Presenting Drug Drug Interaction Alerts to Clinicians According to Severity Level: Acceptance Rates in Ambulatory Practices Recommendations for Further Study

by

Marilyn D. Paterno, BS, BMus

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Has been approved

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Paul Gorman, MD

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ABSTRACT

Context. At Partners Health Care System, drug drug interaction (DDI) alerts are presented at three levels of severity to clinicians at the time of ordering medications. *Objective.* Describe the most frequent DDI alerts, and clinician acceptance rates according to severity level, drug pair, drug family, and patient demographics. *Design.* Descriptive, retrospective analysis of all DDI alerts during a one year period. *Setting.* Ambulatory clinics that use Partners' DDI checking services. *Participants.* All adult patient visits in which a DDI alert occurred were included. *Interventions.* A Level 1 DDI requires the clinician to remove one or both drugs from the patient's medication list. A level 2 alert allows the clinician to keep both, but requires the clinician to provide a reason. A Level 3 DDI is displayed as information only, requiring no action from the clinician. *Main Outcome Measures.* Number of alerts generated at each severity level; percentage of each by age, gender, and race; and acceptance rates for Level 2 interruptible alerts by individual drug pair and class. *Results.* Acceptance of recommendations occurs in just under half of all Level 2 DDI alert warnings. A review of literature supports, in general, the inclusion of the interventions we have in our knowledge base. In some instances the literature does not agree, which may provide clues to clinician non-acceptance of alerts. *Conclusion.* Presenting DDI alerts with varying options according to severity level reduces the number of interruptible alerts during the prescribing session, encouraging clinicians to make informed, clinically appropriate, decisions.

BACKGROUND

Partners Health Care System (Boston, MA) has had drug drug interaction (DDI) alerting in place in one or more of its ordering systems since 1996, when it was introduced into the Order Entry (OE) system in the inpatient setting at Brigham and Women's Hospital (BWH). The initial knowledge base of DDIs on which to alert included both information about the level of severity and a recommended action to be taken. Presentation of the alert at the time a drug is selected for ordering includes listing the interacting drugs, displaying a message describing the interaction, and providing a recommended action based on the severity level of the DDI. All alerts require action by the clinician, who must either accept or reject the recommendation. In order to reject the DDI warning, the clinician must type in the reason for overriding it. Any DDI warning may be overridden; none require the discontinuance of either drug. An important concern in informatics has been "alert fatigue," where too many alerts can result in clinicians overlooking even important ones [1].

In 2001, Partners deployed a new, enhanced version of DDI alerting, using the same knowledge base, but with changes in the manner of presentation and in the response required of clinician users. DDIs, and the expected responses, are now tiered according to the level of severity of the interaction. A very small number of DDIs are life-threatening situations in which the two drugs should never be given together and are assigned to Level 1. Clinicians are required to discontinue one of the drugs involved. Use of this type of "hard stop" constraint on clinicians can be controversial and is used sparingly and carefully. Figure 1 shows a Level 1 alert. The button labeled, "Continue New Order", is inactive until the single option, "Will D/C pre-existing drug" is selected.

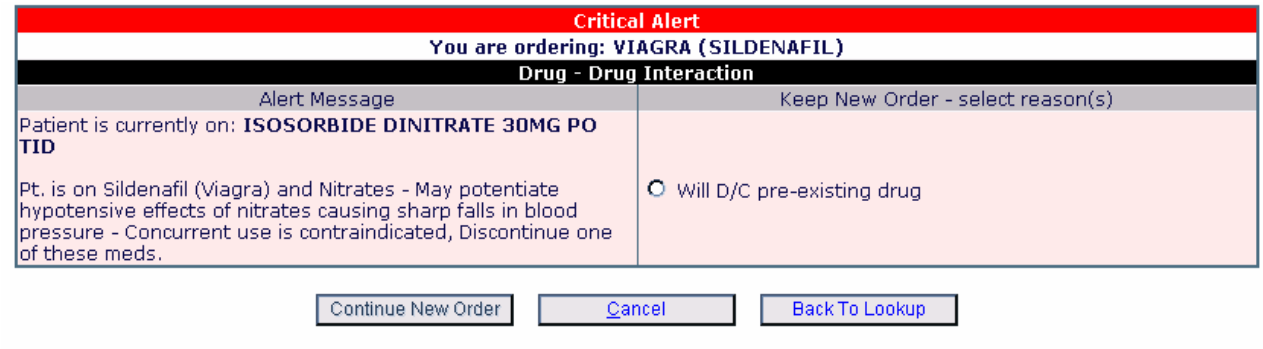

Figure 1. Level 1 Alert

Level 2 DDIs have a lower potential for harm. The clinician may override Level 2 alerts, but must specify the reason for the override, either from a pick list or using free text entry (Figure 2). For Level 1 and 2 alerts, the choice to discontinue (D/C) a pre-existing drug order must be verified electronically. On selection of this option, an order is created that the clinician must accept before proceeding (Figure 3).

