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Prescribers' Knowledge of and Sources of Information for Potential Drug-Drug Interactions

A Postal Survey of US Prescribers

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Abstract

Background: Given the high prevalence of medication use in the US, the risk of drug-drug interactions (DDIs) and potential for patient harm is of concern. Despite the rise in technologies to identify potential DDIs, the ability of physicians and other prescribers to recognize potential DDIs is essential to reduce their occurrence. The objectives of this study were to assess prescribers' ability to recognize potential clinically significant DDIs and to examine the sources of information they use to identify potential DDIs and prescribers' opinions on the usefulness of various DDI information sources.

Methods: A postal questionnaire was developed to assess prescriber knowledge of medications that may interact and prescribers' usual sources of DDI information. Recipients were asked to classify 14 drug pairs as 'contraindicated', 'may be used together but with monitoring' or 'no interaction'. A response option of 'not sure' was also provided. The questionnaires were sent to a national sample of 12 500 prescribers based on past history of prescribing drugs associated with known potential for DDI, who were identified using data from a pharmacy benefit manager covering over 50 million individuals.

Results: Usable questionnaires were obtained from 950 prescribers. The percentage of prescribers who correctly classified specific drug pairs ranged from 18.2% for warfarin and cimetidine to 81.2% for paracetamol (acetaminophen) with codeine and amoxicillin, with 42.7% of all combinations classified correctly. The number of drug pairs correctly classified by the prescribers ranged from 0 to 13. For half of the drug pairs over one-third of the respondents answered 'not sure';

among those drug pairs, two were contraindicated. When asked what source was used to learn more about a potential DDI, a quarter of the prescribers reported using personal digital assistants and another quarter used printed material. The majority of the prescribers (68.4%) reported that they were usually informed by pharmacists about their patients' potential exposure to DDIs. Compared with the prescribers who used other sources, those who used computerized DDI alerts as their usual source of DDI information consistently gave a lower rating score to the five statements that assessed the usefulness of the information.

Conclusion: This study suggests that prescribers' knowledge of potential clinically significant DDIs is generally poor. These findings are supported by other research and emphasize the need to develop systems that alert prescribers about potential interactions that are clinically relevant. Physicians most commonly reported learning about potential DDIs from pharmacists, suggesting further work is needed to improve the drug-prescribing process to identify potential safety issues earlier in the medication use process.

Background

Medication use is extensive in the US and becoming even more so. Approximately four-fifths of adults in the US use at least one medication (prescription or over-the-counter drugs, or supplements) in any given week, and the rate of use increases with age.[1] Based on the 2002 National Ambulatory Medical Care Survey, medication therapy was reported during 577.1 million physician office visits, accounting for 64.8% of all office visits.[2] At each office visit with any mention of medication, an average of 2.3 medications had been reported as being ordered or provided.[2] One risk associated with the use of multiple medications is the possibility of drug-drug interactions (DDIs). DDIs can lead to adverse drug effects that can result in hospital admissions and emergency department (ED) visits[3-6] and sometimes death.[7-14]

The recognition of a potentially interacting drug pair by health care providers is essential in reducing the risk of DDIs and associated drug-related morbidity and mortality. Several studies have been conducted to assess health care providers' ability to identify clinically significant DDIs.[15-20] One study revealed that when computer software was used as the criterion standard, the performance of both general ED physicians and an expert ED physician in identifying potential DDIs was poor, with a sensitivity of 14% and 25%, respectively.[18] In a survey of Veterans Affairs (VA) clinicians, response from a ten-item DDI test indicated that clinicians correctly categorized 53% of drug pairs with known interactions.[17] In a follow-up survey using the same test, it was found that the clinicians correctly categorized similar percentages of the seven interacting drug pairs on the two surveys (53% vs 54%), although the overall recognition of the three contraindicated drug pairs was improved slightly (51% vs 60%).[16]

Given the rate at which new medications are introduced to the market and the diversity of existing drugs, clinicians frequently need to consult information sources when prescribing. One study found that although 62.3% of primary care physicians relied upon themselves as their primary formation source for drug interaction screening, 63.1% of the physicians preferred to use pharmacists as the information source.[21] More recently, a survey of prescribers and pharmacists in VA medical centres examined health professionals' most frequently

used sources of general drug and DDI information.[22] The study results indicated that electronic references (e.g. Micromedex®, the Internet, personal digital assistants [PDAs] and UpToDate®) were used most frequently by both prescribers and pharmacists. The next most frequently used source of DDI information for prescribers was pharmacists; whereas for pharmacists, it was printed references such as the American Hospital Formulary Service and Facts & Comparisons.

