A Longitudinal Analysis of Antihypertensive Drug Interactions in a Medicaid Population

Barry L. Carter, Brian C. Lund, Nobumasa Hayase, and Elizabeth Chrischilles

Background: Drug interactions are a frequent cause of adverse drug events. We evaluated whether the frequency of previously reported antihypertensive drug–drug interactions could be reduced by pharmaceutical case management.

Methods: Patients >30 years of age with hypertension who were enrolled in the Iowa Pharmaceutical Case Management (PCM) program were evaluated. All prescription claims for patients were obtained on their date of eligibility and again 9 months later. A drug interaction database was developed to examine potential drug interactions in each patient’s regimen.

Results: Antihypertensive drugs were taken by 1377 patients at baseline and at 9-month follow-up. Highly significant antihypertensive drug interactions were observed at baseline in 35% of patients (0.47 per patient), and interaction prevalence did not change over time. Decreases in the number of drug interactions tended to occur more commonly among patients of pharmacies that provided the highest intensity of service (11.5% in high-intensity pharmacies vs 9% in low- or zero-intensity pharmacies, but this did not achieve statistical significance). Nearly 75% of patients had an interaction of any significance level, and the total number of interactions increased over time (P = .0067).

Conclusions: This Medicaid population with hypertension had a very high prevalence of potential drug interactions. The prevalence of interactions did not change, but the mean number of all interactions actually increased over time. There was some suggestion that higher-intensity pharmacies might be more successful in minimizing the risk of clinically significant drug interactions when compared with lower-intensity pharmacies. Am J Hypertens 2004;17:421–427 © 2004 American Journal of Hypertension, Ltd.

Key Words: Antihypertensives, drug interactions, computer programs.

It is estimated that 6% to 10% of adverse drug events (ADE) are associated with drug–drug interactions (DI).1–4 The primary risk factor for DI and subsequent ADE is the number of drugs that a patient is taking.5–7 The cost of drug-related morbidity is substantial and may exceed $177 billion per year.8–10

Proper surveillance could prevent 50% to 84% of ADE.1–4 Prevention of DI is more feasible in institutional settings where computer order-entry and interdisciplinary communication is more common than in community settings. Studies have suggested that medication use can be improved by better communication among patients, physicians, and pharmacists.11–15

Depending on their sex and age, up to 48% of patients eligible for the Iowa Medicaid Pharmaceutical Case Management (PCM) program had a potentially highly significant antihypertensive DI.6 The PCM program was designed for patients at high risk for ADE where community pharmacists worked with the patient’s primary physician to resolve medication problems, including unnecessary drugs, patient not receiving needed medication, a DI, or other problems. We previously demonstrated that the PCM program reduced inappropriate medication and that improvements were greatest in the pharmacies that more effectively implemented the service.16 Previous reports examined overall medication use and involved any
potential medical condition. The purpose of this article is to evaluate whether the frequency of potential DI with antihypertensive medications could be reduced by better collaboration between physicians and pharmacists.

Methods

Patient eligibility, the DI computer program, and the frequency of antihypertensive DI when these patients became eligible for PCM (baseline) have previously been reported. Patients who became eligible for the PCM program from October 1, 2000 through July 1, 2001 and who received a 9-month follow-up of antihypertensive DI were included in the present study. The project was approved by the University of Iowa Institutional Review Board and the Iowa Department of Human Services.

Study Population

Ambulatory patients were eligible for PCM services if they took four or more regularly scheduled, nontopical medications and had at least one of the following eligible disease states: congestive heart failure, ischemic heart disease, diabetes mellitus, hypertension, hyperlipidemia, asthma, depression, atrial fibrillation, osteoarthritis, gastroesophageal reflux, peptic ulcer disease, or chronic obstructive pulmonary disease. For the purposes of this evaluation, we included only patients ≥30 years of age who had active antihypertensive medications at both baseline and at the end of the evaluation period.

Each participating pharmacy received quarterly a list of newly eligible patients. The pharmacists’ service included an interview to identify medication-related problems, recommendations to the physician, and follow-up case management as approved or directed by the patient’s primary physician. There were 117 pharmacies that qualified for PCM, but they differed in how extensively they provided this service; therefore, we developed an intensity score to classify pharmacies according to how extensively they adopted the PCM services.

A computer algorithm was developed to construct a list of drugs considered as “active” on the date that a patient became eligible for PCM (the “index” date). The computer algorithm had a sensitivity of 93.8% and a specificity of 91.9% using clinical pharmacist reviewers as the gold standard. The National Drug Code for each active drug was linked to the ingredients in the drug product because some products are combinations. Unique drug ingredients were counted to calculate the number of active drugs on the index date (baseline) and again 9 months later (follow-up date).