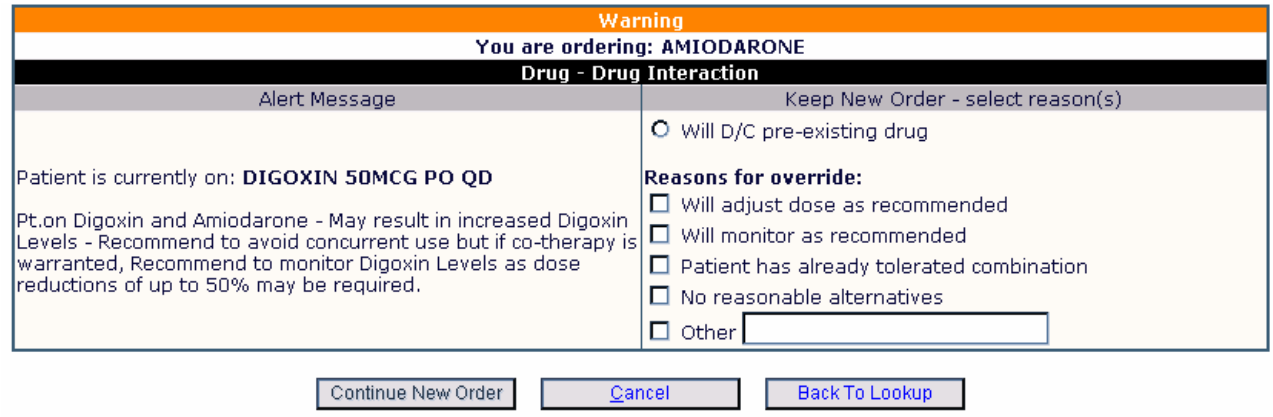

Figure 2. Level 2 Alert

Figure 3. Verification of D/C

By far the majority of DDIs in the knowledge base are assigned to Level 3, reflecting a lower degree of potential hazard. These are presented as information only on the prescribing screen. They are considered non-interruptive, whereas Levels 1 and 2 are interruptive, and require action by the clinician. The mandate for Level 3 alerts is that no keystrokes be required, which limits their presentation to available space on the screen (Figure 4).

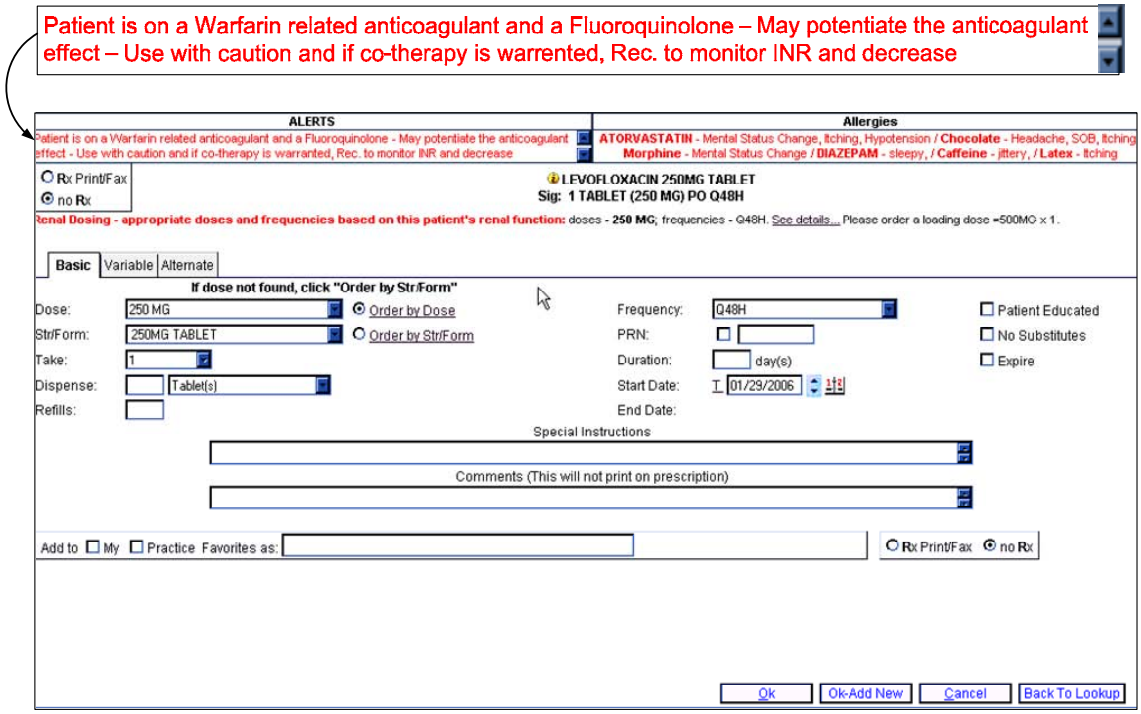

Figure 4. Level 3 alert, and as displayed on a Prescribing Screen

The DDI knowledge base was created for use at BWH. When DDI services were extended across the Partners enterprise, a new committee was formed to evaluate the knowledge base, assign severity levels to DDIs, and gain acceptance from clinical leadership at the various sites. The membership and process of this ongoing Medication Knowledge Committee (MKC), and the effect of tiered alerting on outpatient prescribing in general, was reported by Shah et al [2]. The present study arose in part from the conclusion of Shah et al. that there is a need for further research into the best balance of over- and under-alerting. They reviewed acceptance rates for several types of drug interactions, including drug-disease, drug-lab, drug-drug and drug pregnancy, of which only DDI alerts are implemented across the Partners enterprise. Focus on these interventions, therefore, provides the opportunity to study them in multiple settings. The detailed look that this study provides into DDI interventions and the knowledge base we have created is a next step toward creating the right alert balance.

A clinician is considered to accept a DDI alert if the action taken removes the potential for interaction, either by discontinuing the current order, or by selecting a reason that discontinues the other drug. We anticipate that tiering will reduce the potential for "alert fatigue" and thereby improve compliance for serious DDIs, thus reducing the number of preventable adverse drug events (ADEs). The ultimate goal is to optimize the DDI alert services and modify clinician behavior to improve medication safety for all our patients.

METHOD

All intervention alerts are logged at the time they are presented to clinicians. Data logged include the alert level, action taken by the user, patient identification, and context within the application. The stored data may be linked to the DDI

knowledge base, patient demographic database, and Longitudinal Medical Record (LMR) session to create a full picture of the event. Using these links, we created a data set of all DDI alerts generated from February 1, 2004 through February 1, 2005, including patient age, gender, race, the medication being ordered, the interacting drug already on the profile, the DDI severity level, the user's action and reason, and a timestamp. The study included data from 31 adult primary care practices affiliated with a Partners hospital. The study was approved by the Institutional Review Board of Partners HealthCare System.

