The Extent of Potential Antihypertensive Drug Interactions in a Medicaid Population

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Background: Drug interactions are a frequent cause of adverse drug events and these might be avoided by computer alerts to physicians or pharmacists. We evaluated the frequency of potential drug–drug interactions in patients receiving medications commonly used for hypertension.

Methods: Patients more than 30 years of age with hypertension who were receiving Medicaid and 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. A drug interaction database was developed to examine potential drug interactions in each patient’s regimen.

Results: There were 1574 patients who received a drug typically used for hypertension. Depending on age and sex, 23% to 48% of patients had a potential interaction of high significance and 55% to 84% had at least one potential interaction. Both increasing age (P < .0001, odds ratio [OR] 1.012 [1.005,1.019]) and number of drugs (P < .0001, OR 1.120 [1.092,1.150]) were significantly associated with the potential for a highly significant drug interaction in the univariable models. Female sex was not significant (P = .56, OR 1.074 [0.845,1.364]). The multivariable model found that there was a significant interaction between age and the number of drugs in the regimen (P < .0001).

Conclusions: This study found a very high frequency of potential drug interactions with agents typically used for hypertension. Because of the large volume of potential interactions, these data raise the concern that any attempt to provide physicians and pharmacists with computer alerts about these interactions will result in alerts for the vast majority of patients. Am J Hypertens 2002;15:953–957 © 2002 American Journal of Hypertension, Ltd.

Key Words: Antihypertensive agents, drug interactions.

Adverse drug events (ADEs) are one of the most frequent and costly consequences of medical errors occurring in up to 40% of patients on five or more medications. Costs of drug-related morbidity exceed $177 billion and lawsuits with financial judgments occurred with 56% when there was permanent disability.

It has been estimated that 6% to 10% of ADE are due to drug interactions. Fifty percent to 84% of ADEs are preventable with proper identification and surveillance. Nearly all hospital and outpatient pharmacies have computer software or online services to detect drug interactions, yet many drug interactions go unresolved. Many drug interactions are insignificant and pharmacists override up to 88% of online alerts. Most interactions can be managed by appropriate monitoring and dosage adjustments and pharmacists frequently assume these adjustments are being done by the physician.

The Institute of Medicine report suggested that ADEs might be minimized by computer order entry that alerted physicians when there is a dosage error or drug interaction detected. However, if interaction alerts become so common that physicians ignore them, the utility of these programs is diminished.

The purpose of this article is to characterize potential drug–drug interactions with common medications used to treat hypertension and determine the frequency of potential interactions with one class of medications in a state Medicaid program.

Methods

The evaluation included patients who became eligible for the Iowa Pharmaceutical Case Management (PCM) program from October 1, 2000 through July 1, 2001. The project was approved by the University of Iowa Universi...
tional Review Board and the Iowa Department of Human Services.

Study Population

Patients were eligible for PCM services if they had active prescriptions for four or more regularly scheduled nontropical medications, were ambulatory, and had at least one of the following eligible disease states as predicted by common medications used to treat these conditions: 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, only patients 30 years of age or older are included.

Each participating pharmacy received a list of newly eligible patients once per quarter. Patients included on a list from a previous quarter continued to be eligible for these services as long as they were eligible for Medicaid. Physicians received lists of their eligible patients receiving prescriptions from a participating pharmacy. All claims paid to pharmacies were made available to the investigators so a complete prescription drug list was available for analysis. In Iowa, most over-the-counter (OTC) medications are paid for by Medicaid if they are written as a prescription and would be captured in the database.

Drug Interaction Resource

The reference source for drug interactions was the quarterly updated Drug Interaction Facts. A list of all antihypertensives was generated and categorized into eight drug classes. A database was created that included each interacting drug pair (antihypertensive plus interacting drug) and the significance of the interaction. The significance of the interaction was rated from 1 through 5: 1 = major, 2 = moderate, 3 = minor (levels 1, 2, or 3 could be suspected or probable interaction), 4 = major/moderate (with only possible documentation of the interaction), and 5 = either minor and possible interaction or major/moderate but unlikely documentation of an interaction. Highly significant interactions were considered those rated as level 1 or 2 by Drug Interaction Facts. The significance of the potential interactions are based on the probability and clinical relevance as determined from the literature. Individual ingredients were used to generate the drug interaction pairs using a unique drug code for each individual drug. The interaction database was cross-referenced with all medications that were considered active at the time of enrollment into the PCM project using a computer program developed by the investigators.

Logistic regression analysis was used and age, sex, and overall number of medications were included in the model. The $\chi^2$ statistic was used to evaluate the association of the variables age, sex, and number of drugs in the regimen and odds ratios were generated. A $P$ value of < .05 was considered statistically significant.