Testing prescribers' ability to recognize potential DDIs without the use of drug references could help to assess the necessity and likely influence of prescribing support systems, such as automated DDI alerts, in reducing DDIs. Compared with general pharmaceutical information, less is known about prescribers' sources of DDI information. As such, the purpose of this study was 3-fold: (i) to assess the degree to which prescribers can recognize potential clinically significant DDIs; (ii) to examine how prescribers are usually informed about their patients' potential exposure to a DDI; and (iii) to determine how useful that information is to the prescriber.

Methods

This study used pharmacy claims to identify and survey prescribers with a history of prescribing a drug with the potential to cause a DDI, as well as a control group without such a history.

Sample Selection

Prescription claims between January and May 2005 were obtained from a pharmacy benefit manager covering over 50 million individuals nationwide and reviewed to select prescribers who prescribed one or more medications that could have caused a DDI. A potential DDI was defined in this study as a situation wherein a patient received prescriptions for two medications that have been shown to interact in a way that could lead to harm. A prescriber was eligible for selection if he/she: (i) was listed as the prescriber of record for a pharmacy claim involving a medication that was identified as part of 25 clinically significant DDIs;[23] and (ii) had a Drug Enforcement Agency (DEA) number for provider types of physicians or nurse practitioners (NPs)/physician assistants (PAs). The presence of a DEA number was necessary to link to the prescriber's address using a DEA master file containing the names and addresses of all DEA registrants. Prescribers were included in the 'case' population if they had written at least one prescription for a drug that initiated the potential for an interaction included in the 25 DDIs of interest for this study.[23] The two medications may have been prescribed at the same visit or at separate visits by the same or different prescribers, but the duration of therapy was required to overlap to meet the definition of a potential interaction. For interactions involving multiple prescribers, we selected the prescriber linked to the second medication. From the eligible case population, a random sample of 5500 prescribers was selected. The remaining prescribers in the database were then sampled using a one-to-one match to represent the 'control' group. The control group were prescribers who had written a prescription for either one of the medications in the drug combination but the prescription did not initiate a potential DDI. In addition to having prescribed at least one medication that could interact if the other was prescribed, matching was conducted based on the state where the prescriber practiced, type of provider and prescription volume. Following the selection procedures, a total of 11 000 prescribers nationwide was selected, with 5500 each in the case and control samples.

Survey Questionnaire

A short and a long version of the survey questionnaire were developed for this study. Both versions contained 16 questions about prescribers'

demographics, practice characteristics, workload, general opinions about DDIs and a DDI knowledge test that asked prescribers to classify 14 drug pairs as 'contraindicated', 'may be used together but with monitoring', or 'no interaction'. An option of 'not sure' was also provided. The knowledge test included the drug pair for which the individual prescriber had been selected. For the case sample, this represented a history of prescribing a drug that may initiate the potential interaction of the drug pair. Among the 14 common drug pairs, 6 were interacting combinations selected from the 25 clinically important DDIs[23] and 8 had no known interaction. The test key (i.e. drug pair classification) was reviewed and approved by the expert group who developed the original list of 25 important DDIs. Given the availability of alternative drugs, some of the drug pairs were classified as contraindicated, although arguably they could be given together with close monitoring. The long version of the survey questionnaire included seven additional questions regarding prescribers' sources of DDI information.

Data Collection

Data were collected via a mailed survey packet addressed to the sample of prescribers. The distribution of the mail survey followed a modified Total Design Method approach.[24] Addresses of the prescribers sampled were identified using a DEA database and verified using the US Postal Service National Change of Address database and the Coding Accuracy Support System certification process. An announcement postcard, providing a brief explanation of the study, was sent to the 11 000 sampled prescribers on 21 October 2005. One week later, a survey packet was sent out. The survey packet contained a copy of the survey questionnaire and a cover letter that explained the purpose of the study and contained the essential elements of informed consent. Among the 11 000 prescribers, 1000 were selected at random to receive the long version of the questionnaire and the others were sent the short version. Two weeks following the first survey packet mailing, a reminder postcard was sent encouraging participation in the study. Two weeks after that, a reminder letter was sent along with another copy of the survey questionnaire.