Drug Interaction Resource

Antihypertensive medications were categorized as follows: thiazide diuretics, loop diuretics, potassium-sparing diuretics, angiotensin converting enzyme inhibitors, angiotensin II inhibitors, β-blockers, calcium channel blockers, and antiadrenergic agents. Antiadrenergic agents included α-blockers, reserpine, methyldopa, guanfacine, clonidine, and guanethidine. The reference source for DI was the quarterly updated version of Drug Interaction Facts. A database was created that included each interacting pair of individual drugs (antihypertensive plus interacting drug) and the significance rating of 1 to 5. For the purposes of this report, highly significant interactions are those rated as level 1 or 2 by Drug Interaction Facts. Significance refers only to the potential for an adverse clinical outcome from a given drug interaction pair. Variables such as age, number of medications, or conditions do not influence the significance of a DI with a specific drug–drug pair, but these variables do increase the probability of an interaction in a given patient.

Individual ingredients were used to generate the DI

### Table 1. Definitions of drug–drug interaction significance ratings

<table>
<thead>
<tr>
<th>Significance Rating</th>
<th>Severity</th>
<th>Documentation</th>
<th>Example</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Major</td>
<td>Suspected or probable</td>
<td>Enalapril and amiloride</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Verapamil and digoxin</td>
</tr>
<tr>
<td>2</td>
<td>Moderate</td>
<td>Suspected or probable</td>
<td>Diltiazem and propranolol</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Captoril and ibuprofen</td>
</tr>
<tr>
<td>3</td>
<td>Minor</td>
<td>Suspected or probable</td>
<td>Isradipine and lithium</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Fosinopril and tolmetin</td>
</tr>
<tr>
<td>4</td>
<td>Major/moderate</td>
<td>Possible</td>
<td>Atenolol and glyburide</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Lisinopril and indomethacin</td>
</tr>
<tr>
<td>5*</td>
<td>Minor</td>
<td>Possible</td>
<td>Metoprolol and insulin</td>
</tr>
<tr>
<td></td>
<td>Major/moderate</td>
<td>Unlikely</td>
<td>Chlorothiazide and allopurin</td>
</tr>
</tbody>
</table>

The significance and severity determinations are from Drug Interaction Facts. A level 1 interaction is the highest significance. Severity is a determination from the literature for the clinical consequences of the interaction rated as major, moderate or minor. Documentation is a ranking from the literature indicating the weight of the scientific literature. Probable interactions have typically been identified by controlled trials, whereas possible interactions from several small series or case reports. Possible interactions may be identified by isolated case reports or inferred from the known properties of the class of drugs.

* A level 5 interaction can either be of minor significance and have limited documentation for the interaction, or it can be of major, moderate, or minor significance but the documentation is poor, conflicting, or suggests that the interaction does not occur.
pairs, and the database included a unique drug code for each individual drug. The database was cross-referenced with all active medications at the time of enrollment and at the 9-month follow-up. Any time that two interacting drugs were found in the patient’s drug regimen, a potential interaction was generated.

Pharmacy Intervention and Intensity

The Iowa PCM program services were previously described. Briefly, PCM services were established to reimburse a pharmacist/physician team in the management of drug therapy of high-risk patients receiving Medicaid. Once the patient was identified, the initial assessment by the pharmacist began. This assessment included: a) medication history; b) assessment of indications, effectiveness, safety, and compliance of medication therapy; c) assessment of the presence of untreated illness; and d) identification of medication-related problems. The pharmacist prepared a written report to the physician that included an action plan. If the physician approved the plan, the pharmacist then provided follow-up visits over a 12-month period to resolve any drug-related problems including drug interactions. Anecdotally, pharmacists indicated that the initial visit required 45 to 60 minutes with the patient and that the follow-up visits required 15 to 30 minutes, although these data were not prospectively collected.

The Iowa Department of Human Services required that all eligible patients have access to the intervention. Pharmacists received a list of eligible patients on a quarterly basis. As this was a new service, pharmacies were not uniform in their implementation of the intervention. There were 2834 patients >18 years of age eligible for PCM. Not all patients received the service for various reasons, including: patient access problem (moved, homebound, deceased) 30.7%, inadequate pharmacist time/staffing 22.2%, patient refusal 9.5%, physician refusal 3.5%, and other reasons 34.3%. Some pharmacies enrolled a greater proportion of their eligible patients into the program and received more extensive services. These data suggest that the pharmacy intensity score may be useful to represent the “dose” of collaborative care received by patients. This report examines whether the intensity of pharmacy services can predict changes in antihypertensive drug interactions over time.

