Effect of a Pharmacist on Adverse Drug Events and Medication Errors in Outpatients With Cardiovascular Disease

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Background: Adverse drug events and medication errors are threats to quality care. Inpatient studies suggest that a pharmacist may reduce these events, but outpatient studies have not been forthcoming.

Methods: We conducted a pooled analysis of 2 randomized controlled trials to determine the effect of pharmacist intervention on adverse drug events and medication errors. We studied 800 outpatient cases of hypertension stratified into complicated (n=535) and uncomplicated (n=265). Patients in the complicated stratum had heart failure or other cardiovascular complication. Computer programs examined 1-year electronic record data to identify events classified as adverse drug events and preventable or potential adverse drug events. Medication errors included preventable and potential adverse drug events.

Results: Of the 800 participants (mean [SD] age, 59 [10] years), 484 (90.5%) and 258 (97.4%) participants remained in the complicated and uncomplicated strata, respectively, at 12 months. Compared with the control group, the risk of any event was 34% lower in the intervention group (risk ratio, 0.66; 95% confidence interval [CI], 0.50-0.88), including a lower risk of adverse drug events (risk ratio, 0.65; 95% CI, 0.47-0.90), preventable adverse drug events (risk ratio, 0.52; 95% CI, 0.25-1.09), potential adverse drug events (risk ratio, 0.70; 95% CI, 0.40-1.22), and medication errors (risk ratio, 0.63; 95% CI, 0.40-0.98).

Conclusions: This post hoc analysis suggests that pharmacist intervention to improve medication use in outpatients with cardiovascular disease decreases the risk of adverse drug events and medication errors. Further studies are needed to confirm this finding.

Trial Registration: clinicaltrials.gov Identifiers: NCT00388622 and NCT00388817

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interventions have tested the effect of pharmacists on incident events in outpatients. We therefore determined the effect of pharmacist intervention on incident ADEs and MEs in outpatients with heart failure or hypertension receiving care in a county health care system.

METHODS

Data were pooled from 2 randomized controlled trials, one trial of patients with heart failure and the other trial of patients with hypertension. The trials had similar designs and were conducted in the same health care setting with the same primary objective: to test the effect of pharmacist intervention on medication adherence and relevant health outcomes. Assessment of ADEs and MEs were secondary study objectives. Details of the original studies have been previously described. The studies were approved by the institutional review boards of Indiana University–Purdue University at Indianapolis, Indiana, and the University of North Carolina at Chapel Hill.

STUDY SETTING AND PARTICIPANTS

Participants for both trials were recruited at the outpatient practices of Wishard Health Services, Indianapolis, Indiana. Wishard is located on the campus of Indiana University School of Medicine at Indianapolis and is part of a city-county teaching hospital serving the socioeconomically disadvantaged and medically vulnerable population of Marion County, Indiana. Adult outpatients who receive care at Wishard Health Services are predominately women (66%) with a mean (SD) age of 57 (15) years. Most patients receive their prescription medications through state and local assistance plans at no cost.

Participants were eligible for the heart failure study if they had a diagnosis of heart failure confirmed by their primary care physician, were 50 years or older, and regularly used at least 1 cardiovascular medication for heart failure. Patients were eligible for the hypertension study if they had a diagnosis of hypertension, were at least age 18 years, and were taking at least 1 antihypertensive drug. Participation in either study required that the patient planned to receive all primary care at the study center and their prescription drugs at a Wishard Pharmacy. The heart failure study was conducted from February 2001 to November 2004, and the hypertension study was conducted from January 2002 to May 2005.

