ORIGINAL RESEARCH

Retrospective Drug Utilization Review: Incidence of Clinically Relevant Potential Drug-Drug Interactions in a Large Ambulatory Population

CATHERINE C. PENG, PharmD, BCPS; PETER A. GLASSMAN, MBBS, MSc; INY R. MARKS, PharmD; CURTIS FOWLER, PharmD; BRENDA CASTIGLIONE, PharmD; and CHESTER B. GOOD, MD, MPH, FACP

ABSTRACT

OBJECTIVE: To determine the incidence of clinically relevant potential drug-drug interactions (DDIs) in a large population of ambulatory patients utilizing a computerized, retrospective drug utilization review (DUR) program followed by clinical pharmacist audit.

METHODS: The drug claims database included approximately 2.9 million patients with more than 30 million prescriptions dispensed in the 12-month period from September 2001 through August 2002. Cases were identified by a computerized, retrospective DUR program with embedded triggers to detect 69 prespecified potentially serious DDIs, with "serious" defined as an interaction that would likely require a change in therapy or use of additional clinical or laboratory monitoring. Two types of automated, computerized assessments were conducted: the first simply detected coprescribed drug pairs, and the second assessment used more sophisticated filters to reduce false positive alerts for coprescribed drug pairs. Clinical pharmacist audit then determined the final incidence of clinically relevant warnings; in this audit, coprescribed drug pairs were defined as clinically relevant if they could cause potentially serious DDIs.

RESULTS: Eighteen drug pairs had insufficient cases for inclusion, leaving 51 drug pairs for evaluation. A total of 244,703 cases of potential DDIs were identified (0.8% of total prescription claims) by simple automated screens. More sophisticated DDI filters reduced the 244,703 potential DDIs by 70.8%, to a total of 65,544 pairs (0.2% of total prescription claims). Clinical pharmacist review reduced the number of potential DDIs by an additional 80.6%, to 12,722 drug pairs (0.04% of total prescription claims) deemed clinically relevant. The combination of sophisticated DDI filters and clinical pharmacist review reduced the incidence of potentially serious DDIs by 94.3%.

CONCLUSION: The incidence of potentially serious DDIs is relatively low (less than 1%) among ambulatory patients; however, the incidence depends on the method of case finding. Retrospective DUR programs, especially those with additional automated filters or that utilize additional pharmacist review, appear to be important screening tools in determining true rates of coprescribed drug pairs that can lead to potentially serious DDIs.

KEYWORDS: Drug utilization review, Drug-drug interactions, Medication errors, Ambulatory care

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The Institute of Medicine's report, "To Err Is Human, Building a Safer Health System," heightened awareness of reducing preventable medical errors.[1] One important subset is medication errors, in part, because they are relatively common,[2-3] and, in part, because they increase the risk for adverse drug events.[2] The latter is thought to be responsible for nearly 7,000 lives lost and up to an estimated $136 billion spent annually in additional health care costs.[1,4]

Studies evaluating medication errors have taken a broad-based approach at case finding and usually have limited the evaluations to hospitalized patients or a small cohort of outpatients.[5-13] While the relevance of this type of research should not be underestimated, it does not address concerns about medication errors that might occur in large outpatient populations, where most prescribing occurs in daily practice.

One such group of errors receiving increased focus involves potentially serious drug-drug interactions (DDIs). However, little has been done to categorize the incidence of potential DDIs of any severity in large outpatient populations. Currently available estimates of incidence vary widely, depending on the method of defining and finding potential DDIs and the method of defining the population assessed. Published studies have reported proportions of potential DDIs ranging from 2.2% to 30% in hospitalized patients and from 9.2% to 70.3% in ambulatory patients,[14,15] although evaluations yielding the highest estimates have sometimes included theoretical interactions in addition to documented interactions.

Authors

CATHERINE C. PENG, PharmD, BCPS, is clinical specialist; INY R. MARKS, PharmD, is clinical product development specialist; CURTIS FOWLER, PharmD, is manager of clinical product development; and BRENDA CASTIGLIONE, PharmD, is director of clinical services, Clinical Services Department, Eckerd Health Services, Pittsburgh, Pennsylvania. PETER A. GLASSMAN, MBBS, MSc, is staff physician, Division of General Internal Medicine, VA Greater Los Angeles, West LA Campus, Los Angeles, California, and associate professor of medicine, University of California Los Angeles School of Medicine; CHESTER B. GOOD, MD, MPH, FACP, is chairperson of the Medical Advisory Panel, Department of Veterans Affairs and staff physician, Division of General Internal Medicine, VA Pittsburgh Health Care System, Pittsburgh, Pennsylvania, and associate professor of medicine and pharmacy, University of Pittsburgh School of Medicine.