Statistical Analysis

Univariate \( \chi^2 \) analysis compared baseline and follow-up prevalence of DI. Mean number of DI at baseline and follow-up were compared using \( t \) statistics. To evaluate the pattern of change over time in DI frequency, ordinal logistic regression analysis was used where the primary outcome variable was the categorical observation of whether a patient had an increase, no change, or a decrease in the number of DI during the study period.Multivariable ordinal logistic regression analysis was used to determine the effects of age, sex, number of medications, and pharmacy intensity on this three-level ordinal outcome variable. This approach was chosen because a clinically meaningful intervention was not limited to a decrease in interactions but could also consist of preventing new interactions. This type of evaluation was important because one of the most frequent recommendations pharmacists made was to add a medication for an untreated indication. Ordinal logistic regression allowed these two different outcomes to be considered simultaneously, rather than conducting separate analyses. The Wald \( \chi^2 \) statistic was used to test the significance of the model parameters and odds ratios were generated. All significance tests were two-tailed with \( \alpha = 0.05 \) and conducted using SAS version 8.2 software (SAS Institute, Cary, NC).

Results

Patient Characteristics

There were 2389 patients eligible for PCM services that were \( \geq 30 \) years of age, and 1574 received an antihypertensive agent. There were 1377 patients who received an antihypertensive agent both at baseline and at the end of the evaluation period; these patients are the subject of this report. The 197 patients (mean 55.6 years, 72.3% female) who received an antihypertensive agent at baseline but not at follow-up were not evaluated for the change in antihypertensive drug interactions because they were not receiving one of these drugs at both time periods.

![FIG. 1. Mean number of drug interactions per patient. *P = .0067 compared with baseline.](https://academic.oup.com/ajh/article-abstract/17/5/421/92504/92504)
The patients had a mean age of 62.0 ± 0.39 years, and 1028 of 1377 patients (74.7%) were female. Antihypertensive agents used at baseline included the following: calcium channel blockers 18%, angiotensin converting enzyme inhibitors 19%, β-blockers 19%, loop diuretics 18%, thiazides 14%, potassium-sparing diuretics 5%, antidiurenergic agents 3%, and angiotensin II inhibitors 4%. Patients took a mean of 2.0 antihypertensive agents.

Changes in Interactions Over Time

There was a mean of 0.47 ± 0.02 highly significant DI at baseline, which did not change after the intervention (0.49 ± 0.03, \( P = .34 \); Fig. 1). The prevalence of highly significant DI did not change over time (\( P = .58 \); Fig. 2). There was an increase in the number of DI of any level of significance from 2.2 ± 0.06 at baseline to 2.3 ± 0.06 after the intervention (\( P = .0067 \); Fig. 1). The overall prevalence of DI of any level of significance did not change from baseline to follow-up (\( P = .87 \); Fig. 2). Ordinal logistic regression analysis found no effect of age, sex, the number of medications at baseline, or the intensity of pharmacy services on the probability of changes in highly significant antihypertensive DI over time.

Pharmacy Intensity

Tables 2 through 5 show the prevalence and mean number of interactions by intensity of pharmacy service (Table 2, highly significant interactions; Table 4, all interactions) and the prevalence of increase, no change, or decrease in number of interactions by pharmacy intensity (Tables 3, highly significant interactions; and Table 5, all interactions).

The only trend approaching statistical significance was that patients of high-intensity pharmacies tended to have more decreases in highly significant drug interactions than patients of low- or zero-intensity pharmacies (11.5% v 9%). It should be noted, however, that this trend was observed only in the subgroup of patients at higher-intensity pharmacies who did not receive an active intervention (\( P = .073 \)).

Discussion

This study found a very high potential for significant antihypertensive DI in this Medicaid population. Of these patients, more than 74% had at least one potential antihypertensive DI and 35% of patients had a potential DI that was considered a highly significant interaction.