A comprehensive medication history and medication assessment was conducted by pharmacists at baseline. A research assistant then randomly assigned patients to either an intervention or control group using a computer randomization protocol. In the heart failure study, there were 314 participants (122 in the intervention group and 192 in the control group). In the hypertension study, there were 492 participants (246 in the intervention group and 246 in the control group) of whom 6 had incomplete ADE and ME data and were excluded from this analysis. Participants in the hypertension study were stratified into complicated and uncomplicated strata prior to randomization. Participants were considered to have complicated hypertension if they had prior evidence of a vascular disorder or insult indicating poorly controlled hypertension, including myocardial infarction, coronary heart disease, stroke, heart failure, or renal insufficiency. We ascertained these complications using diagnostic, procedural, radiologic, and laboratory data from the Regenstrief Medical Records System. Patients with uncomplicated hypertension had no history of cardiovascular complications from their disease. We combined participants from the heart failure study with the participants in the complicated stratum of the hypertension study to form a larger group of patients with complicated hypertension. Thus, the combined studies of 800 participants formed 2 strata of complicated (232 intervention and 303 control group patients) and uncomplicated (134 intervention and 131 control group patients) hypertension.

INTERVENTION

The intervention was provided by specifically trained and equipped pharmacists who communicated regularly with intervention participants to dispense medications and provide them with ongoing oral and written instruction. Following the baseline medication history, participants were provided medications in containers that enabled electronic monitoring of adherence to the prescribed cardiovascular medications and medication information designed for persons with low health literacy. The intervention pharmacist used a study computer that was integrated into the electronic medical record system for the purpose of monitoring prescription and nonprescription medications, tracking materials provided to patients, and documenting communications with patients, nurses, and physicians. The intervention was similar in both studies except for its duration and follow-up. In the heart failure study, intervention participants received the intervention for 9 months with a 3-month postintervention follow-up period. In the hypertension study, the intervention lasted for 12 months with a 6-month postintervention follow-up.

CONTROL

Participants assigned to the control arm were observed for 12 and 18 months in the heart failure and hypertension studies, respectively. Participants in the control group received usual care at the same pharmacy from nonintervention pharmacists who did not have access to the study computer, instructional materials, or the study computer monitoring program. Pharmacists serving control participants had similar access to health system physicians and nurses.

MEASUREMENTS

Data on ADEs and MEs were collected for 12 months using a program developed for a separate study. This program examined coded and text electronic health record data to identify triggers suggestive of selected ADEs and MEs in outpatients. A list of triggers was drawn up a priori and included more than 100 ADEs or MEs commonly observed in adult general practices (Table 1). Examples of relevant events included angiotensin-converting enzyme (ACE) inhibitor–related allergy or cough, toxic serum digoxin concentrations, or use of nonsteroidal anti-inflammatory drugs in persons with elevated serum potassium concentrations or renal insufficiency. Computer programs identified triggers by comparing with coded (laboratory and prescription records) and text data (transcribed and dictated physician notes). Coded data were available for both studies; however, we had access to text data only for the heart failure study. Computer programs were run by programmers blinded to treatment group assignment after patients had completed their full participation in the trials. A trained nurse abstractor, also blinded to group assignment, verified whether an ADE or ME had actually occurred using both electronic health records and the paper medical records. The nurse adjudicator was trained using methods similar to those used in previous studies that had good interrater agreement (κ values of 0.81 and 0.89) and had more than 15 years of experience in quality assurance including medication safety research.
OUTCOMES

Events were classified by the nurse as ADEs, preventable ADEs, and potential ADEs as defined by Bates et al.14: ADEs were defined as drug events that produced harm; preventable ADEs were drug events that produced harm and were considered to have been the result of a medication error; and potential ADEs were medication errors that had the potential for harm but no evidence of harm was observed or the error was intercepted before reaching the patient (such as a prescription for a drug to which the patient was reportedly allergic). Our criteria for potential ADEs were similar to those described by Poon and colleagues25 for an inpatient study. Medication errors were mistakes made in prescribing or drug monitoring. For the purpose of this study, MEs were the sum of preventable and potential ADEs.

INDEPENDENT VARIABLES

Data on age, sex, race, years of formal education, marital status, household income adequacy, and insurance were collected at the baseline interview. We categorized perceived income adequacy as “comfortable,” “just enough to get by,” or “not enough to get by.”26,27 Insurance included Medicare, Medicaid, Health Advantage (a medical assistance program available to low-income patients), private, or none. Encounters were any visit made to the health system requiring registration. Co-morbidities included any chronic disorder for which a medication would likely be prescribed.

