A comparison of potential psychiatric drug interactions from six drug interaction database programs

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ABSTRACT

Harmful drug-drug interactions (DDI) frequently include psychiatric drugs. Drug interaction database programs are viewed as a primary tool to alert physicians of potential DDI, but may provide different results as there is no standard to define DDI. This study compared the category of potential DDI provided by 6 commercial drug interaction database programs (3 subscription, 3 open access) for 100 drug interaction pairs. The pairs involved 94 different drugs; 67 included a psychiatric and non-psychiatric drug, and 33 included two psychiatric drugs. The category assigned to the potential DDI by the 6 programs was compared using percent agreement and Fleiss' kappa interrater reliability measure. The overall percent agreement for the category of potential DDI for the 100 drug interaction pairs was 66%. The Fleiss kappa overall interrater agreement was fair. The kappa agreement was substantial for interaction pairs with any severe category rating, and fair for interaction pairs with any major category rating. The category of potential DDI for drug interaction pairs including psychiatric drugs often differs among drug interaction database programs. Modern technology allows easy access to several interaction database programs. When assistance from a drug interaction database program is needed, the physician should check more than one program.

1. Introduction

A drug-drug interaction (DDI) occurs when the clinical effects of one drug are altered by the presence of another drug. Harmful DDIs, which may increase the toxicity or reduce the efficacy of the drug, frequently involve psychiatric drugs (Holm et al., 2014; Margo et al., 2012; Nelson et al., 2016). Risk factors for DDI include older age, polypharmacy (both prescribed and over the counter), medical comorbidity, genetic variability in drug metabolism, drug properties, and multiple prescribers at different locations (Bourgeois et al., 2010; Doan et al., 2013; English et al., 2012; Margo et al., 2012; Ong et al., 2017; Tannenbaum and Sheehan, 2014).

DDI involving psychiatric drugs are of concern as these drugs are frequently prescribed. In 2013, about one in six adults were taking a psychiatric drug, defined as antidepressants, anxiolytics, sedatives and hypnotics, and antipsychotics (Moore and Mattison, 2017). Adults age ≥65 years are often taking ≥1 psychiatric drugs (Maust et al., 2017), and in two studies, nearly 40% of older adults (age ≥65 years and between 62–85 years) were using ≥5 prescription medications (Charlesworth et al., 2015; Qato et al., 2016). Psychiatrists frequently prescribe two or more medications for treatment resistant patients who

may have failed monotherapy trials (Mojtabai and Olfson, 2010). Often, these medications may be prescribed for prolonged periods of time. The majority of psychiatric drug prescriptions are prescribed by non-psychiatric physicians (Mark et al., 2009). In a study of medication regimen complexity, adults age ≥70 years with depression had the highest mean total number of medications (12.1 per patient), even greater than patients with HIV (10.8 per patient) (Libby et al., 2013). Many psychiatric drugs have properties associated with serious DDIs, as reviewed elsewhere, including a narrow therapeutic index, induction or inhibition of drug metabolizing enzymes, and may be impacted by pharmacogenetic polymorphisms (English et al., 2012; Finley, 2016; Johannessen and Landmark, 2010; Spina et al., 2016, 2008).

Automated decision support software is viewed as a fundamental tool to alert the physician to potentially clinically significant DDIs. However, prior research has found considerable variance in results provided by drug interaction database programs for potential DDI (Abarca et al., 2006; Barrett et al., 2018; Ekstein et al., 2015; Khesti et al., 2016; Saverno et al., 2011; Wang et al., 2010; Zorina et al., 2013). With the increasing emphasis on automated clinical decision support, the purpose of this study was to compare the category of potential DDI provided by six commercial drug interaction database

programs for drug interaction pairs that include psychiatric drugs. The six drug interaction database programs tested include three subscription services and three open access programs. All potential DDI pairs tested included psychiatric drugs, paired with either a non-psychiatric or another psychiatric drug.

2. Methods

2.1. Drug interaction database programs

The three subscription drug interaction database programs checked were Clinical Pharmacology, Lexicomp, and Micromedex. Clinical Pharmacology Drug Interaction is owned by Elsevier (Clinical Pharmacology, 2018), Lexicomp Drug Interactions is owned by Wolters Kluwer as included in Uptodate (Lexicomp Interactions, 2018), and Micromedex is owned by IBM Corp. (IBM Micromedex Medication Management, 2018).