We previously reported that pharmacists providing services in the PCM program identified a mean of 2.6 ± 1.6 medication-related problems and they made 3.6 ± 3.0 recommendations to physicians per patient.\(^{16,17}\) Physicians accepted 49.2% of the pharmacists’ recommendations. However, this intervention had no effect on the overall prevalence of any DI. These neutral results are in contrast to our previous findings that the PCM intervention reduced inappropriate medication use in the elderly and improved scores for medication appropriateness.\(^{16}\) Among patients who received PCM services (\( n = 507 \)), indication for medications improved (\( P < .001 \)), as did effectiveness (\( P < .001 \)), dosage (\( P < .001 \)), and directions (\( P = .002 \)), whereas the prevalence of drug–disease interactions (\( P = .002 \)) and therapeutic duplication (\( P = .003 \)) were reduced.\(^{16}\) These findings suggested that the intervention effectively improved overall medication prescribing and medication use but had no effect on the prevalence of DI. These findings for all DI are similar to the results in the present study for antihypertensive DI in the larger cohort of PCM-eligible patients, including those who did not receive an intervention. The only positive effect was a

Table 2. Prevalence and mean number of highly significant antihypertensive interactions by pharmacy intensity*

<table>
<thead>
<tr>
<th>Pharmacy Intensity</th>
<th>Frequency of ≥1 Interaction</th>
<th>Number of Interactions</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline n (%)</td>
<td>Follow-up n (%)</td>
</tr>
<tr>
<td>Zero</td>
<td>68 (35.8)</td>
<td>72 (37.9)</td>
</tr>
<tr>
<td>Low</td>
<td>69 (31.1)</td>
<td>69 (31.1)</td>
</tr>
<tr>
<td>Moderate</td>
<td>238 (33.0)</td>
<td>241 (33.4)</td>
</tr>
<tr>
<td>High</td>
<td>106 (43.6)</td>
<td>107 (44.0)</td>
</tr>
</tbody>
</table>

* Total \( n = 1377 \).
univariate trend for patients to sustain a decrease in the number of antihypertensive DI if they went to higher-intensity pharmacies; however, the effect was not statistically significant and was observed only in patients who did not actually receive an active intervention.

The number of all antihypertensive interactions increased over time, which is difficult to explain because overall medication use improved.16 The medication regimens for these patients were very complex and the addition of any new medication would likely have the potential to increase DI. One of the most common recommendations made by the pharmacists was to add a medication for an untreated or under-treated condition.16 Examples would include a β-blocker after a myocardial infarction or lipid therapy for a patient not being treated. It is possible that the recommended changes increased the number of interactions for some patients. The fact that highly significant interactions did not increase is reassuring and suggests that any increase in interaction frequency occurred with interactions of minor significance.

The trend toward more frequent decreases in number of highly significant antihypertensive drug interactions among patients of high-intensity pharmacies may suggest that pharmacists who provide higher levels of services (as well as greater levels of communication with physicians) may be better able to target highly significant interactions. These pharmacists (and the respective physicians) may feel comfortable with simply monitoring interactions that are listed as lower levels of significance.

Another possible explanation for the increase in interactions of lower significance is that pharmacists and physicians ignore these interactions completely. Because the prevalence of these less significant interactions is so high, computer systems that pharmacists use to identify DI would provide an interaction alert for almost every patient in this study. We have theorized that fatigue from frequent alerts may cause pharmacists to ignore the alerts.6 This fatigue may also become a problem in the future for physicians who use computer order-entry or prescription writing systems to alert them to potential DI. Most DI can be managed by monitoring and dosage adjustments, but we are unable to determine whether these were being performed in the present population.

Numerous studies have evaluated models to improve hypertension management through pharmacist/physician collaboration.11 The present evaluation involved pharmacists and physicians in communities, where distance between providers can impair communication. The interactions in the PCM program were primarily conducted by facsimile, although most pharmacists attempted to have an initial discussion about the PCM program either in person or by telephone with each physician. It is possible that the PCM intervention would have been more potent if the level of collaboration had been even greater. For instance, models in group practices or managed care organizations employ clinical pharmacists whose purpose is to provide physician education (academic detailing) and to assist with managing hypertensive patients.11 Collaboration between physicians and pharmacists has been enhanced in more than two thirds of the states that allow collaborative practice agreements via protocols. The latter models have generally produced greater levels of collabor-

### Table 3. Number of patients (%) with changes in highly significant drug interactions over time as a function of pharmacy intensity*

<table>
<thead>
<tr>
<th>Pharmacy Intensity</th>
<th>Baseline Increase in Interactions at 9 Months</th>
<th>No Change in Interactions at 9 Months</th>
<th>Decrease in Interactions at 9 Months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zero</td>
<td>68 (35.8)</td>
<td>23 (12.1)</td>
<td>149 (78.4)</td>
</tr>
<tr>
<td>Low</td>
<td>69 (31.1)</td>
<td>26 (11.7)</td>
<td>177 (89.7)</td>
</tr>
<tr>
<td>Moderate</td>
<td>238 (33.0)</td>
<td>74 (10.2)</td>
<td>576 (79.8)</td>
</tr>
<tr>
<td>High</td>
<td>106 (43.6)</td>
<td>28 (11.5)</td>
<td>187 (77.0)</td>
</tr>
</tbody>
</table>

* Total n = 1377.