A low response rate was obtained from the national sample; therefore, a second round of surveying was conducted targeting only Arizona prescribers to supplement the data collected from the national survey. Arizona was chosen because of the potentially better response from in-state prescribers. For the Arizona sample, 1500 prescribers were selected from the eligible population with equal distribution between prescribers with and without a history of initiating a potential DDI. The sample selection and survey mailing procedures were conducted in a similar manner to the national survey. The questionnaire used in the Arizona survey included all the questions in the long version questionnaire.

This study was approved by the Institutional Review Board of the Human Subjects Protection Program at the University of Arizona.

Data Analysis

A returned questionnaire was considered usable if (i) the question relating to the drug pair of interest was answered, and (ii) at least 7 of the 14 common DDI knowledge test questions were answered. For the Arizona survey and the long version of the national questionnaires to be considered usable, additional requirements needed to be met (i) the question regarding the prescriber's usual source of DDI information was answered and (ii) four of the five questions assessing the usefulness of the information source were answered. Only the usable questionnaires were included in the analyses. The response rate adjusting for the unusable questionnaires was calculated by dividing the number of usable questionnaires by the number of undeliverable mails

subtracted from the number of mailed questionnaires.

Frequency distributions and means were used to describe categorical and continuous variables, respectively. The percentage of correct responses to each drug pair in the DDI knowledge test and the number of drug pairs correctly classified were also calculated. Because of differences in the severity of the interactions, four of the authors (Murphy, Skrepnek, Armstrong and Reel) classified those pairs with the potential for interaction as clinically serious or not if the patient received the combination. We also evaluated respondents' responses to this subset of interactions. A two-sample t-test was used to compare the mean number of correctly classified drug pairs between cases and controls and one-way analysis of variance (ANOVA) with Scheffe *post hoc* comparisons was used to compare the mean rating scores among different sources of DDI information. In addition, an ordinary least squares regression model was conducted to examine the association between prescribers' DDI knowledge (i.e. the number of drug pairs correctly classified) and potential predictors including prescribers' demographics, workload, specialty, practice characteristics, history of DDI prescribing (i.e. cases or controls), how the risk of DDIs affected the prescriber's drug selection and having previously seen a DDI cause harm. For parsimony, no interaction terms were included in the model. An α-level of 0.05 was used to determine statistical significance. All analyses were performed using SPSS 14.0 (Chicago, IL, USA).

Results

Summary Statistics

Survey packets were mailed to a total of 12 500 prescribers (national: 11 000; Arizona: 1500) in October 2005 and February 2006, respectively, for the national and Arizona samples. After discarding 402 undeliverable surveys, responses were obtained from 1015 prescribers (national: 739; Arizona: 276), of which 65 questionnaires were deemed unusable by predetermined criteria. Thus, data from the remaining 950 respondents were included in the analyses (national: 695; Arizona: 255). The overall adjusted response rate was 7.9% (national short version: 6.5%; national long version: 6.3%; Arizona: 18.5%).

A comparison between respondents and non-respondents indicated that the two groups had a similar proportion of cases and controls, and the mean prescription volumes of the prescribers were not statistically different. However, the respondent group had more NPs/PAs and more prescribers practicing in the West region in the US than those who did not respond ($p < 0.0001$).

The demographic and practice characteristics of the Arizona respondents were similar to those of the national respondents with a few exceptions. Specifically, compared with the national respondents, Arizona respondents had a statistically higher proportion of female prescribers, NPs/PAs, family physicians, cardiologists and office-based group practitioners ($p \leq 0.001$). In addition, on average, national respondents were more experienced than Arizona respondents, with a mean difference of about 5 years in practice ($p < 0.001$).

Summary statistics of the respondents are presented in table I. Cases and controls constituted 49.6% and 50.4% of the respondents, respectively. Compared with the controls, cases were significantly more likely to be internal medicine ($p < 0.001$) or office-based group practitioners ($p = 0.02$) and were significantly more likely to provide care for patients outside their usual panel of patients ($p = 0.04$). In addition, on average, cases had 4.4 fewer years in practice ($p < 0.001$) and spent 2.3 more hours a week seeing patients ($p = 0.03$).