AUTHOR CORRESPONDENCE AND REPRINT REQUESTS: Iny Marks, PharmD, Eckerd Health Services, 620 Epsilon Dr., Pittsburgh, Pennsylvania 15238. Tel: (800) 814-6600, ext. 5023; Fax: (412) 968-2691; E-mail: imarks@ehs.com

The main issues in accurately determining the incidence of DDIs in ambulatory patients are primarily 2-fold. First, evaluations should be prospective and based on a prespecified set of drug pairs. Second, large populations of patients are required to find sufficient DDIs to establish incident rates. In addition to these 2 necessary factors, sufficient technology is required to preliminarily evaluate and categorize potential cases of DDIs. Moreover, some type of secondary audit should occur to confirm the findings of preliminary assessments.

Claims-based analysis using computerized, retrospective drug utilization review (DUR) offers a powerful tool to better understand the incidence of potential DDIs as well as other types of potential medication errors.[16] Yet, despite the popularity of such programs in both the private and public health care sectors, very little data are available on the detection of potential DDIs in ambulatory patients.[17]

Several studies have attempted to assess the effectiveness of small and focused DUR programs.[9,10,12,13,18] For instance, one recent study by Curtis et al.[19] looked at overlapping prescriptions of drugs that may prolong the cardiac QT interval, a measure of the ventricular refractory period on an electrocardiogram associated with life-threatening ventricular arrhythmias. Still, there are little available data on specific DDIs found in various populations. Sharing these data would not only assist in determining which coprescribed drug pairs to target for intervention but also would assist in developing and tracking the success of DUR intervention programs across the United States.

Our study presents data on more than 50 potentially serious DDIs found in a subset of approximately 2.9 million persons, covered mainly by self-funded employer groups and health plans, over the course of 1 year. The study describes the case finding rates for potential drug interaction pairs, generated by a computerized, retrospective DUR system using programmed criteria, before and after pharmacist assessment. It is our hope that detailing the data on case findings of potential DDIs at various steps in the detection process will assist others in determining how to develop and optimize such DUR programs.

Methods

The Retrospective DUR Program

A pharmacy benefits management (PBM) company used a computerized, retrospective DUR program to monitor and intervene in cases of potentially serious DDIs. This DUR program was established in 1999 and continues as an ongoing program within the PBM; however, for the purposes of this study, a 1-year period of time was chosen to determine the incidence of potentially serious DDIs. This program does not involve electronic or other alert messages sent to dispensing pharmacies at the point of sale and is separate from such concurrent alerts. The database for the retrospective DUR program included claims submitted for prescription medications dispensed from more than 56,000 community pharmacies and 3 mail-service facilities in the PBM's pharmacy network. Claims data were updated daily. The DUR program assessed prescription claims each night, allowing for case review within 1 business day after claims were submitted. Available data on prescriptions included selected patient demographics, physician identification, and the name, strength, and quantity of the medications dispensed.

Interventions on potential DDIs were routinely conducted by mail, with alert letters sent to the prescribing clinicians. The alert letter not only described the potential interaction but also the underlying mechanism of that interaction, the possible consequent adverse drug event(s), and recommendation(s) on how the interaction may be avoided or managed. For example, the alert letter on the potential interaction between amiodarone and warfarin informs providers that amiodarone can increase the hypoprothrombinemic response by decreasing the hepatic clearance of warfarin and, hence, the addition of amiodarone to existing warfarin therapy can increase the prothrombin time by 50% to 100%. The letter continues with a recommendation to reduce the warfarin dose by 30% to 50%.

Clinically relevant coprescribed drug pairs were defined as those that could cause a potentially serious DDI. A DDI was defined by the following standard: a "pharmacological or clinical response to the administration of a drug combination different from that anticipated from the known effects of the 2 agents when given alone. The clinical result of a DDI may manifest as antagonism, synergism, or idiosyncratic."[20]

For this DUR intervention program, we utilized standard references[20-24] to determine possible clinically relevant coprescribed drug pairs, with specific drug pairs then chosen for inclusion into the restrospective DUR program by PBM clinical pharmacists in collaboration with an independent advisory board of practicing physicians and external clinical pharmacists. The advisory board consisted of 5 physicians with specialties in general internal medicine (one of whom had a background in pharmacology), gastroenterology, and endocrinology and 2 external clinical pharmacists. Priority was given to coprescribed drug pairs that were either absolutely contraindicated or that, when an interaction occurred, were more likely to cause a serious interaction.

A "serious" interaction was defined as potentially life or organ threatening, as described in at least 1 commonly used standard drug safety reference.[20-24] Additionally, a "serious" interaction would likely require a change in therapy or require additional clinical or laboratory monitoring.

Although the underlying mechanisms of interactions and subsequent harm varied among the drug pairs, the common theme in choosing drug pairs was to include those that have the potential to result in emergency treatment, hospitalization, permanent harm, or death. The general classification and definition of the categories of coprescribed drug pairs are shown in Table 1. Classification into the 6 categories was based on the management of the potential DDI.