At Partners Health Care, drugs may be grouped into tables that are known locally as "drug families." Although a family frequently represents a drug class, this is not required, and a table may include drugs from multiple classes, depending on clinical use. Drug family tables are created manually and maintained both by hand and by automated update, linking ingredients from our medication dictionary to data supplied by First Data Bank©. When a new drug is added to our dictionary, it is linked to the ingredient table in this database, and automatically added to all family tables that include that ingredient. There were 476 drug entries from our dictionary that appeared in DDI alerts during the study period. We reviewed the families to which these drugs belonged and assigned those without families to an appropriate group wherever possible, resulting in 120 family group tables in the study data.

The data was gathered from the Caché production system (Intersystems Corp., Boston, MA) into a Microsoft Access 2003 database. Grouping into drug families was accomplished using Caché 5.0.8 and Microsoft Excel 2003 prior to import into Access, and subsequent queries were exported to Excel to calculate descriptive statistics.

RESULTS

During the study period, 16,603 DDI alert warnings were presented to 1510 clinician users on 10,424 patients. Of these, 73 (0.4%) were Level 1, 3770 (22.7%) were Level 2, and the remaining 12,760 (76.9%) were Level 3. Two-thirds (67.1%) of the Level 1 alerts were accounted for by 5 drug pairs, each of which occurred more than four times. The fifteen most frequent Level 2 pairs each occurred over fifty times; they accounted for about half (50.1%) of all Level 2 alerts. Among level 3 alerts, twenty-five drug pairs occurred over one hundred times each, again accounting for about half (50.3%) of the total. Table 1 shows the most frequently occurring drug pairs at each level, including number of occurrences and percent of the total for each DDI pair.

Table 1. Most Frequent Drug Pairs

	Total	*(%)*	*Drug Pair*
Level 1	14	(28.6)	sirolimus & voriconazole
	11	(22.4)	isosorbide dinitrate & sildenafil
	10	(20.4)	methylphenidate hcl & linezolid
	9	(18.4)	isosorbide mononitrate sustained release & sildenafil
	5	(10.2)	spironolactone & eplerenone
Total 1	*49*		
Level 2	339	(18.0)	gemfibrozil & atorvastatin
	289	(15.3)	cyclobenzaprine hcl & tramadol
	208	(11.0)	warfarin sodium & trimethoprim/sulfamethoxazole double strength
	166	(8.8)	dexamethasone & aprepitant
	146	(7.7)	atorvastatin & nicotinic acid sustained release
	120	(6.4)	fluconazole & warfarin sodium
	106	(5.6)	tamsulosin & sildenafil
	97	(5.1)	digoxin & azithromycin
	76	(4.0)	amiodarone & digoxin
	65	(3.4)	sumatriptan & zolmitriptan
	64	(3.4)	tacrolimus & voriconazole
	55	(2.9)	doxazosin & sildenafil
	53	(2.8)	nicotinic acid & atorvastatin
	52	(2.8)	warfarin sodium & trimethoprim /sulfamethoxazole single strength
	52	(2.8)	gemfibrozil & simvastatin
Total 2	*1888*		
Level 3	619	(9.7)	warfarin sodium & levofloxacin
	583	(9.1)	omeprazole & ranitidine hcl
	559	(8.7)	acetylsalicylic acid & warfarin sodium
	458	(7.1)	levothyroxine sodium & warfarin sodium
	429	(6.7)	fluconazole & lorazepam
	401	(6.3)	lisinopril & triamterene 37.5 mg/hydrochlorothiazide 25 mg caps
	326	(5.1)	albuterol inhaler & amitriptyline hcl
	314	(4.9)	aspirin enteric coated & warfarin sodium
	275	(4.3)	warfarin sodium & azithromycin
	232	(3.6)	amiodarone & warfarin sodium
	230	(3.6)	lisinopril & spironolactone
	214	(3.3)	clonazepam & fluconazole
	183	(2.9)	ciprofloxacin & warfarin sodium
	178	(2.8)	allopurinol & warfarin sodium
	162	(2.5)	ketoconazole & atorvastatin
	142	(2.2)	kcl slow release & triamterene 37.5 mg/hydrochlorothiazide 25 mg caps
	141	(2.2)	acetylsalicylic acid (children's) & warfarin sodium
	137	(2.1)	albuterol inhaler & nortriptyline hcl
	131	(2.0)	spironolactone & kcl slow release
	128	(2.0)	tacrolimus & valganciclovir
	123	(1.9)	atorvastatin & ketoconazole 2% shampoo
	117	(1.8)	metronidazole & warfarin sodium
	116	(1.8)	atenolol & diltiazem extended release
	111	(1.7)	tramadol & citalopram
	104	(1.6)	atenolol & diltiazem cd
Total 3	*6413*		

The complete list of Level 1 DDI pairs that generated alerts during the study period is displayed in Table 2.