Table I. Respondents' self-reported demographic and practice characteristics (n = 950)

Characteristic	Category	n (%)[a]
Sex	Male	766 (80.6)
	Female	182 (19.2)
Profession	Physician	878 (92.4)
	Nurse practitioner	33 (3.5)
	Physician assistant	23 (2.4)
	Dentist	11 (1.2)
	Other	5 (0.5)
Specialty	General/family practice	312 (32.8)
	Internal medicine (other than cardiology)	295 (31.1)
	Psychiatry and neurology	72 (7.6)
	Cardiology	59 (6.2)
	Surgery	36 (3.8)
	Obstetrics and gynaecology	33 (3.5)
	Paediatrics	29 (3.1)
	Emergency medicine	27 (2.8)
	Others	82 (8.6)
National board certification	Yes	831 (87.5)
	No	116 (12.2)
Primary practice site	Office-based practice (solo)	329 (34.6)
	Office-based practice (group)	477 (50.2)
	Hospital-based clinic	57 (6.0)
	Hospital acute care	31 (3.3)
	Urgent care	15 (1.6)
	Other	36 (3.8)
When on-call, provide care for patients	Yes	556 (58.5)
outside usual panel of patients	No	255 (26.8)
	Not applicable	131 (13.8)
Practice in more than one location	Yes	260 (27.4)
	No	682 (71.8)
Most common method used for	Hand-written prescription order	788 (82.9)
prescribing medications	Telephone prescription order	44 (4.6)
	Electronic prescription order	114 (12.0)
Use of electronic medical records	Yes	199 (20.9)
at primary practice site	No	745 (78.4)
Other	Experience (in years) in prescribing medicines	23.9 ± 10.8[b]
	Patients seen per day	31.3 ± 30.1[b]
	Hours per week seeing patients	37.7 ± 15.7[b]

a Percentages may not total 100 because of rounding and missing data.

b Data are mean ± SD.

Prescribers' General Opinions about Drug-Drug Interactions (DDIs)

The majority of respondents reported that the risk for a drug interaction somewhat (36.0%) or very much (55.7%) affected their selection of drug products. Approximately three-quarters of the respondents (72.1%) indicated that they had seen a patient harmed by a DDI. Most of the respondents (80.6%) believed that interactions were more frequently caused by drugs that were prescribed by two different prescribers, rather than by the same prescriber.

Table II. Classification of responses to drug-drug interaction knowledge questions (in percentages)[a,b]

Drug pair[c]	Should not be used together (contraindicated)	May be used together but with monitoring	No interaction	Not sure
Warfarin and cimetidine	**18.2**	62.9	4.0	14.0
Sildenafil and bupropion	5.6	12.1	**50.0**	31.7
Methotrexate and cotrimoxazole (trimethoprim-sulfamethoxazole)	**24.1**	22.1	5.1	47.9
Ciclosporin and rifampicin	21.3	**19.2**	1.4	56.6
Warfarin and verapamil	4.6	36.6	**35.5**	22.0
Valaciclovir and simvastatin	6.4	15.3	**39.7**	35.9
Amoxicillin and paracetamol (acetaminophen) with codeine	0.6	4.2	**81.2**	12.7
Atenolol and ranitidine	1.3	12.3	**64.5**	19.8
Digoxin and clarithromycin	14.4	**49.5**	10.7	24.2
Glibenclamide (glyburide) and alendronate	1.8	8.4	**53.6**	34.1
Sildenafil and isosorbide mononitrate	**80.7**	2.5	0.7	15.4
Zolpidem and oxybutinin	6.2	20.7	**35.5**	36.6
Amantadine and ipratropium bromide	5.5	17.7	**25.4**	50.3
Alprazolam and itraconazole	**21.3**	22.3	18.6	36.9

a Percentages in bold type represent correct answers.

b Percentages may not total 100 because of rounding and missing data.

c Generic names were spelt according to US conventions and US brand names were included on the survey instrument.