Case Finding of Drug Pairs

Case finding of potentially interacting drug pairs proceeded through 3 assessments. The initial 2 assessments were automated, and the third was a manual review conducted by 4 trained clinical pharmacists. The pharmacists were trained by a senior pharmacist who was also the clinical program operations manager. The training included a structured curriculum that utilized standardized reference materials on identifying, classifying, and managing DDIs as well as a proprietary manual on DUR protocols.[20-24] Pharmacists were also specifically trained to evaluate the automated alerts to look for specific inclusion or exclusion criteria for further intervention, as discussed below.

The automated software first searched the claims database to preliminarily identify instances where patients may have been receiving overlapping prescriptions for the 2 specified medications in a given drug pair. In practical terms, this first step of automation provided an initial incidence of 2 potentially dangerous coprescribed drugs. For instance, one system check reviewed individuals with active prescriptions for warfarin and fluconazole, a drug pair with a known DDI.

Second, for each possible concomitant drug pair, a set of additional automated filters was used to help improve accuracy by determining which pairs were likely to be clinically relevant (i.e., have a true potential to cause a clinically relevant interaction). For example, 1 basic filter ensured that there were at least 5 days of potential overlap for specific drug pairs. Therefore, this filter would exclude any patient who was taking warfarin chronically and received only a single dose of fluconazole for the treatment of candidiasis.

These systematic filters varied depending on the drug pair targeted, but the goal of each set of filters was to reduce clinically irrelevant cases (i.e., to increase specificity). Other filters at this stage included assessing total drug dose (e.g., methotrexate of at least 15 mg per week with a nonsteroidal anti-inflammatory drug, or simvastatin of at least 20 mg daily with amiodarone) and duration of drug therapy (e.g., carbamazepine with a duration of therapy for at least 90 days and a macrolide antibiotic, or warfarin with a duration of therapy for at least 90 days and a thyroid product).

After the automated filters identified potentially relevant drug pairs, a clinical pharmacist reviewed the remaining cases. The goal was to ensure that any intervention requiring clinician contact involved a high likelihood of a true positive warning. Common reasons for cases to result in a subsequent pharmacist intervention or no pharmacist intervention (i.e., sending an alert letter or not sending an alert letter to clinicians on a potential DDI) may be found in Table 2. As a matter of due diligence, the reviewing pharmacist confirms the duration of overlap for the coprescribed drug pairs as well as identifies any prior concomitant use of a drug pair and prior warnings to the relevant clinician(s) concerning that drug pair. Thus, an alert letter would not be sent if a prescribing clinician had already been informed of the potential interaction for the same patient within a period of 3 months.

TABLE 1 Classification of Drug-Drug Interaction Pairs

Category	Definition	Examples
I	Drug-drug interaction pairs are contraindicated in at least 1 reference or product package insert.	Sildenafil – Nitrate Ritonavir – Quinidine
II	Avoid combination of drugs, if possible, unless benefits outweigh risks or neither drug can be discontinued.	HMG CoAs* – Gemfibrozil Clonidine – Beta-blocker
III	Drug-drug interaction is not specific to all drugs in a therapeutic class; therefore, may use an alternative drug in the same class.	Macrolide antibiotics – HMG CoAs Warfarin – Sulfonamides
IV	At least 1 of the drugs requires regular monitoring of serum levels or laboratory tests; dosage adjustment may be required.	Digoxin – Loop diuretics Warfarin – Amiodarone
V	Drug-drug interaction that may cause increased levels in 1 drug, which may or may not reach toxic levels. Therefore, therapy requires monitoring for signs of toxicity or lack of efficacy; dosage adjustment may be required.	Verapamil – Beta-blockers Rifampin – Oral contraceptives
VI	Monitor for changes when initiating or discontinuing drug therapy as likelihood of an interaction is increased during such times; dosage adjustment may be required.	Warfarin – Thyroid products Digoxin – Propafenone

**HMG CoAs = HMG CoA reductase inhibitors.*

Data on results of pharmacist interventions are maintained in a longitudinal database that is part of the DUR system. For those interventions that were considered clinically relevant based on pharmacist review, an alert letter was sent by regular mail within 24 hours of review. The pharmacist review provides the closest estimation of a gold standard for the true incidence of clinically relevant coprescribed drug pairs within the pertinent patient population.

Data Analysis

There were 69 active drug pairs in the retrospective DUR program during the study period; however, for the present study, 18 drug pairs were excluded for the following reasons: (1) there were no initial case finding of the coprescribed drug pairs in the claims database, (2) there were fewer than 10 initially identified cases and no pharmacist interventions, or (3) the drug pairs had been in the system for less than 1 year and had fewer than 100 initial case findings. Excluded drug pairs, along with the reason for exclusion, are shown in Table 3.