Table 2. Level 1 DDI Pairs

Level 1 Drug Pair	*Total Alerts*
sirolimus & voriconazole	14
isosorbide dinitrate & sildenafil	11
methylphenidate hcl & linezolid	10
isosorbide mononitrate (sr) & sildenafil	9
spironolactone & eplerenone	5
levofloxacin & gatifloxacin	4
methylphenidate hcl & phenelzine	2
methylphenidate hcl & selegiline hcl	2
sirolimus (onc) & voriconazole	2
sotalol & dofetilide	2
meperidine hcl & phenelzine	2
nortriptyline hcl & selegiline hcl	1
sumatriptan & linezolid	1
selegiline hcl & sumatriptan	1
aldactazide 25/25 & eplerenone	1
sinemet 25/100 & linezolid	1
isosorbide mononitrate (sr) & tadalafil	1
isosorbide mononitrate & vardenafil	1
isocarboxazid & amphetamine/dextroamphetamine	1
fluoxetine hcl & selegiline hcl	1
flecainide & dofetilide	1

The most frequent drug families were defined as those families having more than four alert instances for Level 1, more than one hundred instances for Level 2, and more than five hundred instances for Level 3. These represent 69.9% of all Level 1, 61.8% of Level 2, and 66.2% of Level 3 alerts. The most frequently occurring family pairs at each level, including number of occurrences and percent of the total for each family pair, are shown in Table 3.

Table 3. Most Frequent Drug Families

	Total	*(%)*	*Family Pair*
Level 1	20	(39.2)	nitrate analogues & sildenafil derivatives
	16	(31.4)	azole antifungals & immunosuppressant
	10	(19.6)	linezolid & methylphenidate
	5	(9.8)	eplerenone & k-sparing diuretic
Total 1	*51*		
Level 2	458	(19.7)	fibrate anti-lipidemics & hmg-coa reductase inhibitor
	410	(17.6)	antibiotics & anticoagulants
	289	(12.4)	cyclobenzaprine & narcotics
	277	(11.9)	hmg-coa reductase inhibitor & niacin preparations
	214	(9.2)	alpha antagonists & sildenafil derivatives
	167	(7.2)	antibiotics & digitalis glycosides
	166	(7.1)	aprepitant & corticosteroid
	120	(5.2)	anti-migraine agents & anti-migraine agents
	120	(5.2)	antibiotics & xanthines
	108	(4.6)	ssri's & sympathomimetic agents
Total 2	*2329*		
Level 3	1360	(16.1)	antibiotics & anticoagulants
	1300	(15.4)	antibiotics & estrogen
	1041	(12.3)	acetylated salicylate & anticoagulants
	1002	(11.9)	b-blocker & calcium channel blocker
	927	(11.0)	antibiotics & benzodiazepines
	782	(9.3)	methotrexate & nsaid
	703	(8.3)	h2 blocker & proton pump inhibitor (ppi)
	674	(8.0)	ace inhibitors & k-sparing diuretic
	658	(7.8)	beta-adrenergic agents & tricyclic antidepressant
Total 3	*8447*		

The clinics studied provide adult primary care, and about a third of the patients were under 50, a third were 50 - 65, and a third over 65. Alerts were evenly distributed by age, with one exception: patients over 65 accounted for half the Level 1 alerts (Table 4). The distribution of alerts across age groups does not consider alerts as a percentage of prescriptions written per patient. Where there are more prescriptions written, the rate of alerts per patient decreases. It is reasonable to anticipate that the number of prescriptions per patient might rise as age increases, with a proportionate reduction in rate of DDI alerts per patient in older patients. We did not capture data on all of the study patients' prescriptions as part

of this study, however, and therefore are unable to assess the rate of alerts per patient.

There are more DDI alerts for Levels 1 and 3 for males than for females. This appears to be due to interactions with gender-specific drugs such as sildenafil. There were no significant differences by race. Gender and race data appear in Tables 5 and 6, respectively.

Table 4. Total Alerts by Age

Age	*Total*	*(%)*	*Level 1*	*(%)*	*Level 2*	*(%)*	*Level 3*	*(%)*
< 50	5750	(34.6)	14	(19.1)	1281	(33.9)	4455	(34.9)
50-65	5243	(31.6)	22	(30.1)	1378	(36.6)	3843	(30.1)
> 65	5568	(33.5)	37	(50.7)	1104	(29.3)	4427	(34.7)
Unknown	42	(0.3)	0		7	(0.2)	35	(0.3)
TOTALS	16603		73		3770		12760	

Table 5. Total Alerts by Gender

Gender	*Total*	*(%)*	*Level 1*	*(%)*	*Level 2*	*(%)*	*Level 3*	*(%)*
Female	10266	(61.8)	26	(35.6)	1781	(47.2)	8459	(66.3)
Male	6295	(37.9)	47	(64.4)	1982	(52.6)	4266	(33.4)
Unknown	42	(0.3)			7	(0.2)	35	(0.3)
TOTALS	16603		73		3770		12760	

Table 6. Total Alerts by Race

Race	*Total*	*(%)*	*Level 1*	*(%)*	*Level 2*	*(%)*	*Level 3*	*(%)*
White	11972	(72.1)	67	(91.8)	2760	(73.2)	9145	(71.7)
Black	1367	(8.2)	2	(2.7)	296	(7.9)	1069	(8.4)
Asian	275	(1.7)			66	(1.8)	209	(1.6)
Hispanic	1357	(8.2)			295	(7.8)	1062	(8.3)
Other	1632	(9.8)	4	(5.5)	353	(9.4)	1275	(10.0)
TOTALS	16603		73		3770		12760	

Compliance with Interruptible Alerts

Acceptance of Level 1 alerts is 100%, as the system requires the discontinuance of one of the drug orders. For these alerts, we are able to identify

which drug was discontinued. Of the five most frequently-occurring drug pairs, two pairs involve sildenafil, which was discontinued more frequently than the other drug. In both instances, the second drug was a nitrate. This interaction has been observed and reported on in several studies, and in various countries [3,4,5], and is clearly contraindicated.

The overall acceptance rate for Level 2 DDIs was 46%, which dropped to just under 45% for the most frequent drug pairs and families. Acceptance was calculated from the responses made by the clinicians to the interruption. While they must respond, if they wish to override the alert, they must also provide a reason for doing so. These reasons are captured and stored in the alert log. Where the reason, "will D/C pre-existing drug" was selected, the clinician was presented with the screen to take the action immediately, and these alerts are included in those considered to have been accepted. Rates by drug pair and family are shown in Tables 7 and 8.