Prescribers' Recognition of DDIs

The percentages of prescribers choosing each response category for the fourteen DDI knowledge test questions are presented in table II. Prescribers' correct classification of drug pairs ranged from 18.2% for warfarin and cimetidine (contraindicated drug combination) to 81.2% for paracetamol with codeine and amoxicillin (non-interaction). On average, prescribers correctly classified 42.7% ± 21.5 of the drug pairs. Among the four drugs pairs considered contraindicated in the knowledge test, three were classified correctly by less than one-quarter of respondents. With respect to the two interacting pairs that required monitoring, digoxin and clarithromycin was correctly classified by 49.5% of the respondents whereas ciclosporin and rifampicin was correctly identified by 19.2%. On average, there were 6.8% ± 6.8 false-negative errors (i.e. misclassifying an interacting pair as having no interaction) among the contraindicated or monitoring-required drug pairs; whereas false-positive errors (misclassifying a non-interacting pair as interacting) accounted for 19.9% ± 11.2 of the responses among the drug pairs without known interactions. The three interacting drug pairs that were considered serious by our clinical experts (ciclosporin and rifampicin, digoxin and clarithromycin, sildenafil and isosorbide mononitrate) were misclassified as having no interaction by 1.4%, 10.7% and 0.7% of the respondents, respectively. Depending upon the interaction, between 40.5% and 83.2% classified the interactions as either contraindicated or requiring monitoring. However, respondents answered 'not sure' for an average of 32.1% ± 21.7 of these drug pairs. Overall, the number of drug pairs correctly classified by prescribers ranged from zero to thirteen, with a mean of 6.0 ± 3.1. Cases and controls did not differ in the number of correctly classified drug pairs ($p = 0.13$). In addition, cases and controls were equally likely to answer the DDI of interest question (i.e. the specific DDI that paired cases and controls) correctly ($p = 0.85$).

A multiple regression analysis revealed that when using general/family practitioners as the refer-

Table III. Predictors of drug-drug interaction knowledge

Predictor variable	Unstandardized coefficients	Standardized coefficients	p-Value
Female	−0.33	−0.04	0.24
Prescription volume	<0.01	0.07	0.05
Patients seen per day	<0.01	<0.01	0.96
Hours per week seeing patients	<0.01	<0.01	0.95
Experience (in years) in prescribing medicines	−0.02	−0.06	0.07
Profession			
physician	Reference		
nurse practitioner	0.04	<0.01	0.94
others	0.40	0.02	0.44
Specialty			
general/family practice	Reference		
obstetrics and gynaecology	−2.20	−0.13	<0.001
internal medicine (other than cardiology)	−0.28	−0.04	0.23
cardiology	−1.93	−0.15	<0.001
surgery	−2.89	−0.18	<0.001
psychiatry and neurology	−3.49	−0.30	<0.001
paediatrics	−2.15	−0.12	<0.001
emergency medicine	−0.10	<0.01	0.89
others	−2.17	−0.20	<0.001
Primary practice site			
office-based practice (group)	Reference		
office-based practice (solo)	−0.12	−0.02	0.58
hospital-based clinic	0.57	0.04	0.17
hospital acute care	0.14	<0.01	0.82
others	0.49	0.04	0.27
'Case' status			
controls	Reference		
cases	0.11	0.02	0.59
Most common method used for prescribing medications			
hand-written prescription order	Reference		
electronic prescription order	0.38	0.04	0.27
telephone prescription order	−0.43	−0.03	0.34
Use of electronic medical records at primary practice site			
no	Reference		
yes	−0.42	−0.06	0.13
Degree to which the risk of a DDI affected drug selection			
a little or not at all	Reference		
somewhat	0.43	0.07	0.24
very much	0.83	0.14	0.02
Had seen a DDI cause harm			
no	Reference		
yes	0.34	0.05	0.12

ence group, significant predictors of a lower number of correctly classified drug pairs were being a specialist in psychiatry/neurology, 'other' specialty areas, surgery, cardiology, obstetrics/gynaecology, or paediatrics (in descending order of standardized regression coefficients [table III]). In addition, the

Table IV. Respondents' sources of drug-drug interaction information (n = 316)

Source	n (%)
Q: When you want to learn more about an interaction, what reference/person do you use?	
Package insert	45 (14.2)
Computerized alert system	26 (8.2)
Pharmacist	45 (14.2)
Printed materials	76 (24.1)
PDA	82 (25.9)
Internet	13 (4.1)
Other	29 (9.2)
Q: When one of your patients is about to be exposed to a potential drug interaction, who usually informs you that the interaction may be present?	
Pharmacist	216 (68.4)
Computerized alert system	34 (10.8)
PDA	50 (15.8)
Other	16 (5.1)

PDA = personal digital assistant.

prescribers who reported that their drug selection was affected by the risk of DDI 'very much' correctly classified more drug pairs than those who reported that they were affected by the risk 'a little' or 'not at all' (table III). Overall, 18.8% of the variance was explained by the model.