STATISTICAL ANALYSIS

Comparisons of patient characteristics between the intervention and control groups, stratified by complication status, were made using t tests for continuous variables and χ² tests for categorical variables with a P value less than .05 considered statistically significant. The χ² or Fisher exact tests were also used to test the hypotheses that the ADEs and MEs among participants were independent of intervention or control group assignment. We calculated the overall and specific distribution of ADEs, preventable ADEs, potential ADEs, and MEs experienced by patients in complicated and uncomplicated strata for 12 months. Medication errors were the subset of ADE events involving MEs; namely, preventable ADEs and potential ADEs. Risk ratios for the counts of ADEs or MEs were calculated for intervention and control participants using Poisson regression models.

RESULTS

The Figure is the study participant flowchart. A total of 800 participants with cardiovascular disorders were studied, 314 from the heart failure study and 486 from the hypertension study. These participants formed groups of complicated (n = 335) and uncomplicated hypertension (n = 265) disease for pooled analysis. Considering persons lost to follow-up and deaths at 12 months, 484 (90.5%) and 258 (97.4%) participants remained in the complicated and uncomplicated strata, respectively. Study participants were a mean (SD) of 59 (10) years old; 71.1% were women; and 60.4% were African American (Table 2). Participant balance on important background characteristics between control and intervention groups was good. Counts of prescription medications at 12 months were similar to baseline counts for complicated (P = .53) and uncomplicated (P = .48) strata.

EVENT IDENTIFICATION AND VERIFICATION

The computer monitor identified 1029 triggers that were further analyzed for evidence of ADEs and MEs. Of the 1029 triggers, 694 (67.4%) occurred in the control group, and 335 (32.6%) occurred in the intervention group. After further analysis by the nurse adjudicator, of the 694 triggers in the control group, 135 ADE or ME events were verified (positive predictive values, 19.5% and 10.0% for coded and text data, respectively), and the 335 triggers in the intervention group yielded 75 ADE or ME events (positive predictive value, 22.4%).

Of the 210 events, the 5 most common, occurring in a total of 68 participants, included receipt of a prescription for a drug that should be avoided in elderly patients.
(n = 28), vaginal candidiasis resulting from an orally administered antibiotic (n = 14), an increase in serum creatinine level associated with a medication (n = 10), inadequate monitoring after prescribing (n = 9), and prescription of multiple acetaminophen products (n = 7). Most events involved a cardiovascular medication (n = 44; 21%) followed by drug interactions involving multiple drug classes (n = 39; 18.6%), and then events associated with antimicrobial agents (n = 24; 11.4%) or hypoglycemic agents (n = 12; 5.7%).

**EFFECT OF THE INTERVENTION**

Ninety percent of all events occurred in the complicated stratum and 10% in the uncomplicated stratum. For both strata, events were fewer in the intervention groups compared with controls (Table 3). In the complicated stratum, 121 events were observed in the control group and 68 in the intervention group. The overall mean (SD) number of events per participant was 0.37 (0.9) for the control group and 0.28 (0.8) for the intervention group.
(P = .04). In the uncomplicated stratum, there were 14 events in the control group and 7 in the intervention group. The overall mean numbers of ADEs and MEs per participant were 0.07 (0.30) and 0.03 (0.20) for control and intervention groups, respectively (difference not significant). Table 4 summarizes the types and frequencies of events.

Adverse drug events occurred in 121 participants (15.1%) in the control and intervention groups. Fewer ADEs were observed in the intervention group. In the complicated control group, the mean (SD) number of ADEs per participant was 0.36 (0.9) compared with 0.28 (0.8) in the intervention group (P = .04). While there were also fewer ADEs per participant in the uncomplicated intervention group than in the control group (0.03 [0.20] vs 0.07 [0.30]), the difference was not significant.

