and patterns of prior prescription use. For the automated intervention, 4.2% of prescriptions were abandoned in the intervention group and 4.5% in the control group ($P > 0.1$), with no significant differences for any individual classes of medications. The live intervention was used in a group that had not purchased prescriptions after 8 days and thus had much higher PMN. In this setting 36.9% of prescriptions were abandoned in the intervention group and 41.7% in the control group, a difference of 4.8% ($P < 0.0001$). The difference in abandoned prescriptions for antihypertensives was 6.9% ($P < 0.0001$) but for antihyperlipidemics was only 1.4% ($P > 0.1$).

Conclusions: Automated reminder calls had no effect on PMN. Live calls from pharmacists decreased antihypertensive PMN significantly, although many patients still abandoned their prescriptions.

Key Words: medication adherence, cardiovascular medications, adherence interventions

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Nonadherence to chronic medications contributes to morbidity, mortality, and avoidable health care costs, estimated up to $290 billion a year in the United States.[1] Evaluations of the rates[2,3] and predictors[4–8] of nonadherence have been conducted, and numerous interventions have been implemented to improve medication adherence.[9–12] Historically, little has been known about how often patients are written prescriptions but fail to ever fill the first one—known as primary medication nonadherence (PMN). With the advent of electronic prescribing, researchers have been able to link e-prescriptions to prescription claims records and have found PMN in community settings of 22%–28%.[13,14] Studies in closed health care systems have found slightly lower rates of PMN (15%–26%), although the problem is still substantial.[15–17]

Once PMN can be identified and measured, the challenge is to identify interventions specifically targeting PMN. Systematic reviews of the adherence literature indicate that community pharmacists can play an important role.[10,18] Earlier research analyzed prescriptions abandoned at community pharmacies, a specific subset of PMN, and found important patient and prescription-level characteristics associated with failure to pick up a prescription.[19] Accordingly, strategies using community pharmacists to reduce new prescription abandonment could represent an important approach for addressing PMN. We evaluated 2 interventions

From the *Department of Medicine, Division of Pharmacoepidemiology and Pharmacoeconomics, Brigham and Women's Hospital, Boston, MA; and †CVS-Health, Woonsocket, RI.

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Reprints: Michael A. Fischer, MD, MS, Department of Medicine, Division of Pharmacoepidemiology and Pharmacoeconomics, Brigham and Women's Hospital, 1620 Tremont Street, Suite 3030, Boston, MA 02120. E-mail: mfischer@partners.org.

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implemented by a large pharmacy chain to reduce abandonment of new prescriptions for cardiovascular medications; an initial intervention using automated reminder phone calls to patients and a second intervention using personal phone calls from pharmacists.

METHODS

Overview

CVS designed and implemented 2 interventions to reduce abandonment of new prescriptions for cardiovascular medications. The interventions were conducted before involvement of the academic research team. For new interventions CVS routinely designates a random subset of patients not to receive the intervention. After both interventions had been concluded, the research team agreed with CVS-Caremark to obtain data for an analysis of both interventions.

Population

The service was provided to all patients who used CVS community pharmacies except those born on a small subset of randomly selected birthdays. Control patients received usual care. We evaluated patients who used CVS pharmacies and were also insured by Caremark, a large national pharmacy benefits manager, so that we could use Caremark claims data to more completely assess a patient's medication use subsequent to the intervention regardless of where a prescription was filled.

Interventions

Automated Intervention

In 2007, CVS community pharmacies implemented a nationwide intervention to reduce the portion of PMN accounted for by abandonment of new prescriptions. This specific element of PMN was defined by any prescription that was received and processed at the pharmacy, but not purchased by the patient. Patients received automated phone calls on days 3 and 7 after the prescription was processed but remained unpurchased. The calls reminded patients that their prescription was ready and encouraged them to pick it up. Patients with four randomly selected birthdays served as the control population for this intervention.

Live Intervention

In 2009, CVS community pharmacies began a program in which they identified patients who had not purchased a prescription 8 days after it was bottled, even after receiving automated calls on days 3 and 7. A pharmacist or technician called these patients to better understand barriers to medication adherence and provide counseling and solutions to encourage appropriate medication use. Messaging included education about the importance of treatment, suggestions about lower cost options when relevant, and efforts to engage and motivate patients to adhere to therapy. Records indicated which patients were selected to receive the intervention, but data were not recorded on whether pharmacists or technicians left a message or actually spoke with patients, or on the content of conversations. Patients with eight randomly selected birthdays served as the control population for this intervention.

