

Measuring Patient Safety in Ambulatory Care: Potential for Identifying Medical Group Drug–Drug Interaction Rates Using Claims Data

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Objective: To evaluate the feasibility of using health-plan administrative data to measure potential drug–drug interaction (DDI) rates in the ambulatory setting at the medical-group level and to assess the potential use of DDI rates in performance measurement, quality improvement, and research in patient safety.

Study Design: We combined administrative and pharmacy claims data from 2 large health plans to calculate the rates at which member users of selected chronic medications were potentially exposed to a second drug known to pose a risk of harmful interactions.

Methods: We divided 44 medication combinations with risk of adverse interactions into those with DDIs of moderate/severe clinical significance and those with DDIs of mild significance. We then calculated yearly rates of potential DDIs in continuously enrolled members aged 19 and older from 1998 through 2001. Rates were calculated for all members, overall base-medication users, and individual medical groups responsible for their care.

Results: The analytic data set included 756 047 patient-years of data and 110 to 123 medical groups per year. During the 4-year interval, one or more unique potential DDIs occurred in 6.2% to 6.7% of base-drug users and 2.0% to 2.3% of all adult health-plan members per year. Medical-group mean user rates were slightly lower (5.33%–5.81%), with wide variance (SD = 2.6%–3.1%) and high stability over time.

Conclusion: Potential DDI rates calculated from health-plan data have promise for measurement in patient medication safety. This readily available and inexpensive evaluation tool has potential for monitoring, improvement, and research purposes if further studies validate their relationship to actual adverse events.

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Release of the 1999 Institute of Medicine (IOM) report on medical errors created a public furor and stimulated many research and improvement initiatives.¹ Although the IOM report recommended a 50% reduction in errors over 5 years, it did not discuss measurement of errors or adverse event rates as a means of monitoring trends and improvement efforts.

The studies cited in the IOM report calculated errors with methods too expensive and labor intensive for repeated use in performance monitoring or improvement efforts. Moreover, the studies dealt with hospital incidents only, with uncertain applicability to ambulatory care. Thus, we know very little about the nature or

epidemiology of errors or adverse events in ambulatory care settings, and we lack measurement methods for accountability or improvement.

In the absence of any practical methods of quantifying overall errors, measurement of adverse drug events (ADEs) may be a good way to gauge errors and patient safety in ambulatory care, since studies have found ADEs to be frequent and a significant contributor to emergency department visits and hospitalizations.²⁻¹² Using multiple methods in 2003, Gurwitz found an incidence of 50.1 ADEs per 1000 person-years in those aged 65; 27.6% were deemed preventable.¹³ Gandhi concluded from a patient survey that during a 3-month period, 25% of outpatients with a prescription experienced an ADE, 13% of which were serious and 11% preventable.¹⁴ Both studies are valuable in understanding the approximate rates of ADEs but neither is amenable to repeated measures at the level of individual practices or medical groups.

Although ADEs appear to be relatively frequent, there are practical limitations in relying on chart audits and surveys to detect and monitor them. Drug claim data and member information available from health plans offer an inexpensive and repeatable way to measure potential ADEs, especially drug–drug interactions (DDIs), in ambulatory care. A DDI is “2 or more drugs interacting in such a manner that the effectiveness or toxicity of 1 or more drugs is altered.”¹⁵ A potential DDI should be identifiable from health-plan claims data that show 2 such drugs prescribed simultaneously. Researchers have studied DDI rates in special populations and settings,¹⁶⁻²⁴ but only 2 recent studies have used large population-based pharmacy claims databases to study case rates of specific drug pairs. Peng et al used a drug utilization review program to study potential

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DDIs in a population of 3 million, and Hennessy et al did the same for enrollees in 6 state Medicaid programs.^{25,26} However, no one has studied DDI rates in individual medical groups, the level at which accountability and improvement ability reside. Such analysis can facilitate measurement and comparison of performance and provide medical groups with a basis for quality improvement.