Incidence of clinically relevant potential interactions in the study population was assessed in 3 ways, utilizing 2 denomina-

TABLE 2 Common Examples of Why Alert Letters Were Sent or Not Sent to Physicians

Alert Letter Sent to Physician(s) (Pharmacist Intervention)	No Alert Letter Sent to Physician(s) (No Pharmacist Intervention)
Multiple physicians involved with the prescribing of medications with potential DDIs	Patient has been maintained on both medications in a drug pair for an extended period of time, with time periods specific for each drug pair
Multiple pharmacies involved with the dispensing of potentially interacting medications	Prior intervention (alert letter sent to the relevant clinician) within the past 3 months
Greater than a specified number of days overlap between potentially interacting medications, with days overlap specific to each drug pair	Past response from a clinician that indicates the patient is being closely monitored for a potential DDI
No previous history of an intervention (alert letter sent to physician) for a potential DDI in a patient	Past response from clinician that indicates the combination is medically necessary (benefits outweigh risks)

TABLE 3 Drug-Drug Interaction Pairs Excluded From Analysis

Drug Pairs With No Initial Case Findings
MAOIs* – Anorexiants
Penicillins – Tetracyclines
Protease inhibitors – Ergot alkaloids
Ritonavir – Amiodarone
Ritonavir – Clozapine
Ritonavir – Bepridil
Ritonavir – Quinidine
Methotrexate – Penicillins
Bosentan – Cyclosporine
Warfarin – Clofibrate
Drug Pairs With <10 Initial Case Findings and No Pharmacist Intervention
Cyclosporine – Rifampin
Meperidine – MAOIs
Protease inhibitors – Rifabutin
Protease inhibitors – Rifampin
Selegiline – Meperidine
Drug Pairs With <100 Initial Case Findings and <1-Year-Old in the Retrospective DUR System
Protease inhibitors – Oral contraceptives
Methotrexate – Probenecid
Bosentan – Glyburide

**MAOIs = monoamine oxidase inhibitors.*

tors. First, we evaluated incidence as the number of cases (i.e., detected drug pairs) per 1,000 paid prescription claims for all medications and per 1,000 utilizing members (patients). Claims that were rejected or were reversed within 1 business day were not included. Second, we evaluated the incidence as the number of drug pairs, following automated filtering by the retrospective DUR program, using the same denominators. Finally, we evaluated the number of potential interactions deemed clinically relevant by clinical pharmacist review and used the same denominators to calculate the incidence.

Paid prescription claims, which included both new and refilled drugs for eligible members in the study population, were reviewed for potential inclusion during the 1-year study period from September 1, 2001, through August 31, 2002. We calculated an average for the number of eligible members and for the number of utilizing members (patients) over the course of the study period because the actual population varied by month, depending on enrollment changes among the various pharmacy benefit plans.

Results

The study population contained an average of 2,889,000 members (48% male) that were eligible for the retrospective DUR program during the 12-month study period from September 1, 2001, through August 31, 2002; of those individuals, 2,026,000 members (70% of eligible members) had utilized their prescription benefits at least once over the study time period and, thus, were included for screening of clinically relevant potential DDIs. The total number of prescription claims utilized by those individuals was 30,174,549.

Over the course of 1 year, the first automated assessment found 244,703 cases of potential interactions for the 51 prespecified drug pairs out of a total of 30,174,549 prescription claims (0.8%) and for 2,026,000 patients (12.1%) (Table 4). Systematic software filters reduced this count from 244,703 to 65,544 cases (27% of those drug pairs initially identified), giving a revised overall incidence of 2 per 1,000 prescriptions (0.2%) and 32 per 1,000 patients (3.2%).

Pharmacist reviewers evaluated the 65,544 cases and, of those, 12,722 cases (6% of those drug pairs initially identified) were considered to be potentially clinically relevant (i.e., true positive alerts), requiring an intervention with the relevant prescriber(s). Thus, the final incidence was 0.4 per 1,000 claims (0.04%) and 6.3 per 1,000 patients (0.6%) (Table 4).

Among all drug pairs, the overall true positive case finding rate (percentage of cases resulting in intervention divided by cases reviewed by a pharmacist) was 19% (12,722 of 65,544 cases; range 0% to 100% for each specific drug pair), which led to 22,364 alert letters sent to relevant prescribing clinicians over the course of the year. The true positive case finding rates by individual drug-pair categories for cases reviewed by a pharmacist (see Table 1 for definition of categories) were as follows: 65% for Category I drug pairs, 21% for Category II drug pairs, 50% for Category III drug pairs, 10% for Category IV drug pairs, 21% for Category V drug pairs, and 9% for Category VI drug pairs. Table 5 shows the top 10 drug interaction pairs by the incident rate per 1,000 prescription claims, after clinical pharmacist review.