Table 7. Acceptance Rates for Top Drug Pairs

Drug Pair	*Total Alerts*	*Accept*	*(%)*	*Override*	*(%)*
gemfibrozil & atorvastatin	339	128	(37.8)	211	(62.2)
cyclobenzaprine hcl & tramadol	289	181	(62.6)	108	(37.4)
warfarin sodium & trimethoprim/sulfamethoxazole double strength	208	93	(44.7)	115	(55.3)
dexamethasone & aprepitant	166	47	(28.3)	119	(71.7)
atorvastatin & nicotinic acid sustained release	146	57	(39.0)	89	(61.0)
fluconazole & warfarin sodium	120	49	(40.8)	71	(59.2)
tamsulosin & sildenafil	106	46	(43.4)	60	(56.6)
digoxin & azithromycin	97	51	(52.6)	46	(47.4)
amiodarone & digoxin	76	36	(47.4)	40	(52.6)
sumatriptan & zolmitriptan	65	59	(90.8)	6	(9.2)
tacrolimus & voriconazole	64	18	(28.1)	46	(71.9)
doxazosin & sildenafil	55	22	(40.0)	33	(60.0)
nicotinic acid & atorvastatin	53	20	(37.7)	33	(62.3)
warfarin sodium & trimethoprim /sulfamethoxazole single strength	52	17	(32.7)	35	(67.3)
gemfibrozil & simvastatin	52	24	(46.2)	28	(53.8)
TOTALS	1888	848	(44.9)	1040	(55.1)

Table 8. Acceptance Rates for Top Family Pairs

Family Pair	*Total Alerts*	*Accept*	*(%)*	*Override*	*(%)*
fibrate anti-lipidemics & hmg-coa reductase inhibitor	458	179	(39.1)	279	(60.9)
antibiotics & anticoagulants	410	172	(42.0)	238	(58.0)
cyclobenzaprine & narcotics	289	181	(62.6)	108	(37.4)
hmg-coa reductase inhibitor & niacin preparations	277	108	(39.0)	169	(61.0)
alpha antagonists & sildenafil derivatives	214	86	(40.2)	128	(59.8)
antibiotics & digitalis glycosides	167	84	(50.0)	84	(50.0)
aprepitant & corticosteroid	166	47	(28.3)	119	(71.7)
anti-migraine agents & anti-migraine agents	120	57	(47.5)	63	(52.5)
antibiotics & xanthines	120	100	(83.3)	20	(16.7)
ssri's & sympathomimetic agents	108	28	(25.9)	80	(74.1)
TOTALS	2330	1042	(44.7)	1288	(55.3)

Users had the option to select multiple reasons for override: when “other” was selected, a text box was presented and the user was required to type in a reason. The most frequently selected reason (Table 9) for overriding an alert was “Will monitor as recommended.” Some of the DDIs in which the selected reason for override included, “No reasonable alternatives” included Warfarin & Bactrim, Gemfibrozil & statins, and Amiodarone & Digoxin. These are all instances in which the combination can be used judiciously, though it is not possible to determine from these data alone exactly why this selection was deemed appropriate by the clinician writing the orders.

Table 9. Reasons for Overriding Alerts

Reason	*Total*
Will monitor as recommended	520
Will D/C pre-existing drug	254
Will adjust dose as recommended	228
Patient has already tolerated combination	214
Other	93
No reasonable alternatives	33

Acceptance rates for Level 3 alerts were not calculated for this study.

LITERATURE REVIEW

A literature review checked the most frequent interactions using two interactive web programs, provided by *The Medical Letter* [6] and *Micromedex* [7]. In general they were in agreement with the importance of the DDIs that we are presenting. References to published papers were provided as available, but in several instances the only reference made was to the manufacturer's package insert. Some interactions, such as Fluconazole and Warfarin, had many references available, and the information supplied by the two sources was consistent. One drug interaction instance that is a Level 2 warning in our knowledge base appears to be more closely related to a duplication warning. The information provided for these, Sumatriptan and Zolmitriptan, is that there is an additive effect when a patient takes both drugs, which are classified as "Triptans" by *The Medical Letter*. The programs provided by *The Medical Letter* and *Micromedex* organize their information differently, making it hard to determine with any precision how closely Partners' MKC agreed with them. In one instance, that of Cyclobenzaprine and Tramadol, the MKC has taken a position consistent with one but not the other, in setting the severity at Level 2. *The Medical Letter* found no interaction, but *Micromedex* suggested caution due to the possibility of seizure, and rated the severity as "Major". Other than this example, the DDIs that occurred most frequently seem to be rated at about the same severity by these organizations as by our MKC.

Despite the limitations of our family tables, it is useful to look at DDIs in aggregated groups of drugs with similar properties. It was clear that the tools used to search for drug interactions also made use of a classification system, as the literature provided several examples such as the one cited previously [6], where the

warnings and references were identical, and referred to the drugs by a classification name instead of or in addition to the name of the individual drug. Though it is assumed that this classification is done on the basis of the same or similar-acting ingredients, neither of the two sites identified the source of its classification scheme. In some instances, they did not identify the specific drug by name, but returned only the interaction data for the group to which the drug belongs.