Results

The database from the reference source included 3501 potential pairs of interactions with antihypertensives. This included 288 (8.2%) level 1, 786 (22.5%) level 2, 225 (6.4%) level 3, 1266 (36.2%) level 4, and 936 (26.7%) level 5 interactions. When the 478 duplicate antihypertensive interactions (eg, diltiazem–atenolol and atenolol–diltiazem) were eliminated, there were 3262 unique pairs of potential drug interactions in the interaction database.

There were 2389 patients more than 30 years old who were eligible for PCM services. There were 1766 women (73.9%) and 623 men (26.1%). The mean age was 56.6 ± 15.6 years (range 30 to 100 years).

The 1574 patients who received an antihypertensive agent are the subjects of the remainder of this report. The patients receiving antihypertensive agents were older (mean age, 61.2 ± 15.0 years) and they had a similar percentage of women (74.4%) when compared to all eligible patients. There were 594 (37.7%) on one, 539 (34.2%) on two, 326 (20.7%) on three, and 115 (7.3%) on four or more antihypertensive agents (mean, 2.0 agents per patient). The frequency of use of antihypertensives was: calcium channel blockers 18.3%, angiotensin converting enzyme (ACE) inhibitors 19.3%, β-blockers 18.6%, loop diuretics 17.8%, thiazide diuretics 13.7%, potassium-sparing diuretics 5.2%, antiadrenergic agents 3.4%, and angiotensin II inhibitors 3.7%. In addition to these antihypertensive drugs, patients took an average of 7.2 ± 4.0 nonantihypertensive agents.

The medication profiles for the 1574 patients were evaluated for potential interactions by age and sex (Table 1). Both increasing age ($P = .0007$, odds ratio [OR] 1.012 [1.005,1.019]) and number of drugs ($P < .0001$, OR 1.120 [1.092,1.150]) were significantly associated with the potential for a highly significant (level 1 or 2) drug interaction in the unvariable models. Female sex was not significant ($P = .56$, OR 1.074 [0.845,1.364]). The multivariable model found that there was a significant interaction between age and the number of drugs in the regimen ($P < .0001$) (Fig. 1). That is, the age effect was minimal among patients receiving relatively few medications, but was pronounced in patients receiving the highest number of medications. There was no significant difference between men and women in the rates of clinically significant drug–drug interactions.

Table 2 lists the frequency with which various categories of antihypertensive agents were found to have a potential interaction with another drug. These are ranked by the frequency of interactions with a potential for high significance. For instance, 163 patients were receiving a potassium-sparing diuretic, of which 37.4% of the patients had a potential interaction of high significance. In addition, one could interpret the chances that a given agent would cause a potential interaction when added to a typical regimen for a patient in this population. In this case, adding a loop diuretic would potentially generate a com-
puter interaction alert in 91.2% of patients and an alert of high significance in 27.4% of patients. This same loop diuretic would interact with (on average) 2.34 existing medications in the patient’s medication profile.

**Discussion**

We found a very high rate of potentially significant drug interactions with antihypertensive agents in this Medicaid population. There was a significant increase in the frequency of potential interactions with age particularly in patients taking a greater number of drugs. Any computer system used to identify a potential drug-drug interaction with a new antihypertensive agent would likely generate an alert to the pharmacist or a physician (with prescription order entry) for the majority of these patients. The fatigue and annoyance from these frequent alerts could cause pharmacists or physicians to simply over-ride the alerts and this could pose serious problems when the interactions are potentially significant.

Technology could reduce the probability that a drug–drug interaction might occur. In fact, drug interaction software has been available in nearly every pharmacy for many years. Although pharmacists identify many interactions and alert physicians, many interactions go unchallenged and the computer alert is simply over-ridden by the pharmacist. The only randomized, controlled trial of computer-assisted drug therapy reviews in community pharmacies found no effect of the system on changes in drug therapy or health outcomes. The problem with most of these computer systems is that they are not integrated with the medical data. Because potentially life-threatening drug–drug interactions can often be managed by monitoring and dosage adjustments, the pharmacist may assume that the physician has made the appropriate adjustments and ignore the alert.

Another solution might be to implement physician prescription order entry systems with decision support. These systems are now available and offer great promise and may prevent ADEs. Unfortunately, much more work must be done to validate screening criteria for computer-based systems. Depending on the software, physicians might receive an alert for nearly every patient adding significant time to the prescribing process. Physicians too could become complacent and simply over-ride the alerts. In addition, software from the same vendor can have very different algorithms for drug interactions. One study examined digoxin interaction criteria from 17 state Medicaid programs and found 23 different interactions from reference texts. Only five of these interactions were included by the majority of the states in their criteria and no interaction was included by each states’ sets of criteria. Even more alarming was the fact that no two states used the same sets of criteria, although they used the same software vendor. Therefore, it will be important to consider these factors when constructing physician order entry software.