TABLE 4 *Results of Investigation of Potential Drug-Drug Interactions From September 1, 2001, to August 31, 2002*

Coprescribed Drug Pairs		Category	Number of Initial Coprescribed Drug Pairs Identified by DUR System	Number of Coprescribed Drug Pairs After Automated Filters	Number of Coprescribed Drug Pairs Clinically Relevant by Pharmacist Review	True Positive Rate of Case Finding (%)*	Incidence per 1,000 Patients†	Incidence per 1,000 Prescription Claims†
Drug 1	**Drug 2**							
Digoxin	Loop diuretics	IV	77,237	10,872	853	8	0.4210	0.0283
Warfarin	Thyroid products	VI	36,733	12,475	1,095	9	0.5404	0.0363
HMG CoAs	Gemfibrozil	II	14,627	1,937	628	32	0.3100	0.0208
Verapamil	Beta-blockers	V	13,959	2,225	413	19	0.2038	0.0137
Warfarin	Amiodarone	IV	13,654	6,141	602	10	0.2971	0.0200
Potassium-sparing diuretics	Potassium	II	13,306	4,579	533	12	0.2630	0.0177
Digoxin	Verapamil	IV	13,108	834	73	9	0.0360	0.0024
Digoxin	Amiodarone	IV	11,166	4,001	335	8	0.1653	0.0111
Clonidine	Beta-blockers	II	10,393	1,735	278	16	0.1370	0.0092
Macrolide antibiotics	HMG CoAs	III	9,459	7,955	4,453	56	2.1977	0.1476
Sumatriptan	SSRIs	V	6,210	3,083	695	23	0.3430	0.0230
Methotrexate	NSAIDs	V	4,289	256	31	12	0.0153	0.0010
Digoxin	Propafenone	VI	2,802	799	64	8	0.0316	0.0021
Digoxin	Quinidine	IV	2,390	534	18	3	0.0089	0.0006
Warfarin	Sulfonamides	III	2,286	1,714	547	32	0.2700	0.0181
Warfarin	Quinidine	IV	1,295	337	28	8	0.0138	0.0009
Lithium	NSAIDs	IV	1,187	523	284	54	0.1402	0.0094
Warfarin	Fluconazole	IV	910	612	138	23	0.0681	0.0046
Verapamil	Carbamazepine	II	908	312	52	17	0.0256	0.0017
Warfarin	Barbiturates	VI	775	269	29	11	0.0143	0.0010
Warfarin	Cimetidine	III	772	319	54	17	0.0267	0.0018
Theophylline	Fluoroquinolones	II	767	548	200	36	0.0987	0.0066
Warfarin	Metronidazole	II	746	644	224	35	0.1106	0.0074
Warfarin	Zafirlukast	III	565	200	30	15	0.0148	0.0010
Warfarin	Erythromycin	IV	496	360	162	45	0.0799	0.0054
TCAs	Clonidine	II	463	185	25	14	0.0124	0.0008
Methotrexate	Sulfonamides	V	447	350	120	34	0.0592	0.0040
Sildenafil	Nitrates	I	444	373	242	65	0.1194	0.0080
Verapamil	Quinidine	V	372	40	8	20	0.0039	0.0003
Selegiline	SSRIs	II	342	24	9	38	0.0044	0.0003
Sibutramine	SSRIs	II	335	224	115	51	0.0567	0.0038
Carbamazepine	Macrolide antibiotics	II	326	246	169	69	0.0834	0.0056
Digoxin	Cyclosporine	V	276	109	8	7	0.0039	0.0003
Theophylline	Macrolide antibiotics	III	226	91	52	57	0.0257	0.0017
Warfarin	Capecitabine	IV	222	137	24	18	0.0118	0.0008
Theophylline	Cimetidine	VI	220	80	8	10	0.0039	0.0003
Allopurinol	Azathiopurine	II	182	85	12	14	0.0060	0.0004
Cyclosporine	Phenytoin	IV	147	63	5	8	0.0025	0.0002
Methotrexate	Salicylates/aspirin	II	134	3	0	0	0.0000	0.0000
Rifampin	Oral corticosteroids	V	129	88	27	31	0.0133	0.0009
Ketoconazole	H2RAs	V	89	74	24	32	0.0118	0.0008
Amiodarone	Quinidine	IV	83	45	12	27	0.0060	0.0004
Selegiline	Venlafaxine	I	73	4	1	25	0.0004	0.0000
Lovastatin	Cyclosporine	V	37	2	1	50	0.0004	0.0000
Warfarin	17-akyl androgens	IV	31	16	6	38	0.0029	0.0002
Rifampin	Oral contraceptives	V	30	12	11	92	0.0054	0.0004
Ergot alkaloids	Macrolide antibiotics	III	20	10	10	100	0.0049	0.0003
MAOIs	SSRIs	I	18	9	7	78	0.0034	0.0002
MAOIs	Amphetamines	I	12	7	4	57	0.0020	0.0001
MAOIs	Sumatriptan	II	4	2	2	100	0.0010	0.0001
MAOIs	TCAs	I	1	1	1	100	0.0004	0.0000
Total			**244,703**	**65,544**	**12,722**	**19**	**6.2779**	**0.4216**