The three open access programs checked were drugs.com, Medscape and Epocrates. The drugs.com interactions checker is provided by Cerner Multum, Inc., while the drugs.com website is owned and operated by the Drugsite Trust (Drugs.com, 2018). Medscape Drug Interaction Checker is part of the WebMD Network (Medscape, 2018), and Epocrates Interaction Check is owned by Athenahealth, Inc (Epocrates, 2018).

2.2. Drug interaction pairs

100 drug interaction pairs were selected for analysis based on prior research about DDI. This included studies that identified potentially serious DDI in prescribing data from primary care and national registries (Barrett et al., 2018; English et al., 2012; Holm et al., 2014; Jazbar et al., 2018; Spina et al., 2016), drug pairs used in prior testing of interaction database programs (Khesti et al., 2016; McEvoy et al., 2017; Patel and Beckett, 2016), and lists of frequently prescribed drugs (Kane 2018; Grohol 2018). Drawing from these sources, drug interaction pairs involving psychiatric drugs were chosen. Drugs that are routinely prescribed by psychiatrists were considered psychiatric drugs, even though some are also prescribed for indications outside of psychiatry. For example, duloxetine was considered a psychiatric drug although it is also an FDA approved treatment for diabetic peripheral neuropathic pain. The 100 drug interaction pairs include 94 different drugs: 43 psychiatric drugs and 51 non-psychiatric drugs. As shown in Table 1, of the 100 drug interaction pairs, 67 include a psychiatric and non-psychiatric drug, and 33 include two psychiatric drugs.

2.3. Drug interaction category

For every drug interaction pair entered, the six drug interaction database programs provide a general category for a potential DDI along with explanatory information in different formats. All database programs define similar categories, though these categories do not share the same names. The category of the potential DDI provided by the drug interaction database programs were converted into five categories for analysis: severe (contraindicated), major, moderate, minor and none, as shown in Table 2. If more than one category of potential DDI was returned for an interaction pair, the most serious was selected. All interaction pairs were searched in the six drug interaction database programs between 11/21/2018 and 12/14/2018.

Table 1
The 100 drug interaction pairs checked.

Psychiatric plus non-psychiatric drug pairs
alprazolam + hydrocodone/acetaminophen
alprazolam + ketoconazole
alprazolam + omeprazole
amitriptyline + linezolid
bupropion + tramadol
buspirone + phenytoin
buspirone + rifampin
buspirone + verapamil
carbamazepine + diltiazem
carbamazepine + nifedipine
carbamazepine + tacrolimus
carbamazepine + warfarin
citalopram + sumatriptan
citalopram + efavirenz
citalopram + levofloxacin
citalopram + meloxicam
citalopram + metoclopramide
citalopram + omeprazole
clonazepam + oxycodone
clonazepam + ritonavir
diazepam + cimetidine
duloxetine + amiodarone
escitalopram + enoxaparin
escitalopram + fluconazole
escitalopram + ibuprofen
escitalopram + linezolid
escitalopram + ondansetron
escitalopram + selegiline
fluoxetine + clopidogrel
fluoxetine + propranolol
fluoxetine + tramadol
fluoxetine + warfarin
fluvoxamine + theophylline
fluvoxamine + tizanidine
haloperidol + potassium chloride
lamotrigine + conjugated estrogens
lamotrigine + rifampin
lithium + amiodarone
lithium + hydrochlorothiazide/triamterene
lithium + lisinopril
lithium + naproxen
lurasidone + ketoconazole
lurasidone + rifampin
mirtazapine + zolmitriptan
olanzapine + ciprofloxacin
olanzapine + potassium chloride
paroxetine + propafenone
paroxetine + tamoxifen
phenelzine + zolmitriptan
quetiapine + atazanavir
quetiapine + phenytoin
quetiapine + ritonavir
risperidone + metoclopramide
sertraline + aspirin
sertraline + clarithromycin
sertraline + rivaroxaban
sertraline + warfarin
tranylcypromine + procarbazine
trazodone + digoxin
trazodone + metoclopramide
venlafaxine + quinidine
venlafaxine + vemurafenib
vortioxetine + sumatriptan
ziprasidone + furosemide
ziprasidone + pramipexole
ziprasidone + sotalol
ziprasidone + zonisamide

Table 1 (*continued*)