### Table 4. Prevalence and mean number of all antihypertensive interactions (any level of significance) by pharmacy intensity*

<table>
<thead>
<tr>
<th>Pharmacy Intensity</th>
<th>Frequency of ≥1 Interaction</th>
<th>Number of Interactions</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline n (%)</td>
<td>Follow-up n (%)</td>
</tr>
<tr>
<td>Zero</td>
<td>146 (76.8)</td>
<td>148 (77.9)</td>
</tr>
<tr>
<td>Low</td>
<td>158 (71.2)</td>
<td>157 (70.7)</td>
</tr>
<tr>
<td>Moderate</td>
<td>528 (73.1)</td>
<td>528 (73.1)</td>
</tr>
<tr>
<td>High</td>
<td>198 (81.5)</td>
<td>195 (80.2)</td>
</tr>
</tbody>
</table>

* Total n = 1377.
oration, greater improvements in blood pressure control, and improved medication regimens. Innovative solutions will likely be required to strengthen further the extent of collaboration between physicians and pharmacists based in communities where physical separation is a challenge. Periodic patient “rounds” and office protocols for managing information transfer are examples of methods that may enhance collaboration in the community.

Several factors should be considered when evaluating the generalizability of this study. First, this study evaluated only patients who were receiving Medicaid and who were taking four or more oral medications in their entire medication regimen. Thus, these patients were naturally at higher risk for a drug interaction. Although we included every patient eligible for PCM who received an antihypertensive, this evaluation cannot be used to interpret the potential for drug interactions in patients taking one to three oral medications (including both antihypertensive and other medications), as these patients were not eligible for PCM services. In our experience, however, most older patients receiving Medicaid take more than three medications and would have been included in our study.

Our study required the presence of an antihypertensive agent both at baseline and at follow-up to assess antihypertensive DI changes. For this reason, 197 patients were excluded who took an antihypertensive drug at baseline but not at follow-up. It is possible that we under-estimated the reduction in DI if the antihypertensive drug was discontinued to avoid an interaction. However, our estimates are accurate for patients requiring ongoing treatment with antihypertensive medication. Our results are generalizable to patients at higher risk by virtue of their taking four or more medications and to those who require an antihypertensive agent as chronic treatment.

Another limitation is that we could not verify that patients were taking antihypertensive agents for hypertension versus some other indication. However, this report provides a description of the potential interactions with this class of drugs. All DI resources are limited by the level of reporting and interpretation from the literature. Therefore, the frequency and significance of any interaction is subject to these variables. An additional limitation is that we were able only to observe and to report the prevalence of potential drug interactions, as opposed to actual interactions (that is, interacting drug pairs that produced an observed clinical effect). However, the presence of a potentially interacting pair of drugs confers future risk for an actual interaction, and a greater number of potential interactions in a given regimen is a proxy measure of greater risk for an actual interaction in the future. Thus, an intervention that eliminates a potentially interacting drug pair reduces the future risk of an ADE and is an important means to prevent ADE.

In conclusion, we found a very high frequency of potential DI with antihypertensive agents in this Medicaid population who were taking four or more oral medications in their total medication regimen. The prevalence of antihypertensive DI did not change but the mean number of interactions per patient increased over time. However, this increase in mean number of interactions appeared to be restricted to interactions of low clinical significance. The number of interactions remained high despite an intervention designed to reduce overall medication-related problems. There was some suggestion that higher-intensity pharmacies may have been more successful in minimizing the risk for clinically significant DI when compared with lower-intensity pharmacies.

Acknowledgments
The authors acknowledge the assistance and support of Thomas Temple and the Iowa Pharmacy Association, Nancy Bell, Cheryl Clarke, Shari Chen-Hardee, Tae-Ryung Park, Linda Rubenstein, Angela Kuehl, Randal McDonough, William Doucette, Karen Farris, Jay Currie, Michael Ernst, William Miller, Gary Rosenthal, Margaret Voelker, David Scholz, and Joseph T. Hanlon.

References