HMG CoAs = HMG CoA reductase inhibitors. *H2RAs = histamine-2 receptor antagonists.* *SSRIs = selective serotonin reuptake inhibitors.*
MAOIs = monoamine oxidase inhibitors. *NSAIDs = nonsteroidal anti-inflammatory drugs.* *TCAs = tricyclic antidepressants.*

** Case finding was determined by the number of coprescribed drug pairs considered clinically relevant by pharmacist review. The true positive rate of case finding was defined as the percentage of cases resulting in an intervention divided by total number of cases reviewed by a pharmacist for each drug pair (i.e., number of cases found by automated filters).*
† The incidence was calculated by dividing the case finding rate, per pharmacist review, by eligible patients (2,026,000) or by prescription claims (30,174,549).

TABLE 5 Top 10 Drug-Drug Interaction Pairs by Incidence per 1,000 Prescription Claims*

Coprescribed Drug Interaction Pairs		Number of Cases Found by Pharmacist Review† (n)	Incidence per 1,000 Prescription Claims*	True Positive Rate of Case Finding‡ (%)
Macrolide antibiotics	HMG CoAs	4,453	0.1476	56
Warfarin	Thyroid drugs	1,095	0.0363	9
Digoxin	Loop diuretics	853	0.0283	8
Sumatriptan	SSRIs	695	0.0230	23
HMG CoAs	Gemfibrozil	628	0.0208	32
Warfarin	Amiodarone	602	0.0200	10
Warfarin	Sulfonamides	547	0.0181	32
Potassium-sparing diuretics	Potassium	533	0.0177	12
Verapamil	Beta-blockers	413	0.0137	19
Digoxin	Amiodarone	335	0.0111	8

HMG CoAs = HMG CoA reductase inhibitors. SSRIs = selective serotonin reuptake inhibitors.
** The incidence was calculated by dividing the case finding rate, after pharmacist review, by total prescription claims (30,174,549).*
† Case finding was determined by the number of coprescribed drug pairs considered clinically relevant by pharmacist review.
‡ The true positive rate of case finding was defined as the percentage of cases resulting in an intervention divided by total number of cases reviewed by a pharmacist for each drug pair (i.e., number of cases found by automated filters).

Discussion

Medication errors may have significant clinical and economic impact. While a medication error does not necessarily lead to an adverse drug event,[25] it is estimated that 28% to 56% of adverse drug events are preventable.[5,26-28] Among such errors, there is little doubt that the coprescribing of potentially interacting drugs can have devastating consequences.[29] However, the incidence of such potential DDIs serious enough to lead to hospitalization or another measurable and serious adverse event remains unclear.

Composite estimates of serious DDIs have been around 2% to 3%,[14,27] although a review by Jankel et al. found that the incidence may vary widely, with estimates from 2% to 17%, depending on the population assessed.[14] The incidence of overlapping QT-interval-prolonging drugs found by Curtis et al. was 9.4%, but that figure, as pointed out by the authors, includes pairs with questionable clinical importance, and the assessment did not involve manual audit.[19] Among the large and diverse outpatient population we assessed, we found that the incidence of clinically relevant potential DDIs was most likely between 6 and 32 cases per 1,000 patients (0.6% to 3.2%), depending on the type of audit method utilized (automation with and without pharmacist review).

Unfortunately, there are little supportive data on the incidence of potential DDIs in other large ambulatory populations. Few published studies have determined such errors exclusively, with most aggregating various types of potential medication errors. Many times, the determination of medication errors found in studies has been part of a planned intervention that might include medication selection or dosage assessment,[30-32] laboratory monitoring,[13,33,34] or inappropriate prescribing.[12-13] Moreover, most studies on medication errors have involved interventions in hospitalized or institutionalized patients, but not in outpatients.[2,7,13,29,31,35-37]

The available studies that have focused on potential DDIs in the outpatient setting have had methodological problems or other limitations that prevent epidemiological assessment.[38,39] The study by Landorf et al. used retrospective case finding to assess 276 emergency room patients and found that 15% had a potential for a DDI.[39] The study, while intriguing, was too small to be generalizable.