Psychiatric plus psychiatric drug pairs
amphetamine/dextroamphetamine + bupropion
amphetamine/dextroamphetamine + citalopram
aripiprazole + duloxetine
aripiprazole + topiramate
atomoxetine + citalopram
atomoxetine + ziprasidone
brexpiprazole + duloxetine
bupropion + clozapine
bupropion + perphenazine
carbamazepine + clozapine
clonazepam + escitalopram
clonidine + propranolol
diazepam + carbamazepine
divalproex + lamotrigine
divalproex + topiramate
escitalopram + aripiprazole
escitalopram + duloxetine
escitalopram + gabapentin
escitalopram + quetiapine
fluoxetine + haloperidol
fluvoxamine + clozapine
lamotrigine + sertraline
lurasidone + carbamazepine
methylphenidate + citalopram
paroxetine + carbamazepine
pimavanserin + escitalopram
quetiapine + benztropine
quetiapine + carbamazepine
quetiapine + diphenhydramine
ramelteon + fluvoxamine
risperidone + paroxetine
trazodone + ziprasidone
venlafaxine + bupropion

2.4. Interrater agreement and reliability

The category provided by the six drug interaction database programs was compared using both percent agreement and Fleiss' kappa. The percent agreement in the category provided by the six programs was calculated for each drug interaction pair (McHugh, 2012). For each drug pair, if the category of potential DDI agrees in all six database programs, the percent agreement would be 100%, five of six would be 83%, four of six would be 67%, three of six would be 50%, and two of six would be 33%. With six databases and five categories, the minimum percent agreement is 33% as two databases must agree. Next, the overall percent agreement was calculated as the mean percent agreement for all 100 drug interaction pairs (McHugh, 2012).

The Fleiss' Kappa statistic was used to summarize the agreement in the category of potential DDI provided by the six drug interaction database programs. The Fleiss' kappa is a measure of interrater reliability that removes agreement expected by chance and is suitable for three or more raters. A kappa value varies between −1 and 1, with 1 indicating

Table 3
Range of categories provided by the six drug interaction database programs for the 100 drug interaction pairs.

Least severe–Most severe category	Number	Percent
None–Severe	5	5%
None–Major	20	20%
None–Moderate	12	12%
Minor–Severe	1	1%
Minor–Major	5	5%
Moderate–Severe	4	4%
Moderate–Major	36	36%
Major–Severe	7	7%
All major	4	4%
All severe	6	6%
All	100	100%

perfect agreement, −1 indicating perfect disagreement, and 0 indicating agreement expected by chance (Fleiss, 1971). The interpretation of Fleiss' kappa values is based on guidelines established by Landis and Koch such that < 0.0 is poor agreement, 0.0–0.2 is slight agreement, 0.21–0.40 is fair agreement, 0.41–0.60 is moderate agreement, 0.61–0.80 is substantial agreement and 0.81–1.00 almost perfect agreement (Landis and Koch, 1977). *P*-values are calculated for the kappa, with a $p < 0.05$ meaning that rater agreement was unlikely to be due to chance. High agreement among raters does not always mean the answer is correct, and low agreement does not always mean the answer is incorrect. All Fleiss' kappa calculations were made using the R software package "irr" Version 0.84 (Gamer et al., 2015).

3. Results

The overall percent agreement in category provided by the six drug interaction database programs for the 100 drug interaction pairs was 66%. The range of category results returned (least to most severe category) for the 100 drug interaction pairs is shown in Table 3. The drug interaction pairs with the broadest category ranges (none-severe, minor-severe, none-major, minor-major) are shown in Table 4. The overall Fleiss kappa was 0.257 (fair agreement), as detailed in Table 5. The kappa was 0.695 (substantial agreement) for interaction pairs with any severe category rating, and 0.247 (fair agreement) for interaction pairs with any major category rating.

4. Discussion

The category of potential DDI for the 100 drug interaction pairs involving psychiatric drugs was often different among the six drug interaction database programs. Although the interrater reliability was substantial for potential DDI in the severe (contraindicated) category, the overall interrater reliability was only fair. Physicians should be aware that the results of potential DDI searches often varies among drug interaction database programs.

Table 2
Conversion of category returned by the six drug interaction database programs to study category.