Medication errors occurred in 58 participants (7.3%) in the control and intervention groups. There were fewer MEs with the intervention in both the complicated and uncomplicated strata, but the difference was significant only in the uncomplicated stratum: a mean (SD) 0.06 (0.20) MEs per participant were observed in the control and 0.01 (0.10) MEs in the intervention groups (P = .04). In the complicated stratum, there were 0.14 (0.5) MEs per participant in the control group and 0.10 (0.4) in the intervention group (difference not significant).

Risk ratios comparing control and intervention effects by group are listed in Table 5. Compared with the control group, the risk of any event was 34% lower in the intervention group (risk ratio, 0.66; 95% confidence interval [CI], 0.50-0.88) including a lower risk of ADEs (risk ratio, 0.65; 95% CI, 0.47-0.90); preventable ADEs (risk ratio, 0.52; 95% CI, 0.25-1.09), potential ADEs (risk ratio, 0.70; 95% CI, 0.40-1.22), and MEs (risk ratio, 0.63; 95% CI, 0.40-0.98). These effects of the intervention were consistent within complicated and uncomplicated strata.

The results of this post hoc analysis suggest that pharmacist intervention to improve medication use in adult outpatients with cardiovascular disease decreases ADEs and MEs. While these findings were the result of a pooled estimate involving 2 studies, the effects were consistent within individual studies. Most of the events (90%) derived from individuals with complicated cardiovascular disease such as heart failure who had more complicated drug regimens.

The focus of the intervention was aimed at improving adherence and medication use by pharmacists spending more of their time instructing patients on the appropriate use of their medications, drug monitoring, and communication with patients’ primary care physicians.14,18 Intervention group participants received (1) careful instruction on how the medications should be used, (2) patient-centered oral and written information, and (3) answers to their medication questions. It is reassuring that the intervention aimed at improving adherence did not increase the risk of ADEs that could occur with increased adherence. However, it is likely that much of the intervention’s effect on reducing the risk of
such events in this study derived from pharmacist drug monitoring and communicating with physicians and nurses.

Pharmacists regularly communicated with physicians and nurses concerning patient-reported symptoms, drug-related problems including ADEs and MEs, and changes in important drug-monitoring parameters such as laboratory results affected by drugs. In the 314 patients with heart failure, we previously found that pharmacist intervention improved adherence to cardiovascular medications and patient satisfaction and reduced health care utilization and direct costs of care.3,22 While fewer patients experienced ADEs and MEs (37.3% vs 47.4%) (P = .09), the study was not statistically powered to reveal the effects of the intervention on patient safety factors. As such, we pooled the data from similarly designed studies involving patients with heart failure and hypertension and observed a decreased risk of adverse events associated with the intervention. The Institute for Safe Medication Practices28,29 has emphasized the importance of interventions by pharmacists to improve adherence, offer instruction aimed at mitigating deficiencies in health literacy, and enhance communication between health care providers and patients.

Measurement of ADEs and MEs was accomplished using a computer program that had been developed for the purpose of other research.3,32 The identification of ADEs and MEs using this method underestimates the true incidence of these events for several reasons. First, events were defined a priori based on a list of commonly observed ADEs and MEs in adult outpatients, and as such the universe of events is not represented herein. Also, our inability to assess text data in the hypertension study likely resulted in fewer ADEs manifested by symptoms in that cohort.

Second, methods to identify events using computer programs have generally provided lower estimates than direct observation and survey methods.6,6 While the negative predictive value of computer-based identification is very good (>80%), positive predictive value is low (<25%).3,32 Furthermore, we could not determine errors of administration and other events that frequently occur in patients’ homes. Nonetheless, we believe that the use of the standardized computer program with blinded expert verification of events adds an important contribution to safety assessment in studies like ours by offering identical event identification protocols for intervention and control groups. Others have suggested that computer-based surveillance methods may be reasonable for assessing the impact of interventions.30,31