A case study by Stein and Read [8] of a patient with Parkinson's disease led to a closer investigation of the actions taken on the interaction of tramadol and cyclobenzaprine. The case discussed was presented to illustrate the difficulties of treating complex conditions. The elderly patient's disease was complicated by severe depression, and in the course of treatment, she was given tramadol, which was deliberately augmented with cyclobenzaprine in order to help her sleep. No side effects from the tramadol were noted. The interactions report from *The Medical Letter* [6] for this drug pair reports, "No interactions found." By contrast, *Micromedex* [7] reports, "Seizures have been reported in patients using tramadol. Some medications, including cyclobenzaprine, are known to reduce the seizure threshold. The risk of seizures may be enhanced when cyclobenzaprine and tramadol therapy are combined (Prod Info Ultram®, 1998)." Given that these three information sources present differing viewpoints, it was reasonable to look more closely at the study results. This was the second most frequent Level 2 drug pair occurring during the study period. The acceptance rate is nearly 63%. In descending order of frequency, the reasons for overriding included, "Will monitor as recommended" (43), "Will adjust dose as recommended" (27), "Patient has tolerated combination" (19), "Other" (16), and "No reasonable alternative" (5). Reproducing the interaction using a simulated patient, to see what the message displayed, revealed no suggested dose change provided with this alert (Figure 5). We would

like to conclude that a clinician who selected the option, “Will adjust dose as recommended” was indicating an intention to adjust the dose, despite the fact that there was no “as recommended” dose provided on the screen. In the absence of a documented reason why he or she selected the option, however, we can only report the selection, and make no inference as to motivation.

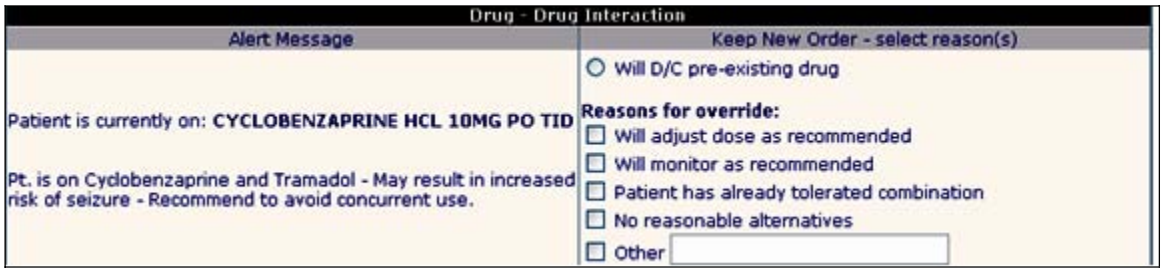

Figure 5. Tramadol & Cyclobenzaprine

Not all drug or family pairs had ambiguities show up in the literature. The existence and severity of the interaction between sildenafil and nitrates [3-7] is consistent across all the sources reviewed, and this consensus is reflected in the assignment of it to Level 1 in Partners’ DDI knowledge base. A theme that did surface in the various studies and articles about particular drugs or drug classes is that there is a need to consider possible interactions in complicated instances, and especially when a patient is taking one of the drugs in the pair over an extended period of time, such as for a chronic illness [8-11].

DISCUSSION

The primary purpose for studying the results of DDI alerting is to ascertain what works and capitalize on it, and isolate what does not work and to improve on that. Questions that may be asked are, “Do clinicians accept the alert warnings?”,

“Are the DDIs identified at the right severity level?”, “Does an alert that displays information without requiring even an acknowledgement that it has been read make any difference in clinician behavior?”, “Are the reasons given for overriding the warnings adequate? Should we downgrade some Level 2 DDIs, or upgrade some Level 3’s, based on those reasons?” Taken together, they ask, “Are we making a difference – are we doing any good?” To answer these questions, we need to see just what we have done, understand what the information can tell us, and identify what additional knowledge will help us begin to answer these questions.

DDI Knowledge Base & Drug Families

In evaluating the DDIs that came up most frequently, one issue that was immediately obvious was that several of them represented the same pair of ingredients interacting, but because our medication ordering dictionary does not identify relationships among drugs containing the same active ingredients, they appear as independent entries and show up in the DDI alert log as distinct interactive drug pairs. For example, “isosorbide dinitrate & sildenafil” and “isosorbide mononitrate sustained release & sildenafil” both appear in the list of most frequently appearing Level 1 alerts, with 11 and 9 instances respectively. These represent essentially the same interaction. The family table “sildenafil derivatives” includes both these drugs, and the interaction between it an “nitrate analgues” is the most frequently-occurring family pair in Level 1. Two other Level 1 DDIs that showed up, though not often enough to make it into the most frequent category, are “nitrate analogues & tadalafil” and “nitrate analogues & verdanafil”. The two drugs tadalafil and verdanafil should probably be included in the same family as sildenafil derivatives. This would provide a more complete and accurate picture of the number of intervention alerts presented for this family pair.

The fact that, in the above example, the drug pairs are stored in separate DDI rows in the knowledge base did not affect their being caught and alerted on in the ordering session. The knowledge base contains a mixture of individual drug pairs and drug families, reflecting decisions made by the MKC that considers potential interactions at both levels. Care is taken to include all appropriate data in each interaction record; for example, new drugs that belong to the same drug class are included in a family based on that class. Some family definitions may include only a subset of a given class, and automated updating needs to take this into consideration. It is for this reason, and to ensure that interactions defined as occurring between individual drug pairs include all instances of the drug in the ordering dictionary, that automated updating is done at the ingredient level for both drug family and DDI knowledge base tables.

The process of keeping the DDI knowledge base accurate and up to date requires, in addition to the work of the MKC as described by Shah et al., periodic evaluation of how the knowledge base and family tables are designed and implemented. Where it is possible to use standard vocabularies and classifications, this is to be preferred, and will facilitate the extension of DDI alerting out to other institutions in the Partners enterprise. There is not a standard drug vocabulary at this time that is universally accepted. Until one is adopted nationally, our standard is that provided by First Data Bank's National Drug Data File Plus™ (NDDF). This database also provides therapeutic classification modules that will be used to enhance and improve our current drug family tables, correcting issues such as the sildenafil/tadalafil/verdanafil example described above, where current processes do not capture all instances of drug classifications.