Therefore, we combined administrative data from 2 large health plans to answer the following questions:

1. Is it feasible to use health-plan data to identify potential DDI rates in relation to the individual medical groups responsible for member care?
2. Is the frequency of potential DDIs high enough to characterize medical groups or clinics?
3. How much variation in rates exists among medical groups?
4. Are these rates stable enough over time to serve as a credible way to measure trends and changes?

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METHODS

We studied the frequency of potential DDIs from 1998 through 2001 in health-plan members served by the medical groups contracting with 2 HMOs. The primary data sources were pharmacy claims, medical care claims, and membership files. The institutional review boards at both organizations approved the study.

The HMOs participating in this study were HealthPartners in Minnesota and Lovelace Health Plan in New Mexico. In 2000, HealthPartners covered 657 000 members through contracts with 50 medical groups, and Lovelace Health Plan had 240 000 members cared for by approximately 240 medical groups.

The study included all medical groups that provided primary care for at least 30 health-plan members from 1998 through 2001. Location, based on US Bureau of the Census designation, and other descriptive data about these medical groups were collected from health-plan records.

We identified HMO members who were 19 or older as of January 1 in the study year, had continuous membership (with up to a 45-day break) with pharmacy benefits during the study year, and had a known affiliation with an eligible medical group. Descriptive data about members were obtained from membership and claims records.

We included in our analysis 44 combinations of drugs (a base drug and a conflicting drug or drugs) known to have potential adverse interactions and in which the base drug is taken chronically by large numbers of people (**Table 1**). We used 3 key references to identify drug

interaction combinations: (1) Hansten and Horn's Drug Interactions, Analysis and Management, (2) the DRUG-REAX[®] System of MICROMEDEX, and (3) Evaluations of Drug Interactions[™] (EDI).²⁷⁻²⁹ Because there is so much variation among standard texts about what combinations represent a DDI of what severity, we required that each DDI combination be identified as a problem in at least 2 of these 3 references and have a clinical significance rating of 1, 2, or 3 (on a scale of 1 to 5), as assigned by Hansten and Horn.^{27,30,31}

1. Severe interaction ("Avoid administration of the combination. The risk of adverse patient outcome precludes concomitant administration.")
2. Moderate interaction ("Avoid administration unless it is determined that the benefit of co-administration outweighs the risk to the patient. Patients should be monitored closely.")
3. Mild interaction ("Minimize risk by considering alternative agents or change dosage or route of administration. Patient monitoring is suggested.")

An initial list of DDI combinations was reviewed by a panel of clinical pharmacists, by several primary care physicians, and by the Pharmacy & Therapeutics Committee of one of the two participating plans. Reviewers deleted from the list DDI combinations deemed irrelevant to current clinical practice or of questionable risk. Deleted combinations include furosemide and steroids, angiotensin-converting enzyme (ACE) inhibitors and potassium-sparing diuretics. For analysis, the combinations were divided into potential DDIs of moderate/severe clinical significance (Hansten and Horn ratings 1 and 2) and potential DDIs of mild significance (Hansten and Horn rating 3).

Individual drug fills were identified from pharmacy claims data using the National Drug Codes (NDC). A comprehensive list of NDCs for the study medications was gathered. The Master Drug Data Base (MDDB[®]), a commercial database maintained by Medi-Span, Indianapolis, Ind,³² was used to ensure the inclusion of all NDCs ever registered with the Food and Drug Administration.

To determine potential DDIs in this patient population, we identified patients with both a pharmacy fill for a base drug in the year of interest and a fill for a conflicting drug. The days' supply of the conflicting drug must have overlapped with that of the base drug by 10 or more days. Coprescription of a given DDI combination was counted only once per year for a given patient, regardless of the number of fills for either drug. However, if the same patient had overlapping fills for a different DDI combination during the same year, this was counted as a separate potential DDI.