Data

New prescriptions for cardiovascular medications (antihypertensives, antihyperlipidemics, antiarrhythmics, nitrates, digoxin) received at CVS community pharmacies were identified. The time window for prescriptions was from January 1, 2008 to November 30, 2008 for the automated intervention and from January 1, 2010 to November 30, 2010 for the live intervention. Transaction data from the CVS community pharmacies were linked with prescription claims data from Caremark, from June 2007 to December 2008 for the automated intervention analysis and from June 2009 to December 2010 for the live intervention analysis. The linkage of records was performed by CVS-Caremark, which already had access to all patient information.

Claims data were used to identify previous and subsequent dispensings at any pharmacy. The date the new prescription was ordered and prepared at the pharmacy was defined as the index date. A prescription was considered new if there were no claims in the same therapeutic class 6 months before the index date. Patients without at least 6 months of eligibility before the index date were excluded unless they had another prescription that satisfied the inclusion criteria. Claims data for 30 days after the index date were used to identify dispensing of any drug from the

TABLE 1. Automated Intervention: Patient Characteristics (At the Time of the First Index Rx; Prior Use Assessed Over the Period of 6 mo Before Index Date)

Characteristic	Intervention Group (N = 852,612)	Control Group (N = 9282)
Total number of index prescriptions	1,226,834	13,178
Age in years, mean (SD)	59.1 (16.2)	59.3 (16.2)
Age group, n (%)		
0–17	8219 (1.0)	91 (1.0)
18–34	45,952 (5.4)	475 (5.1)
35–49	179,432 (21.0)	1951 (21.0)
50–64	303,009 (35.5)	3275 (35.3)
65 and older	316,000 (37.1)	3490 (37.6)
Female sex, n (%)	463,577 (54.4)	5032 (54.2)
Mean no. index prescriptions per patient	1.44	1.42
Prior use of medications (%)		
Statins	21.6	22.3
Antihypertensive meds	54.0	53.8
Antidepressants	18.6	18.3
Antipsychotics	3.2	3.3
Inhaled asthma/COPD meds	10.3	10.6
Oral diabetes medication	15.0	15.1
Hydrocodone-APAP	14.4	14.4
Insulin	5.1	5.3
Osteoporosis medications	6.0	6.1
Proton pump inhibitors	18.0	17.8
Thyroid medications	10.4	10.4
Warfarin	5.3	5.1
Mean no. different medications	7.69	7.63

same therapeutic class as the index prescription at any pharmacy. Patient characteristics were assessed on the index date and during the 6-month prior period. Before data were provided to the research team all identifiers were removed. The study was approved by the Institutional Review Board at the primary author's home institution.

Outcome

The primary outcome was prescription abandonment, defined as a reversed Caremark claim for a new cardiovascular prescription with no subsequent claim for a medication from the same therapeutic class within 30 days following the index date.

Analyses

Patient characteristics at baseline were assessed using descriptive statistics. We compared proportions of prescriptions abandoned in the intervention group and controls. The unit of analysis was the prescription and proportions were expressed as number of prescriptions abandoned divided by total prescriptions initially processed by the pharmacy. We used a generalized linear model with logit link function to adjust for clustering of prescriptions within patients. Results were further stratified by medication classes. All analyses were performed using SAS software, version 9.3 (SAS Institute, Cary, NC).

Role of the Funding Source

The research was funded by the National Association of Chain Drug Stores Foundation. Study design, conduct, and reporting were determined independently by the research team.

RESULTS

The automated intervention included 852,612 patients and 1.2 million prescriptions, with a control group of 9282 patients and 13,178 prescriptions. The live intervention included 121,155 patients and 139,502 prescriptions with a control group of 2976 patients and 3407 prescriptions. Control and intervention groups were balanced by age, sex, and prior prescription use (Tables 1 and 2). Most patients received 1 new cardiovascular prescription during the study period, but a substantial fraction received 2 or more (Table 3).

Table 4 shows the main results for the automated intervention. The proportion of abandoned prescriptions was 4.2% in the intervention group and 4.5% in the control group ($P = 0.23$). For antihypertensives the proportion of abandoned prescriptions was 3.7% in the intervention group and 4.1% in the control group ($P = 0.06$), whereas for antihyperlipidemics the proportions were the same (6.0%). The intervention did not have a significant impact on abandoned prescriptions for other CV medications.

The live intervention was used in patients who had received the automated intervention but not purchased prescriptions after 8 days. Table 5 shows that in this setting the proportion of abandoned prescriptions was 36.9% in the intervention group and 41.7% in the control group, a difference of 4.8% ($P < 0.0001$). The difference for antihypertensives was 6.9% ($P < 0.0001$) but for antihyperlipidemics was only 1.4% ($P = 0.25$). Inclusion of prescriber characteristics, copayment, median income for the patient's zip code or patient demographics in multivariate models did not substantively change any findings.