**Table 1.** Percent of patients with potential antihypertensive drug interactions

<table>
<thead>
<tr>
<th>Sex</th>
<th>Age</th>
<th>N</th>
<th>Frequency (%) of Interaction*</th>
<th>Average Number of Interactions</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>High Low Any</td>
<td>High Low Any</td>
</tr>
<tr>
<td>F</td>
<td>30–39</td>
<td>77</td>
<td>23.4% 45.5% 54.5%</td>
<td>0.29 0.84 1.13</td>
</tr>
<tr>
<td>F</td>
<td>40–49</td>
<td>171</td>
<td>28.7% 65.5% 67.8%</td>
<td>0.37 1.58 1.95</td>
</tr>
<tr>
<td>F</td>
<td>50–59</td>
<td>260</td>
<td>32.3% 68.8% 74.2%</td>
<td>0.47 1.81 2.27</td>
</tr>
<tr>
<td>F</td>
<td>60–69</td>
<td>239</td>
<td>41.8% 69.0% 77.8%</td>
<td>0.60 1.81 2.41</td>
</tr>
<tr>
<td>F</td>
<td>70–79</td>
<td>253</td>
<td>36.0% 70.8% 78.3%</td>
<td>0.47 1.91 2.38</td>
</tr>
<tr>
<td>F</td>
<td>&gt;80</td>
<td>171</td>
<td>40.4% 78.9% 84.2%</td>
<td>0.54 2.35 2.89</td>
</tr>
<tr>
<td>M</td>
<td>30–39</td>
<td>40</td>
<td>40.0% 35.0% 57.5%</td>
<td>0.31 1.09 1.40</td>
</tr>
<tr>
<td>M</td>
<td>40–49</td>
<td>93</td>
<td>30.1% 62.4% 76.3%</td>
<td>0.35 1.71 2.05</td>
</tr>
<tr>
<td>M</td>
<td>50–59</td>
<td>112</td>
<td>24.1% 65.2% 70.5%</td>
<td>0.55 1.58 2.14</td>
</tr>
<tr>
<td>M</td>
<td>60–69</td>
<td>74</td>
<td>41.9% 63.5% 71.6%</td>
<td>0.49 1.83 2.32</td>
</tr>
<tr>
<td>M</td>
<td>70–79</td>
<td>59</td>
<td>35.6% 69.5% 74.6%</td>
<td>0.68 1.80 2.48</td>
</tr>
</tbody>
</table>

High reflects high significance drug interaction (level 1 or 2).
Low reflects low significance drug interaction (level 3, 4, or 5).
* The high and low frequency do not add up to “any frequency” as there could have been more than one interaction per patient.

![Graph](image.png)

**FIG. 1.** Frequency of highly significant potential drug interactions by age and number of total drugs in the regimen. Highly significant was determined by using the definition in Drug Interaction Facts.9
Our data cannot be used to support the conclusion that one class of antihypertensive agent is less likely to cause an interaction than another agent for several reasons. The chance of an interaction being listed in a reference source is related to how long an agent has been on the market and the strength of evidence in the literature. Thus, it is not surprising that “older” antihypertensives were associated with a greater frequency of potential drug interactions. Second, the probability of an interaction is related to the frequency of use in the general population and the probability of generating an interaction. Agents that are new, or not commonly used, may be less likely to appear in a compendium or resource as an interacting drug.

These data, however, provide evidence that there is a high probability of a potential interaction for patients receiving an antihypertensive. The fact that these combinations were actually dispensed indicates these drugs were approved by both the prescribing physician and the dispensing pharmacist. Of greatest concern is the marked increase in risk in elderly patients taking nine or more medications.

One limitation of this study is that we could not verify that the patient was taking an agent for hypertension because these drugs were used as indicators for hypertension. Thus, it is not certain that these medications were used strictly for hypertension and in fact were probably used for other coexisting conditions. Even so, this report provides a description of the potential interactions with this class of drugs. Second, the significance rating for any specific interaction is determined by the weight of the evidence in the literature and the interpretation of this literature. The significance rating in the compendia we used does not necessarily predict what will occur in a given patient. Finally, because of the inclusion criteria, the findings can only be generalized to a Medicaid population with similar chronic conditions.

In conclusion, this study found a very high frequency of potential drug interactions with medications typically used to treat hypertension. It is likely that similar frequencies of interactions might be expected in other populations receiving multiple medications. Most of the interactions were not clinically significant. However, depending on sex and age, 23% to 48% of patients had at least one interaction that might be highly significant. Because of the large volume of potential interactions, these data raise the concern that any attempt to provide physicians and pharmacists with computer alerts about these interactions will result in alerts for the vast majority of patients.

Acknowledgments
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References