Each member was linked with the medical group responsible for their care as of January 1 in the year of interest. After determining that there was no significant difference in rates between the 2 health plans, data were combined for a single analysis. Medical group-specific rates were then calculated for only those medical groups with at least 30 chronic users of measured base drugs or classes. Stability in rates over the 4 study years was evaluated by calculating Pearson correlation coefficients between individual medical group rates for consecutive years. Potential DDI error rates were calculated for each year from 1998 through 2001 among (1) base-drug users and (2) all HMO members who could be connected with a medical group in the analysis. A Cochran-Armitage trend test analysis of rates across the 4 years was also performed.

RESULTS

The analytic data set included 756 047 patient-years of data, with 199 373 in 1998, 181 955 in 1999, 189 955 in 2000, and 194 084 in 2001. The number of medical groups eligible each year from 1998 through 2001 was 109, 107, 123, and 110, respectively. Table 2 lists characteristics of the medical groups in 2001 only, since there was relatively little difference from one year to the next. Medical groups varied greatly in number of clinics, number of clinicians, and number of HMO members. Users of the base drugs were predominantly female and middle-aged.

During this period, there was a significant increase ($P < .001$) in the percentage of the HMO population using any of the base drugs (33.04% in 1998 to 34.80% in 2001). In addition, the mean number of medications used by patients increased significantly ($P < .001$) among patients using base drugs of moderate/severe significance (8.14 in 1998 to 8.58 in 2001) and among patients using base drugs of mild significance (7.07 in 1998 to 7.74 in 2001).

Table 1. Drug-Drug Interaction Combinations

Chronic Base Drug	Conflicting Drug
Anticonvulsants	
phenytoin	cimetidine
phenytoin	fluconazole, isoniazid, sulfonamides, trimethoprim
phenytoin	phenylbutazone
phenytoin	disulfiram
phenytoin	doxycycline
phenytoin	theophylline
valproic acid	barbiturates
carbamazepine	propoxyphene*
Antilipemics	
lovastatin	erythromycin
simvastatin	clarithromycin
HMG-CoA reductase inhibitors	gemfibrozil*
HMG-CoA reductase inhibitors	erythromycin
HMG-CoA reductase inhibitors	itraconazole
Cardiovascular	
verapamil	propranolol, atenolol, metoprolol, timolol
clonidine	tricyclic antidepressants*
clonidine	propranolol
nitrates	sildenafil*
ACE inhibitors	COX-2 inhibitors, NSAIDs
spironolactone	
triamterene	potassium*
digoxin	erythromycin, itraconazole, tetracycline
digoxin	verapamil
digoxin	cholestyramine
digoxin	spironolactone
diltiazem	nifedipine
furosemide	cholestyramine, colestipol
propranolol	rifampin
propranolol	
metoprolol	cimetidine
Gastrointestinal	
cimetidine	theophylline
sucralfate	levofloxacin, ciprofloxacin
Hematologic	
warfarin	cimetidine*
warfarin	erythromycin, sulfonamides, metronidazole
warfarin	rifampin, carbamazepine, phenytoin
warfarin	lovastatin, fluvastatin, gemfibrozil, clofibrate
warfarin	barbiturates*
warfarin	cholestyramine, colestipol
Hormonal	
oral contraceptives, combination pills	barbiturates
oral contraceptives, combination pills	rifampin
insulin	propranolol
steroids	barbiturates, rifampin
Psychoactive	
lithium	thiazides
tricyclic antidepressants	cimetidine
tricyclic antidepressants	fluoxetine, paroxetine
alprazolam	fluoxetine
SSRIs	selegiline
Respiratory	
theophylline	erythromycin, ciprofloxacin

*Rated as 1 or 2 (interaction of moderate or severe clinical significance) by Hansten and Horn;²⁵ all others are rated as 3 (interaction of mild clinical significance). HMG-CoA indicates 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors; ACE, angiotensin-converting enzyme; COX-2, cyclo-oxygenase-2 inhibitor; NSAID, nonsteroidal anti-inflammatory drug; and SSRI, selective serotonin reuptake inhibitor.