TABLE 2. Pharmacist Intervention: Patient Characteristics (At the Time of the First Index Rx; Prior Use Assessed Over the Period of 6 mo Before Index Date)

Characteristic	Intervention Group (N = 121,155)	Control Group (N = 2976)
Total number of index prescriptions	139,502	3407
Age in years, mean (SD)	56.6 (14.3)	57.3 (14.4)
Age group, n (%)		
0–17	0	0
18–34	6714 (5.5)	154 (5.2)
35–49	30,997 (25.6)	720 (24.2)
50–64	51,860 (42.8)	1276 (42.9)
65 and older	31,584 (26.1)	826 (27.8)
Female sex, n (%)	63,602 (52.5)	1593 (53.5)
Mean no. index prescriptions per patient	1.15	1.14
Prior use of medications (%)		
Statins	17.7	18.1
Antihypertensive meds	46.3	46.1
Antidepressants	19.2	19.3
Antipsychotics	2.7	2.6
Inhaled asthma/COPD meds	9.4	9.4
Oral diabetes medication	17.8	17.8
Hydrocodone-APAP	15.4	15.7
Insulin	6.5	6.3
Osteoporosis medications	3.5	3.5
Proton pump inhibitors	16.7	17.3
Thyroid medications	10.1	10.6
Warfarin	4.0	4.9
Mean no. different medications	6.63	6.65

TABLE 3. Patients and Number of New Cardiovascular Prescriptions in the Cohort

	N (%)	
	Intervention	Control
Automated intervention		
Patients	852,612	9282
Prescriptions	1,226,834	13,178
Patients with 1 index Rx	608,159 (71.3)	6681 (72.0)
Patients with 2 index Rxs	161,752 (19.0)	1756 (18.9)
Patients with 3 index Rxs	52,517 (6.2)	545 (5.9)
Patients with 4+ index Rxs	30,184 (3.5)	300 (3.2)
Mean index Rxs per patient	1.44	1.42
Live intervention		
Patients	121,155	2976
Prescriptions	139,502	3407
Patients with 1 index Rx	106,612 (88.0)	2631 (88.4)
Patients with 2 index Rxs	11,671 (9.6)	282 (9.5)
Patients with 3 index Rxs	2178 (1.8)	46 (1.6)
Patients with 4+ index Rxs	694 (0.6)	17 (0.6)
Mean index Rxs per patient	1.15	1.14

TABLE 4. Automated Intervention: Prescription Abandonment, Total and by Drug Class

	Intervention Group			Control Group			
Drug Class*	**Total Rx**	**Abandoned†**	**%**	**Total Rx**	**Abandoned†**	**%**	***P*******
All classes	1,226,834	51,890	4.2	13,178	596	4.5	0.23
Antihypertensives	814,187	29,683	3.7	8718	361	4.1	0.06
ACEI/ARBs	189,053	8071	4.3	2030	90	4.4	0.73
β-blockers	166,456	5201	3.1	1753	61	3.5	0.38
Ca channel blockers	102,119	3411	3.3	1050	38	3.6	0.62
Diuretics	220,186	6201	2.8	2396	87	3.6	0.02
Antiarrhythmics	11,336	296	2.6	138	2	1.5	0.40
Antihyperlipidemics	328,323	19,544	6.0	3504	210	6.0	0.93
Others	72,988	2367	3.2	818	23	2.8	0.50

*Antihypertensive combination products were only counted in the "antihypertensives" class category; therefore, the sum of the specific antihypertensive classes does not add up to the category "antihypertensives"; "others" category includes digoxin, peripheral vasodilators, phosphodiesterase inhibitors, nitrates, and other antianginals.

†Abandoned are prescriptions for which no medication from the same therapeutic class (identified by the first 4 digits of the Generic Product Index) was purchased by a patient at any pharmacy within 30 days following the index prescription processing.

***P* values from generalized linear model adjusted for clustering of prescriptions within patients.

ACEI indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker.

DISCUSSION

We evaluated 2 pharmacy-based interventions designed to reduce PMN for cardiovascular medications. We found that automated calls from the pharmacy did not significantly reduce prescription abandonment. Adding live telephone calls if patients still had not picked up their new prescriptions did reduce abandonment by almost 5%. This effect was driven by increased filling of antihypertensive medications—there was no effect of the live intervention on antihyperlipidemics or other cardiovascular medication classes. This difference may indicate that patient decisions about whether to fill antihypertensive medications are more amenable to intervention than such decisions for other medications. Our data cannot indicate reasons for this difference, although possible explanations could include patient perceptions of the seriousness of hypertension versus hyperlipidemia. Future qualitative research assessing patient reasons for PMN, degree of openness to interventions, and reasons for these perceptions could inform new interventions.