Prescribers' Source of DDI Information

Questions regarding prescribers' DDI information sources were included only in the Arizona sample and the long version of the national survey sample. Prescribers' responses to these questions are presented in table IV and table V. When the prescribers wanted to learn more about an interaction, 25.9% used PDAs and 24.1% used printed materials. The next most commonly used references were package inserts and pharmacists, each reported by 14.2% of the respondents.

According to 68.4% of the prescribers, when a patient was about to be exposed to a potential DDI, it was a pharmacist who usually informed them of the potential for interaction. The next most frequently reported DDI information source was PDAs (15.8% of the respondents), followed by computerized alert systems (10.8%) and 'other' sources (5.1%).

Table V presents prescribers' mean ratings on five statements about their usual sources of DDI information. Overall, 78.2% of the respondents reported that the DDI information from their usual source was often useful in future prescribing and 80.1% thought it sufficient to manage the interaction. About half (49.1%) of the respondents found that the information often changed their initial prescribing decisions and 49.3% of the respondents believed that the information was often relevant to patients. However, only 13.9% of the prescribers found the information received usually or always new to them. Chi-squared analyses results indicated that cases and controls did not differ in their use or ratings of DDI information sources (all $p > 0.17$).

Prescribers who used computerized DDI alerts as their usual source of DDI information consistently gave lower rating scores to the five statements on their views about the sources than those who used other sources. ANOVA results indicated a significant difference among the four source groups for two statements: whether the information was rele-

Table V. Respondents' views about their usual source of drug-drug interaction information (n = 316)

Question posed[a]	Mean ± SD	% Often[b]
How often does the drug interaction information change your initial prescribing decisions?	3.5 (0.8)	49.1
How often is the drug interaction information new to you?	3.0 (0.5)	13.9
How often is the drug interaction information relevant to the patient?	3.6 (0.9)	49.3
Is the drug interaction information sufficient for you to manage the interaction?	3.8 (0.6)	80.1
How often is the drug interaction information useful to you in future prescribing?	4.0 (0.8)	78.2

a Possible responses were: 1 = never, 2 = seldom, 3 = sometimes, 4 = usually, 5 = always.

b Includes those who responded usually and always.

vant to the patient and whether the information was useful in future prescribing. The Scheffe test indicated that DDI information provided by 'other' sources was more often useful to the prescriber in future prescribing than that provided by computerized DDI alerts ($p < 0.05$). DDI information provided by 'other' sources was more often relevant to the patient than that provided by pharmacists, DDI alerts, or PDAs ($p < 0.05$), although few prescribers who reported using 'other' sources for DDI information specified the source. There were no other significant differences between ratings of the sources.

Discussion

This study assessed the ability of a national sample of prescribers to recognize clinically significant drug combinations. On average, less than half of the drug pairs (42.7%) were correctly classified by respondents. Study results also indicated that most respondents used printed materials (24.1% of the respondents) or PDAs (25.9%) to learn more about DDIs, whereas prescribers reported they were usually informed about DDIs by the pharmacist. Prescribers generally considered their usual source of DDI information to be sufficient for them to manage the potential for interaction.

Although there is concern about discrepancies in the severity ratings and listing of DDIs in various compendia,[25-27] this study used six interactions that had been determined to be of clinical importance by an expert panel.[23] Based on the results of the respondents' answers to the drug pair list, it appears that many prescribers may not recognize all the potentially harmful DDIs and also may believe that interactions exist when none have been shown. Among four drug pairs that were considered contraindicated, only sildenafil and isosorbide mononitrate was correctly classified by the majority (80.7%) of respondents. Another contraindicated drug pair, alprazolam and itraconazole, was correctly identified infrequently (21.3%), which may explain the high prevalence of the co-prescription of the benzodiazepines alprazolam and triazolam with azole antifungal drugs.[28] Even if one argued that the drug combinations classified as 'contraindicated' could be used with close monitoring and considered prescribers choosing either 'contraindicated' or 'use with monitoring' to be correct, up to 47.9% of prescribers remained unsure if there was the potential for interaction.