Study category	Category returned by the drug interaction database program					
	Clinical pharmacology	Micromedex	Lexicomp	Epocrates	Drugs.com	Medscape
Severe	Level 1. Severe-contraindicated; Severe-avoid	Contraindicated	(X) Avoid combination	Contraindicated	Major-contraindicated	Contraindicated
Major	Level 2. Major	Major	(D) Consider therapy modification	Avoid/use alternative	Major	Serious-use alternative
Moderate	Level 3. Moderate	Moderate	(C) Monitor therapy	Monitor/modify treatment	Moderate	Monitor closely
Minor	Level 4. Minor	Minor	(B) No action needed	Caution advised	Minor	Minor
None	None	Unknown	(A) No known interaction	No significant interactions found	Unknown	No interactions found

Table 4
Drug interaction pairs with the largest range in categories provided by the six drug interaction database programs.

Category range	Drug interaction pairs	Percent agreement	All category results
None to Severe	atomoxetine + ziprasidone	50%	3 none, 1 severe, 1 major, 1 moderate
	escitalopram + fluconazole	33%	2 severe, 2 moderate, 1 major, 1 none
	haloperidol + potassium chloride	67%	4 none, 2 severe
	olanzapine + potassium chloride	50%	3 severe, 3 none
	venlafaxine + quinidine	50%	3 major, 1 severe, 1 minor, 1 none
Minor to Severe	citalopram + metoclopramide	50%	3 major, 1 severe, 1 moderate, 1 minor
None to Major	aripiprazole + topiramate	67%	4 moderate, 1 major, 1 none
	atomoxetine + citalopram	50%	3 none, 1 major, 2 moderate
	bupropion + perphenazine	50%	3 major, 2 moderate, 1 none
	buspirone + phenytoin	50%	3 major, 2 moderate, 1 none
	citalopram + efavirenz	67%	4 moderate, 1 major, 1 none
	diazepam + carbamazepine	50%	3 moderate, 2 major, 1 none
	diazepam + cimetidine	33%	2 major, 2 minor, 1 moderate, 1 none
	divalproex + topiramate	50%	3 moderate, 2 major, 1 none
	escitalopram + aripiprazole	50%	3 moderate, 1 major, 1 minor, 1 none
	escitalopram + enoxaparin	33%	2 major, 2 moderate, 1 minor, 1 none
	escitalopram + pimavanserin	50%	3 major, 3 none
	lithium + amiodarone	50%	3 none, 2 major, 1 moderate
	methylphenidate + citalopram	50%	3 moderate, 1 major, 1 minor, 1 none
	sertraline + clarithromycin	33%	2 major, 2 none, 1 moderate, 1 minor
	sertraline + rivaroxaban	50%	3 moderate, 2 major, 1 none
	venlafaxine + bupropion	67%	4 moderate, 1 major, 1 none
	venlafaxine + vemurafenib	50%	3 major, 3 none
	ziprasidone + furosemide	50%	3 moderate, 1 major, 1 minor, 1 none
	ziprasidone + pramipexole	67%	4 moderate, 1 major, 1 none
	ziprasidone + zonisamide	33%	2 moderate, 2 none, 1 major,1 minor
Minor to Major	bupropion + clozapine	67%	4 major, 1 moderate, 1 minor
	escitalopram + quetiapine	50%	3 major, 2 moderate, 1 minor
	olanzapine + ciprofloxacin	67%	4 moderate, 1 major, 1 minor
	sertraline + aspirin	67%	4 moderate, 1 major, 1 minor

Table 5
Kappa indices of agreement between six drug interaction database programs for the 100 drug interaction pairs.

Category	Kappa	*P*-value	Strength of agreement[a]
None	0.170	< 0.001	Slight
Minor	−0.024	0.347	Poor
Moderate	0.112	< 0.001	Slight
Major	0.247	< 0.001	Fair
Severe	0.695	< 0.001	Substantial
Overall[b]	0.257	< 0.001	Fair

[a] Landis and Koch, 1977.
[b] Fleiss kappa.

Potential DDI are difficult to predict, requiring expert level knowledge of pharmacology, pharmacogenetics, clinical medicine across specialties, and evidence evaluation for potential side effects, including rare events. It is hard to determine clinical impact even when DDI are demonstrated pharmacologically (Bykov and Gagne, 2017; Sutherland et al., 2015). The audience for drug interaction database programs has varying knowledge of DDI and includes physicians and mid-level prescribers from all specialties, as well as pharmacists (Ko et al., 2008; Warholak et al., 2011). Commercial drug interaction database programs use different information sources, alternate rating criteria and procedures, and select varying levels of acceptable risk (Kongsholm et al., 2015; Scheife et al., 2015; Tilson et al., 2016; Vitry 2007). For over a decade, a lack of consistency among drug interaction database programs and compendia has been reported (Abarca et al., 2006; Chao and Maibach, 2005; Roblek et al., 2015; Vitry 2007; Wong et al., 2008), including from studies focused on psychiatric drugs (Liu et al., 2017; Zorina et al., 2013). Despite efforts to improve the selection of DDI evidence, there is no broadly accepted standard for defining DDI risk (Scheife et al., 2015; Romagnolie et al., 2017; Hines et al., 2012; Tilson et al., 2016). Given the complexity, differing results from drug interaction database programs is not surprising and should be recognized.