As PMN has not been widely measured until recently, there is limited prior literature on the impact of interventions to increase primary adherence to newly prescribed medications. DeRose et al[17] evaluated automated telephone calls and follow-up letters to 2606 patients who had not filled a new statin prescription, finding a significant increase in statin filling with the intervention, very different from our results. The intervention studied by DeRose and colleagues took place in the Kaiser Permanente system, a large integrated health care system and the outreach to patients was from their health care provider, and included multiple modalities, whereas the intervention that we studied was initiated by the pharmacy to which the prescription was sent.

There are important limitations to consider when interpreting these findings. Patients may have filled prescriptions that were not captured in the claims data—for example, if patients paid cash for a prescription or had additional drug insurance coverage. This would lead us to overestimate prescription abandonment and might obscure potential impacts of the intervention. Given that we did not

TABLE 5. Live Intervention: Prescription Abandonment, Total and by Drug Class

	Intervention Group			Control Group			
Drug Class*	**Total Rx**	**Abandoned†**	**%**	**Total Rx**	**Abandoned†**	**%**	***P*******
All classes	139,502	51,455	36.9	3407	1419	41.7	<0.0001
Antihypertensives	82,373	29,106	35.3	1993	841	42.2	<0.0001
ACEI/ARBs	21,600	7756	35.9	541	222	41.0	0.02
β-blockers	16,276	5645	34.7	400	176	44.0	<0.001
Ca channel blockers	9726	3466	35.6	220	79	35.9	0.93
Diuretics	18,525	6179	33.4	426	182	42.7	<0.0001
Antiarrhythmics	667	239	35.8	15	5	33.3	0.84
Antihyperlipidemics	51,254	20,180	39.4	1284	524	40.8	0.25
Others	5208	1930	37.1	115	49	42.6	0.22

*Antihypertensive combination products were only counted in the "antihypertensives" class category; therefore, the sum of the specific antihypertensive classes does not add up to the category "antihypertensives"; "others" category includes digoxin, peripheral vasodilators, phosphodiesterase inhibitors, nitrates. and other antianginals.

†Abandoned are prescriptions for which no medication from the same therapeutic class (identified by the first 4 digits of the Generic Product Index) was purchased by a patient at any pharmacy within 30 days following the index prescription processing.

***P* values from generalized linear model adjusted for clustering of prescriptions within patients.

ACEI indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker.

see an impact when we added copayments to the model we do not think that cost-related nonadherence affected our findings; prior studies have shown that cost is a factor in medication nonadherence but with a relatively small absolute impact.[7,13,20] We did not have data on whether individual pharmacies were calling patients before the intervention start, or on the extent to which individual pharmacists complied with live phone call protocols. Imbalance in the randomly selected intervention and control groups could lead to biased results, but Tables 1 and 2 show that the randomly selected control population resulted in excellent comparability of the intervention and control groups. Only 6 months of preintervention claims data were available, so we may have included patients who had used the index drugs previously. We evaluated an intervention in a single community pharmacy chain and for only cardiovascular medications, which could limit the generalizability of our findings.

Our results have important implications for clinical and policy approaches to improving medication adherence. Automated reminder calls from pharmacies are used commonly, but in this study they did not improve primary medication adherence. We evaluated only newly prescribed medications; automated calls may be useful for patients refilling existing medications. Live intervention results were more promising; on the basis of the changes in adherence that we observed, 15 live calls would yield 1 additional filled prescription for an antihypertensive medication. The live intervention was for patients who had not picked up prescriptions after 8 days despite automated calls; whether the impact would differ if the intervention were implemented sooner is not clear from these data. The cost-effectiveness of this approach would depend on the time required for each call and the long-term clinical impact of improved adherence. Primary care clinicians, pharmacists, and insurers will need to consider these results when designing new interventions targeting PMN. Recent conclusions from the CBO that increased spending for prescription drugs is offset by reduced health services utilization highlight an important additional consideration for risk-bearing providers such as accountable care organizations or patient-centered medical homes.[21]

In conclusion, we analyzed 2 large, national populations of patients and prescriptions who received interventions to improve primary medication adherence. Although automated interventions did not improve adherence, the addition of live interventions increased the filling of new prescriptions for antihypertensives. Even with the positive changes with the addition of the live intervention, many patients still abandoned their prescriptions at the pharmacy. While pharmacy-based interventions can play an important role in improving medication adherence, this study makes clear that truly improving adherence, and thus patient outcomes, is likely to require multiple interventions targeting the different elements of this complex behavior.

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