Research on ambulatory patients has often focused on either one or relatively few types of interactions.[33,40-43] For instance, McMullin et al. assessed the incidence of dangerous coprescribed drug pairs involving cisapride, before and after a DDI screening program,[42] and Schiff et al. looked at the prescribing of potassium to patients with high serum potassium levels.[33] These assessments found the incident rates of DDIs to be around 2%. More recently, Curtis et al. studied the overlap of coprescribed QT-interval-prolonging agents in approximately 5 million outpatients and found an incidence of 9.4%.[19] This important study, which also used a claims database and retrospective utilization review, included at least some interactions that would not be listed as "serious" in standard references. Thus, it is difficult to compare our results to those findings.

The lack of reliable population data has implications for drug safety improvement programs since, logically, intervention protocols should first and foremost focus on the most common serious coprescribing errors in a population. Clearly, it is difficult to optimize existing technology and methods of intervention without understanding how often a problem, or a potential problem, occurs. Surprisingly, there are little data from private or public health care sectors on the incidence of potential med-

ication errors that cause concern even though reliance on retrospective DUR programs is widespread.

As Schulman et al. euphemistically noted, the literature on the benefit of DUR is "underdeveloped,"[44] echoing the findings of Soumerai and Lipton, who found that computer-based DUR programs have been "implemented without satisfactory evidence of . . . efficacy and safety."[17] Even so, DUR programs rapidly expanded into general use after 1990, when the Omnibus Budget Reconciliation Act (OBRA '90) mandated states to provide such reviews for ambulatory Medicaid patients.[45,46] Programs vary widely not only by the types of interventions performed but also by the frequency of reviews. These differences mitigate the potential for improving drug safety because, if for no other reason, there are little shared data among DUR users.

One of the most comprehensive assessments of medication errors in a large outpatient population has been the work by Monane et al.[12] That study attempted to determine whether a computerized DUR intervention system could improve quality of pharmaceutical care in an elderly population. The intervention alerted pharmacists, trained in geriatrics, of potentially inappropriate medication use. The pharmacists subsequently contacted the prescribing physicians to inform them of the alert and discuss possible treatment alternatives. Based on their results (24% rate of change), Monane et al. concluded that interventions driven by an integrated DUR computer system and pharmacists contacting physicians improved prescribing patterns and increased quality of care.

We hope that our research, along with findings already published by Monane et al.,[12] and, most recently by Curtis et al.,[19] will increase awareness about the utility of using claims-based DUR programs to catalog the type and severity of various prescribing errors among ambulatory populations. We obviously would encourage other health care systems and PBM companies to release data on the incidence of coprescribing errors, however determined. Without such data, it is difficult to assess the success of various programs and intervention methods.

The present study has other important implications for those who wish to develop and optimize targeted DDI warning systems, regardless of whether or not utilization review is prospective, concurrent, or retrospective. As Peterson and Bates have noted, a high number of warnings that are not clinically relevant, or "noise," may lead to alert fatigue.[27]

Our data show how threshold points for sending an alert can change the proportion of clinically relevant alerts. More specifically, if an alert letter or an automated electronic warning, such as those found in some physician order-entry systems, were to be triggered at our highest sensitivity point, providers would be likely to receive many irrelevant warnings.

For example, the retrospective DUR program's simplest automated system on active coprescriptions for digoxin and quinidine would have sent warnings to clinicians 2,390 times, while the more sophisticated automated system decreased the warnings by 78% to 534. Furthermore, if the true positive warning "signal" was best approximated by the pharmacist review, the number of true alerts was 18 (99% reduction of the initial 2,390 warnings). Put another way, pharmacist review in addition to the sophisticated automated DUR system resulted in a "signal"-to-"noise" ratio of nearly 1 in 30 (534 divided by 18) instead of a ratio of nearly 1 in 130 (2,390 divided by 18) with the simplest automated system.

Additionally, in order to decrease "noise" to providers, an alert letter would not be sent if one had already been generated for the same potential DDI case over the past 3 months. Hence, the importance of programs and protocols that identify relevant, potential DDIs while decreasing false positive alerts cannot be overemphasized. One concern that our study raises is that studies depending only on computerized systems to determine incidence may overestimate potential DDIs or other medication errors. Clearly, further research is required in this regard.

This raises the obvious question of what constitutes a true positive—or even a false positive—warning. Although a complete discussion is beyond the scope of the current paper, evidence suggests that clinicians often ignore or override serious and potentially life-threatening DDI alerts.[13,37,47] Thus, clinical relevance, from a safety perspective, cannot be solely determined by a clinician's perspective, and we would argue that an alert is clinically relevant based on the potential severity and/or incidence of an actual subsequent adverse event from a DDI and not on whether the receiving clinician concurs with the warning. For instance, warnings about the coadministration of sildenafil and a nitrate, tranylcypromine and an amphetamine, or ritonavir and amiodarone are relevant, regardless of the subsequent clinical action because of their absolute contraindications and subsequent adverse events.