Patient Demographics

Instances and acceptance of alerts fell into patient age, gender, and race groups that matched that of the population, with two exceptions. First, there were more instances of men having Level 1 DDIs than women, despite the fact that there were more women than men in the study population. Second, there were more Level 1 alerts in the over 65 population than in the others. These both seem to be explained by the frequent incidence of sildenafil being ordered in the presence of nitrates. Since sildenafil is prescribed for the gender-specific condition of erectile dysfunction, which tends to occur more frequently in older persons, and is contraindicated with the use of nitrates, this explains the difference.

Tables 10, 11, and 12 summarize the rates by patient age, gender, and race for the most frequent DDI drug pairs. The rates by gender and age are of the same proportion as the total. Acceptance rate breakdown by race of patient varies somewhat, but there is insufficient information by which to make a judgment as to the importance of the differences and whether the data are statistically significant.

Table 10. Acceptance Rates of Top Drug Pairs by Age

Age	*Total*	*Accept*	*(%)*	*Override*	*(%)*
< 50	591	283	(48)	308	(52)
50 - 64	670	298	(44)	372	(56)
> 64	624	266	(43)	358	(57)
Unknown	3	1	(0)	2	(0)
All	1888	848	(45)	1040	(55)

Table 11. Acceptance Rates of Top Drug Pairs by Gender

Gender	*Total*	*Accept*	*(%)*	*Override*	*(%)*
Female	879	427	(49)	452	(51)
Male	1006	420	(42)	586	(58)
Unknown	3	1	(0)	2	(0)
All	1888	848	(45)	1040	(55)

Table 12. Acceptance Rates of Top Drug Pairs by Race

Race	*Total*	*Accept*	*(%)*	*Override*	*(%)*
Asian	35	15	(43)	20	(57)
Black	116	59	(51)	57	(49)
Hispanic	155	80	(52)	75	(48)
White	1372	612	(45)	760	(55)
Other	210	82	(39)	128	(61)
All	1888	848	(45)	1040	(55)

Study Limitations

In this study, we did not assess Level 3 alerts. The DDI alert log includes only those responses that are made by the user when he or she is interrupted. It does track references to the session or visit when an alert of any level occurred, and this link can be used to search the medication profile of the patient at the time the session or visit ended. Such a search was outside the scope of this study. Due to time constraints, evaluating the free text reasons for overriding alerts was also beyond the scope of this study.

A limitation that makes drawing valid conclusions difficult is the lack of a control group. These alerts were presented to all clinicians on all patients in the ambulatory setting. An important question that we seek to understand is the impact that tiering the alert presentations according to severity level has on clinician behavior. This requires a control group against which to compare results. Anecdotal evidence suggests that tiering reduces the number of alerts a busy clinician must respond to, but this should be tested formally.

Data for this study are drawn entirely from the electronic record. Clinician views were not sampled, and therefore we are unable to make conclusions about whether they find the tiered presentation of DDI alerts more productive.

CONCLUSION

To maintain the right balance of alerting, we must ensure that alerts are presented appropriately. In instances where the literature is inconsistent in its ranking of the interaction, frequent overrides are not surprising; however, the responses to the alerts should be evaluated to determine whether the assigned levels are appropriate. Information that is not part of this data set may be useful in determining whether the decision to override an alert was the best one. For example, one reason that there may not have been a reasonable alternative for the clinician may be due to other items on the patient's problem list, allergies recorded, or lab results for the patient.

Adverse drug events contribute to emergency room visits and hospital admissions, and may be an increasing problem in elderly patients, due to the frequently large number of drugs that are prescribed for them [12-14]. There is general agreement [15] that alerting on drug interactions at the point of ordering or prescribing is a good thing, in both hospital and ambulatory settings. The focus now shifts to alerting on the right instances, under circumstances that will provide the best outcomes, and taking into account all available evidence. [1,16-21] A drug interaction by itself tells the clinician only some facts about the ingredients and their chemical reactions to each other. It does not indicate whether his or her patient will be adversely affected, or whether that effect is worse than the alternative of not giving one of the drugs. To that end, we need to institute further studies that will provide us with such information. This paper concludes with some recommendations for such studies.

RECOMMENDATIONS FOR FUTURE STUDY

The data and results described by this study about what drug interactions occur most frequently, and to whom, needs to be supplemented by other information about both the patients and the clinicians in order to propose optimal changes in the DDI alert process. This section proposes studies that may result in increased effectiveness of and improved acceptance rates for DDI alerts.

The following paragraph is from a request to the Institutional Review Board (IRB) at Partners to use medical record data from our electronic systems to study DDI interventions and acceptance rates, with an emphasis on the efficacy of tiered alerting. The IRB has approved this request, and work will begin shortly to design one or more studies.

"The premise of tiered alerts is that it reduces excess alerting and interruptions, and therefore improves acceptance by clinicians for the more severe interactions. To test this hypothesis, this study will compare results from untiered alerts at BWH with results from tiered alerts at MGH. The goals of the study are, first, to publish our findings in an appropriate journal so that other institutions may learn from our experience. The second goal is to make recommendations regarding the implementation of tiered alerts at BWH, and if possible, changes in process or knowledge in those already running at MGH."

Questions that may be considered include these:

1. Does presenting alerts in a tiered fashion improve acceptance by clinicians?
2. Do Level 3 alerts have any effect on clinician behavior?
3. Can we define an algorithm that will recognize instances where the override reason given represents acceptance of the alert?