Similar levels of knowledge of DDIs by prescribers was found in another study, although the drug pairs evaluated were not completely identical to this study.[17] Among the DDIs selected for the knowledge test, sildenafil and isosorbide nitrate was the most highly recognized interaction in both studies. Sildenafil could increase the hypotensive effects of nitrates and cause adverse effects such as acute myocardial infarction or even death.[28] Nonetheless, it is worrying that 15.4% (this study) to 28% (Glassman et al.[17]) of healthcare providers were unsure of this DDI. Clinicians who correctly classified sildenafil and isosorbide nitrate as contraindicated had increased to 82% in a follow-up study by Glassman et al.,[16] which is similar to the proportion reported in the present study. Consistent with their earlier findings,[17] on average <50% of the drug pairs were correctly classified in this study, which indicated prescribers' insufficient DDI knowledge even though some of the drug pairs selected involved commonly prescribed medications. The generally poorer recognition of interacting drug combinations found in the present study may have been a result of asking the respondents to restrict use of drug references when answering, whereas clinicians were allowed to consult reference materials in the previous study.[17]

With the advances in information technology, health practitioners can obtain information from electronic sources such as Micromedex®, the Internet and PDAs, which were not available decades ago. Compared with the findings of a recent survey

of VA prescribers by Ko et al.,[22] the present study found that a lower proportion of the prescribers consulted electronic references when they needed to learn more about DDIs (51% in Ko et al. vs 38% in the present study). In the VA prescriber study, pharmacists were equally as likely to be consulted by prescribers as electronic references (each reported by about half of the respondents), whereas a lower proportion of the prescribers in the present study (14.2%) reported consulting pharmacists for DDI information.[22] However, more than two-thirds of the respondents in this study reported that they were informed about their patients' potential exposure to DDIs by pharmacists. The findings confirm the important role pharmacists play in reducing the risks of DDIs.

This study found that prescribers' ratings of the usefulness of computerized DDI alerts were lower than those for other DDI information sources, although not all differences reached statistical significance. Other researchers have also raised concern about the relevance and specificity of DDI alerts.[17,29] About half of the VA clinicians surveyed in a previous study reported that too many non-relevant alerts limited utility of the alerts.[17] Similarly, a survey of general practitioners in the UK reported that although 90.4% of the respondents agreed that drug interaction alerts were a useful tool in prescribing, 73.5% agreed that the alerts were sometimes not applicable or relevant to the patient.[29] These findings demonstrate that there is still room for improvement to make DDI alerts a better aid in safe prescribing.

There are several limitations of the study. A primary limitation is the limited generalizability of the study results. Despite the efforts made in the development and distribution of the survey, the response rate achieved was low. As such, the study results may not be generalizable to all national or Arizona prescribers. Selection bias is another potential limitation of this study because it is possible that those who were more knowledgeable about DDIs or interested in DDI-related issues were more likely to return the questionnaire, and non-respondents may have had lower DDI knowledge scores than respondents. As a result of the limited information about non-respondents, it was difficult to assess how representative the respondents were. Nevertheless, with the data available it was found that the respondents and non-respondents did not differ in prescription volume or in the proportion of cases and controls. One limitation of using mail survey techniques is that it is impossible to know the conditions under which a respondent completed the questionnaire. Although it was clearly stated in the questionnaire that the prescriber should answer the DDI knowledge test items without the use of drug references, it is conceivable that respondents may have consulted an information source while answering these questions. As a result of the self-administration and self-report design of the survey, the accuracy of reported demographic and practice characteristics also cannot be assessed. Furthermore, because there is limited agreement on the listing and contraindication/monitoring classification of DDIs in the literature, the key to the DDI knowledge test used for the scoring in this study may not be agreed upon by all clinicians. Some DDIs classified as 'contraindicated' may be 'used under careful monitoring' if the patient has tolerated the DDI for a period of time with no adverse effect. That said, the test key was reviewed and approved by an expert group, so there was a clinical rationale for each DDI classification.

Conclusion

This study demonstrates the limited ability of prescribers to recognize the potential for clinically significant DDIs without the aid of reference materials, which indicates the necessity for and potential importance of prescribing support systems in reducing DDIs and drug-related morbidity and mortality. This study also improved the understanding of

where prescribers usually learn about DDIs involving their patients and the relative usefulness of various information sources.

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