Even so, in many circumstances, the actual clinical significance of a warning will depend on patient comorbidities, preferences for treatment, provider characteristics, and a balancing of risks and benefits of particular drug combinations. For example, in some instances involving severe vascular disease, the provider and patient may concur that the potential benefit of combining an HMG CoA reductase inhibitor and a fibric acid derivative to adequately address a severe underlying dyslipidemia and, thus, reduce the risk of subsequent vascular events, outweighs the risk of myopathy and rhabdomyolysis when the 2 medications are taken together.

Therefore, our definition of clinical relevance of an alert is predicated primarily on potential severity and incidence of an interaction and not on the clinical significance. For instance, our top 10 potential DDIs by incidence (Table 5) might not correspond to the top 10 potential DDIs that prescribing physicians perceive as most relevant. Clinical significance would perhaps be better assessed by evaluating clinical actions in response to a warning. Thus, we can only speculate until further studies on this issue are available.

Nonetheless, using our perspective on clinical relevance, the true positive warning rates after a pharmacist's review varied by both drug pairs (Table 4) and drug pair classification scheme (Table 1). One concern when developing such categorizations is that there is no singular consensus about a standardized classification scheme.[48] Indeed, while clinicians will no doubt disagree about clinical significance, there is also a lack of uniformity about potential severity of DDIs across commonly used reference materials,[49] making classifications of such interactions even more difficult. In any case, our data suggest that there may be differences in the clinical relevance of automated alerts and that varying levels of manual input are needed to ferret out the true positive from the false positive warnings. In fact, the benefit of retrospective claims-based analysis is that such programs allow clinical pharmacists to reduce the number of irrelevant alerts.[45] We expect that such findings can ultimately guide technological improvements in automated case finding.

Limitations

We acknowledge certain study limitations. We included only submitted, paid claims for dispensed, prescription medications. Our methodology would therefore undercount coprescribing errors when a claim for at least 1 of the drugs in a pair was purchased without the submission of a claim through a prescription benefit plan. This would not be a common occurrence for most prescription medications but could occur, for example, in a prescription for lithium and coincident use of a nonsteroidal anti-inflammatory drug since many nonsteroidal anti-inflammatory drugs can be purchased over the counter. We also did not formally assess the pharmacist audits against a secondary blinded review or otherwise verify the reliability of clinical pharmacist review. Therefore, we cannot be certain that variations in case finding are not at least partially attributable to variations in the individual pharmacist method. However, case finding was performed by a small group of 4 trained pharmacists who often conferred with each other.

We also did not assess the relevance of coprescribed pairs that were dropped by the second automated review; it is possible that a few cases may have been clinically relevant, but we do not know how often this occurs. However, the filters were built over time to account for many of the false positives that were observed by the clinical pharmacists, and, as our data show, the automated filters provided far more alerts than were considered relevant by pharmacists.

As is common in prescription drug plan populations, activity in enrollment and disenrollment required that we calculated an average enrolled study population over the 12-month study period. Moreover, we defined incidence by using an eligible population of those members who had prescription claims throughout the year; this was done because we were interested in the incidence of potential DDIs across a large, covered population from the perspective of a PBM firm. Put another way, we wanted to know how many prescription claims and how many patients might require an intervention. Thus, it is important to note that the incidence would change if we defined our population differently, such as in patients who filled at least 2 prescriptions, in patients who filled 2 or more overlapping drugs, or in patients who used at least 1 of the target drugs in a given drug pair during the course of the year.

Our study did not assess clinical outcomes such as changes in drug therapy or therapies that resulted from alert letters to the prescribing physician(s) or whether or not interventions we assessed as clinically relevant were indeed clinically significant based on patient outcomes. The scope of our study did not address actions taken by prescribers in response to drug interaction alert letters, and we did not use certified mail to determine if all the letters were actually received by the prescribers at their offices. We also did not determine to what extent or frequency prescribers reviewed the information.

Conclusion

We found that the use of more sophisticated, electronic comparison of clinically relevant potential DDIs identified by simple drug pairs reduced the incidence of DDI alerts by 70.8%. Additional clinical pharmacist review reduced the incidence of potentially serious DDIs by an additional 80.6%. Combination of the 2 methods reduced the incidence of apparent serious DDI by 94.3%.

It is important that private and public health plan sponsors and PBM firms share available data on the types and incidence of clinically relevant potential medication errors and their methods used to make these determinations. Doing so will assist in better understanding the fundamentals of retrospective DUR intervention programs in ambulatory populations.

Future research is needed to determine how often and to what extent prescribers respond to such alerts about apparent medication errors. In addition, future research is needed to determine the methods and procedures that will make DUR warning systems most effective in obtaining acceptance and cooperation from prescribers in reducing the incidence of adverse drug events.

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