In an era of increasing emphasis on automated clinical decision support, more discussion of the appropriate expectations and limitations of drug interaction database programs is needed. The variability among drug interaction database programs should be recognized as a limitation. In some cases checking only one program could endanger the patient. For example, in this study, three programs classified the concurrent use of olanzapine and the solid form of potassium chloride as contraindicated due to risks of gastric and intestinal ulceration and irritation, while three programs classified as no potential DDI. Prior research related to program inconsistency has recommended that clinicians consult more than one DDI reference (Boyce et al., 2012; Liu et al., 2017). Physicians should not assume that any one database program provides the final word in defining potential DDI. Since most physicians have ubiquitous connectivity to online resources, more than one program can usually be checked. In this digitally interconnected world, easy access to many drug interaction database programs should be recognized as a benefit. Given the complexity of drug interactions, and lack of standardization of programs, the medical field is well served to have multiple independent opinions available.

The physician must interpret the information about potential DDI in relation to patient-specific characteristics, such as age, comorbid medical conditions, concurrent medications, laboratory test results, drugs doses and dosing schedules. Yet current clinical practice poses diverse challenges. Many patients are taking unique drug regimens. In a large prescription database, of those age ≥ 65 years who were taking three or more medications, there were ≥ 98 unique drug regimens per 100 people (Sutherland et al., 2015). Of 353 patients on a stable treatment regimen for bipolar disorder, there were 231 unique drug regimens (Bauer et al., 2013). Medication lists in electronic medical records are often incorrect (Sutherland et al., 2018), due in part to patients receiving treatment from multiple physicians. Although multimorbidity is prevalent in those with chronic illness (Barnett et al., 2012), disease-specific treatment guidelines may not mention potential DDI with drugs included in guidelines for commonly co-occurring conditions. For example, an investigation of UK National Institute of Health and Care Excellence (NICE) guidelines for depression, diabetes and heart failure found many potentially serious DDIs (Dumbeck et al., 2015).

Many physicians are dissatisfied with drug interaction database programs (Smithburger et al., 2011) for reasons including alert fatigue (Bryant et al., 2014; Isaac et al., 2009), workflow disruption (Hawyard et al., 2013), and feeling that most DDI alerts are unnecessary or clinically irrelevant (van der Sijs et al., 2006). Physicians often assess the risk of DDI for an individual patient as being lower than that of a drug interaction database program (Armahizer et al., 2013). In a survey of 118 psychiatrists, half thought information from electronic prescribing systems on drug interactions was incorrect (Phillips and Citrome, 2019). However, physicians vary in knowledge of potential DDI, and treat patients selected by specialty. With 3934 approved drugs listed in the 2018 FDA Orange Book (FDA, 2018) and new drugs added yearly, physicians cannot be aware of all potentially serious DDI. At times, all physicians must rely on drug interaction database programs to assist with identifying potential DDI. When assistance from a drug interaction database program is needed, physicians should seek another opinion from another source and/or other expert.

There are limitations to this study. Only the overall category of potential DDI were compared. Other features and functions, ease of use, integration with EMR, and clinical value of the drug interaction database programs were not investigated. Results could change due to frequent program updates, or with the use of a different set of drug interaction pairs. It was assumed that each program has strengths and weaknesses. The accuracy of DDI information for psychiatric drugs was not investigated (Phillips and Citrome, 2019), such as by comparing with drug package inserts. No attempt was made to evaluate the methodology used to determine DDIs by the six drug interaction database programs, or the frequency of use of these programs. Legal issues associated with the use of drug interaction database programs (Greenberg and Ridgely, 2011), and ongoing efforts to improve usability (Luna et al., 2017; Tolley et al., 2018) were not discussed.

In conclusion, the category of potential DDI for drug interaction pairs including psychiatric drugs often differs among drug interaction database programs. When assistance from a drug interaction database program is needed, physicians should recognize this limitation and check more than one program.

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Declaration of interest

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