4. What additional information should be considered when determining whether to alert on a potential DDI interaction?

5. Should the severity level of any DDI interactions in our knowledge base be changed?

6. Is there a significant difference in DDI alert acceptance rates between the inpatient and outpatient setting?

7. Are there any trends in acceptance according to specialty or educational level of clinicians responding?

Tiered and Non-Tiered Alert Acceptance Rates.

1. *Improved Acceptance Rates.* One proposed study would look at acceptance rates for DDI alerts in Partners' two academic medical centers, BWH and MGH. Both hospitals use the same drug dictionary as does the LMR to order or prescribe, and all use the same DDI knowledge base. As noted at the beginning of this paper, BWH has not adopted tiering the presentation of alerts. Given this, we would be able to define two study populations that may be matched as closely as possible, and have alert acceptance data that will allow us to compare rates with tiered and non-tiered displays. The two populations would include only adult patients, as BWH does not have a pediatrics department. The data would be gathered for a single time period. The primary goal would be to determine if tiered alerting reduces the "noise" sufficiently to determine if there is any difference in acceptance of Level 2 alerts between the two institutions.

Since alerts at BWH can be separated into the same three levels for study, and comparisons made against similar results at MGH, other results may also be studied. For example, Level 1 alerts that are overridden may provide insights into whether any should be downgraded to Level 2.

2. *Level 3 Effect on Clinician Behavior.* In order to determine whether a Level 3 alert may have had an effect on drug orders at MGH, we need to include order session data in the data set. The alert logs include links to this information, which is available from the Computerized Provider Order Entry (CPOE) database. We would collect the medication profile for the patient at the end of the order session in which the alert was displayed. This medication list will also indicate if an alert that was overridden was later reconsidered, and may be of assistance in reducing duplication. For example, an alert that is accepted could be overridden during the same session and the second drug ordered. These data may be compared with the acceptance rates for comparable Level 3 alerts at BWH.

Alert Acceptance and Intervention Algorithm

3. *Improve the Alert Acceptance Algorithm.* At this time, only removing one of the drugs represents acceptance of a DDI alert. In some circumstances, the alert may actually be accepted, i.e., the potential interaction removed, by other actions. Among these may be adjusting the dose or performing a lab test. Examination of order session data will indicate whether the dose was actually adjusted or not, and relevant lab orders and results may indicate whether the alert can be considered to have been accepted. The definition of which DDI alerts are candidates for a broader definition of "acceptance" would be a desired outcome of this study.

4. *Identify Additional Information needed.* Patient allergies and problems affect the decisions of what drugs to order. A review of these data in instances where DDIs have been overridden may provide insights that result in a refinement of the intervention algorithm. If a drug being ordered contains the potential for interaction with another drug on the patient's medication profile, review of lab results, problems, or allergies might result in the alert being voided, or conversely, in its being upgraded, for example from Level 3 to Level 2.

Other changes in the alerting algorithm may result from a study of the reasons provided for overriding alerts. Text that is typed in when "Other" is selected is captured in the alert log, and may be collated and reviewed. A review of these results may suggest changes in the pick list of reasons provided.

5. *Identify changes to the DDI Knowledge Base.* The results of the above studies may be used to evaluate the appropriateness of the severity classification of the alerts. This may be accomplished as a goal of the study, or as a separate evaluation following from one or more other studies.

Inpatient – Outpatient Alert Results and Demographics

6. *Inpatient-Outpatient Comparison.* The DDI knowledge base is the same regardless of whether the setting is in the hospital or an ambulatory practice. It is possible that some DDIs are more suited for alerting at their current levels in one setting versus the other. A patient who is hospitalized is more easily monitored for an adverse event than is one who comes to an outpatient clinic. A study that examines what DDIs occur in each setting, and compares their acceptance rates may provide recommendations for changes to the presentation of alerts according to venue.

7. *Evaluation of clinician demographics.* Clinicians responding to alerts in the inpatient setting are generally residents and interns. By contrast, in ambulatory settings they may be physicians who have completed residency, physician assistants, or nurse practitioners. Reviewing alert results by clinician demographics may indicate areas where additional education is indicated. Cross-matching results by clinician specialty and patient demographics may provide additional insight into where changes in the process are appropriate.

Other Work

There are a variety of further studies of DDI alerting that can be used to improve our knowledge base, process, and acceptance rates. Not all of those suggested here may be included under the current IRB-approved proposal; the design of some may require a new proposal. In addition, the value of each should be carefully considered prior to initiating the effort it will require, and caution is recommended against starting too many studies. The investigators' focus needs to be on studies that will improve patient outcomes to the greatest degree.

The new IRB-approved proposal has generated strong interest among physician researchers, hospitalists and pharmacists. Several have recommended other participants, and others have asked to be included. Given this interest, it seems that an unanticipated outcome of the proposal is increased interest in and opportunity to do studies of this sort by several persons who heretofore have not participated in them. Another positive outcome is the inclusion of persons across the enterprise who have been working on similar studies in isolation. Joining together and pooling knowledge, interest, and expertise can only enhance the result. The challenge of the study will be to make the best judgments based on what we learn, that will improve the care of patients, especially in the area of medication safety.

SUMMARY

Presenting DDI alerts according to severity level can significantly reduce the number of interruptions to which clinicians must respond during a medication ordering session. Having fewer instances where they must make a decision regarding the current order can encourage them to take time to review the information provided and make a more clinically appropriate decision.

There are two keys to the success of this process. First is regular attention to the DDI knowledge base, both to keep it up to date with changes in drugs and drug classifications, and to take advantage of new evidence with regard to drug interactions as it becomes available. Second, it is important to recognize that there is more to DDI interactions than the ingredients themselves. Consideration of other data about a patient's condition contributes to better knowledge of when "acceptance" means discontinuing one of the drugs, when more limited measures may sufficient, and when it is important to override the alert.

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