Although the severity of harm was not specifically ranked, most of the events were mild; none were life-threatening. The intervention was effective in reducing some but not all harmful events, as illustrated by ACE inhibitor and β-blocker prescribing for patients with heart failure. In the control group, there were more ACE-associated rashes in patients with new prescriptions for these drugs in the intervention group than among controls (intervention, n = 4; control, n = 1). However, an important part of the intervention in the heart failure study was to remind physicians of the importance of prescribing ACE inhibitors to patients with heart failure. Therefore, it would be expected that prescriptions for these drugs in ACE inhibitor–naïve patients would lead to a greater risk of allergies. In contrast, while prescribing β-blockers for patients with heart failure was appropriately encouraged by pharmacists, fewer patients experienced β-blocker–associated bradycardia (pulse, <60 beats/min) in the intervention group, presumably owing to heightened vigilance by pharmacists who regularly monitored patients’ pulses (intervention, n = 0; control, n = 3). Evidence of bleeding associated with nonsteroidal anti-inflammatory drugs including aspirin can be especially concerning and occurred in 5 and 2 patients in the control and intervention groups, respectively; however, none of these events was severe.

Another potential limitation of the study is that we analyzed 12 months of data for both heart failure and hypertension studies, but the intervention ran only 9 months for the heart failure study. Our reasoning was that there would be future benefits of pharmacist activities to improve the quality and safety of medication use. For example, some nonurgent recommendations made by e-mail or paper notation would be executed by the physician at the patient’s next visit, resulting in a delayed benefit. This assumption might not be accurate. In our previous study of pharmacist effects on adherence in these patients, when the intervention stopped, the effects dissipated.14 However, the adherence effects were largely believed to be the result of direct pharmacist interaction with the patient, while the effects on ADEs and MEs were primarily due to interactions with physicians and nurses.

It is possible that interventions such as ours could have favorable effects on the costs of care. Our economic analysis indicates lower actual direct health care costs associated with the overall effects of the multifaceted interven-

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Table 5. Comparison of Intervention and Control Group Medication-Related Events and Errors

<table>
<thead>
<tr>
<th>Study Group</th>
<th>All Events</th>
<th>ADEs</th>
<th>Preventable ADEs</th>
<th>Potential ADEs</th>
<th>Medication Errors</th>
</tr>
</thead>
<tbody>
<tr>
<td>All participants (N=800)</td>
<td>0.66 (0.50-0.88)</td>
<td>0.65 (0.47-0.90)</td>
<td>0.52 (0.25-1.09)</td>
<td>0.70 (0.40-1.22)</td>
<td>0.63 (0.40-0.98)</td>
</tr>
<tr>
<td>Complicated hypertension (n=535)</td>
<td>0.74 (0.55-0.99)</td>
<td>0.68 (0.46-0.95)</td>
<td>0.54 (0.25-1.17)</td>
<td>0.98 (0.53-1.81)</td>
<td>0.77 (0.48-1.24)</td>
</tr>
<tr>
<td>Uncomplicated hypertension (n=265)</td>
<td>0.49 (0.20-1.22)</td>
<td>1.23 (0.33-4.58)</td>
<td>0.98 (0.06-15.73)</td>
<td>0.20 (0.04-0.90)</td>
<td>0.27 (0.07-0.96)</td>
</tr>
</tbody>
</table>

Abbreviations: ADEs, adverse drug events; CHF, chronic heart failure.

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tation compared with those of usual care (−$2676 per patient [95% CI, −$578 to −$5166]). In this same health care setting, Burton et al recently determined that the mean charge for an ADE was $926 in 2006 dollars. Notwithstanding a number of important assumptions, we offer a crude estimate of savings deriving specifically from the intervention’s effects on ADEs and MEs. If ADEs amenable to intervention occur in 5% of adult outpatients each year, and the effects of our intervention are generalizable to other disorders in outpatients, then the 35% lower risk of ADEs (observed in this study) in a 50,000-patient outpatient practice could result in a reduction in annual charges to payers of approximately $631,000. We hope that investigators of future studies of pharmacist interventions will more precisely determine such costs. In conclusion, this post hoc analysis of a pharmacist intervention to improve medication use in adult outpatients suggests a lower risk of adverse drug events and medication errors. Further studies are needed to confirm this finding.

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REFERENCES