Table 2. Characteristics of Medical Groups and Base-Drug Users, 2001

Characteristic	Frequency (%) or Mean, Median (SD)	Range
Medical Groups (n = 110)		
Primary care practice only	55.4%	NA
Location		
• Urban	44.5%	NA
• Rural	10.9%	NA
Number of clinics	7.3, 3.0 (12.1)	1-67
• 1	35.4%	
• 2-5	37.3%	
• 6 or more	27.3%	
Number of clinicians	113.0, 19.5 (238)	1-1136
• 1-10	38.2%	
• 11-50	27.3%	
• 51 or more	34.6%	
Number of primary-care clinicians	58.0, 15.0 (109)	0-702
Number of HMO members	3696, 486 (14 305)	76-123 159
• 30-300	36.4%	
• 301-1000	29.1%	
• 1000 or more	34.6%	
Medical-Group HMO Members		
• % males	47.0, 47.4 (6.0)	25.4-61.2
• % aged 40-64	51.9, 52.2 (9.0)	9.4-79.0
• % aged 65+	6.1, 4.6 (5.2)	0-24.2
• Number of clinic visits/year	3.3, 3.3 (0.6)	1.0-5.4
• Number of drugs/patient/year	3.4, 3.3 (1.0)	1.0-7.7
Base-Drug Users (n = 141 478)		
Male	35.1 %	NA
Age group		
• 19-39	31.0 %	NA
• 40-64	56.4 %	NA
• 65+	12.6 %	NA
Number of drugs/patient/year	7.3 (5.8)	1-98

NA indicates not applicable.

Table 3 shows the percentage of HMO members who had at least 1 potential DDI from 1998 through 2001. Percentages are given for all HMO members and for chronic users of base drugs. In each case (except for the percentage of base-drug users with risk of moderate or severe reactions) the rates increase gradually over the 4-year time interval ($P < .001$). Base drugs with the most users were selective serotonin reuptake inhibitors, oral contraceptives, 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors, ACE inhibitors, and steroids. The rate of individual potential DDIs varied from 0% for phenytoin plus phenylbutazone, digoxin plus cholestyramine, and propranolol plus rifampin to 16.5% for ACE inhibitors plus nonsteroidal anti-inflammatory drugs/cyclooxygenase-2 inhibitor.

Table 4 shows the potential DDI rates of medical groups for their HMO panel members and for their users

of the base drugs. It illustrates the variation in DDI rates among medical groups in any year (eg, 0% to 17%). At the same time, it shows how little DDI rates change from one year to the next, since Pearson correlation coefficients for consecutive years are rather high. The 10 to 13 largest medical groups (serving at least 5000 HMO members) had potential DDI rates 5% to 10% higher than those of the smaller groups (data not shown). The rates for the larger groups were also much more stable over time, probably as a result of larger sample sizes.

Table 5 provides medical-group rates and variances for users of base drugs in various drug classes by body system. The data show that, when limited to those medical groups with at least 30 base-drug users in a drug class, the numbers drop substantially. Only half of the classes of base drugs (antilipemics, cardiovascular, hormonal, and psychoactive) have enough medical groups with an adequate number of users to permit inclusion in such an analysis, and 2 classes have especially high mean rates (cardiovascular and hematologic).

DISCUSSION

These results confirm that it is feasible to calculate rates of potential DDIs from HMO administrative data regarding individual medical groups. The rates are high enough (6.2%-6.7% of base-drug users on average) and stable enough over time to permit their use for accountability and improvement. Even if restricted to moderate or severe potential DDIs, 3.5% of base-drug users are at risk in any given year. At the same time, there is quite a bit of variation in rates among the medical groups providing care for these members (SD = 2.6-3.0), as well as among the individual drugs and drug classes. However, shifting focus from overall potential DDIs to specific classes of drugs loses 35% to 54% of medical groups for 4 classes, and the remaining 4 classes lose much more.

Table 3. Rate of Members with ≥1 Potential Drug-Drug Interactions by Total and Severity, 1998-2001

Year	All HMO Members (%)			Base-Drug Users (%)			Rate per 1000 Base Users		
	Combined	Mod/Sev	Mild	Combined	Mod/Sev	Mild	Combined	Mod/Sev	Mild
1998	2.04	0.52	1.59	6.16	3.55	5.64	67	36	60
1999	2.11	0.56	1.63	6.28	3.53	5.71	68	36	60
2000	2.18	0.60	1.68	6.43	3.47	5.87	70	35	62
2001	2.32	0.63	1.79	6.66	3.43	6.11	72	35	64

Mod/Sev indicates moderate or severe interactions.

Table 4. Variation in Medical-Group Panel Member and Base-Drug User Rates of Potential Drug-Drug Interactions Over Time

Year	Medical-Group Panel Member Rate				Medical-Group Base-Drug User Rate			
	% of Panel Members with ≥1 Potential DDIs		Pearson Correlation*		% of Base-Drug Users with ≥1 Potential DDIs		Pearson Correlation*	
	N	Mean (SD)	N	Coefficient (P)	N	Mean (SD)	N	Coefficient (P)
		Range				Range		
1998	109	1.68 (1.03) 0-4.87	NA	NA	109	5.33 (2.83) 0-13.58	NA	NA
1999	107	1.56 (0.74) 0-3.77	96	.55 ($<.001$)	107	5.39 (2.61) 0-14.88	96	.46 ($<.001$)
2000	123	1.67 (0.92) 0-4.33	98	.66 ($<.001$)	123	5.62 (3.06) 0-17.14	98	.57 ($<.001$)
2001	110	1.70 (0.88) 0-4.50	98	.55 ($<.001$)	110	5.81 (2.89) 0-16.67	98	.38 ($<.001$)

*Variables tested were individual medical-group rates for consecutive years. The rank-order correlation included only those groups with 30 members with rates for each consecutive year.

It would be difficult to apply these rates to individual clinic sites or physicians.

The proportion of actual adverse reactions from these “potential” rates must be studied because these rates appear to be good candidates for measures of ambulatory-care medication safety, at least for medium to large medical groups. They seem to provide a useful way to compare the quality of care among medical groups and may provide a means for those groups to target and monitor quality improvement actions. Because determination of these rates requires sufficiently large health-plan membership, however, they cannot be used to compare individual clinicians or small medical groups.

While this is the first use of health-plan data for such measurement at the medical group level, rates for entire populations (eg, a city or state) have been calculated with other types of computerized databases. Using Medi-Cal claims, Laventurier found an overall potential-DDI rate of 7.57% for 6 base-drug groups.²⁰ Jinks used Medicaid records to find that 11.3% of users of 3 drugs had potential DDIs.²¹ Three recent studies using large pharmacy population databases in Scandinavia found that 1.4% to 3% of all prescriptions presented a risk of a major DDI. Overall potential DDI rates were 13.6% and 31% in 2 of those studies.^{18,23-24} Peng performed retrospective drug-utilization review of pharmacy claims for 3 million people

DRUG SAFETY

Table 5. Rate of Members with >1 Potential Drug–Drug Interactions by Drug Class and for Medical Groups, 2001*

Drug Class	Base-Drug Users, N	Overall Rate, %	Medical Groups, N	Rates for Medical Groups With More than 30 Base-Drug Users in a Class			
				Minimum No. of Members	Mean (SD)	Range	
Overall	141 478	6.67	110	77	167	4.25 (2.96)	0-20.0
Anticonvulsants	3935	1.65	95	15	3421	1.14 (1.38)	0-4.08
Antilipemics	30 118	4.12	110	51	416	3.49 (2.19)	0-10.71
Cardiovascular	49 220	13.3	110	65	244	11.70 (3.84)	0-21.74
Gastrointestinal	6260	0.26	98	15	1704	0.22 (0.38)	0-1.28
Hematologic	4599	9.02	99	13	3204	10.0 (4.29)	4.8-21.0
Hormonal	57 040	0.23	110	71	167	0.13 (0.28)	0-1.64
Psychoactive	48 512	3.07	110	65	212	2.74 (1.73)	0-9.09
Respiratory	706	0.57	58	4	30 471	1.05 (1.16)	0-2.63

*Medical-group rates are for those groups with at least 30 chronic users of a base drug from that therapeutic class. The mean error rate was computed by averaging each medical group's rate by therapeutic class with the associated standard deviation and range.

and found that 245 000 potential DDI cases (0.8% of claims) could be identified using coprescription of any of 51 DDI pairs.²⁵ More sophisticated automated screens (like the ones we used) reduced Peng's rates by 70%, and pharmacist review of this group reduced the number by an additional 80% to 6.3 per 1000 members.

In our study, both the mean number of medications used per patient and the proportion of base-drug users with potential DDIs increased between 1998 and 2001. This is consistent with the recent findings of Hennessy et al, who found no reduction in the rate of potential prescribing errors or hospitalization in their retrospective drug utilization review with alerts for exceptions sent to prescribing physicians.²⁶ It is well established in the quality improvement field that, with few exceptions, change in clinician behavior requires local system change rather than exhortation, and that is the type of change that broader performance measurement and feedback could provide.

One of the reasons that individual case alerts are ineffective is that the coprescription of 2 drugs that interact with potentially adverse consequences is not necessarily erroneous. Physicians must weigh both the benefit and the risk of drug combinations when deciding what to prescribe. Additionally, many drug interactions can be managed through appropriate laboratory and symptom monitoring or by instructing the patient to adjust the timing or dosage of a drug. Only a fraction of patients with a potential DDI actually suffer adverse consequences. Mitchell et al found that, of 160 ambula-

tory patients with potential for a DDI, only 8 of the potential DDIs were of major clinical significance.¹⁹ Herr and colleagues found that 7.5% of 201 emergency department (ED) patients at risk for a DDI, due to either ED medication or medication taken prior to the ED visit, had clinically relevant adverse interactions within 4 weeks after the ED visit.²² These researchers also found that medications prescribed during the ED visit put 26% of ED patients at risk for a DDI, and 3% of this group experienced a clinically relevant adverse interaction within 4 weeks. These rates are higher than those in hospital patient studies reviewed by Jankel, but unfortunately there are no published studies of actual adverse events for large populations identified through pharmacy records or claims data.³³

This study has several limitations. In order to get a rate high enough to characterize individual medical groups, we were forced to combine mild with moderate–severe DDIs. Consequently, we included many DDIs that could be managed by close monitoring or by changes in dosage or route of administration. This complication highlights the need to focus on comparison of DDI rates among medical groups rather than elimination of each potential DDI.

Identifying prescription drug use from computerized claims records provides only an indirect picture of actual patient drug intake. Some drugs may have been purchased but not taken by the patient, or the patient may not have taken both drugs simultaneously. Also, we were unable to ascertain occurrence of actual symptoms or

adverse events as a result of taking 2 interacting drugs. Neither could we determine whether the prescribing physician performed appropriate laboratory monitoring or instructed the patient to change the dosage or timing of a medication to avoid an adverse interaction. Thus, these rates represent only a theoretical maximum risk of interactions. Before these rates can be used to monitor performance, additional research must ascertain how often adverse outcomes actually occur in patients with potential DDIs and whether appropriate monitoring or patient instruction is being provided. It is also important to learn whether there is a relatively constant ratio between potential DDIs and actual adverse events.

Once this clarifying information is obtained, potential DDI rates determined from claims data could be an important tool for improving patient safety. With their rates of potential DDIs identified, medical groups can begin to work on improvement. On a larger scale, reduction of these rates may help us to know whether we have made progress toward the 50% reduction in medical errors proposed in *To Err is Human*.¹

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