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Potential Drug Interactions with Drugs Used for Bipolar Disorder: A Comparison of 6 Drug Interaction Database Programs

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ABSTRACT

Background Patients with bipolar disorder frequently experience polypharmacy, putting them at risk for clinically significant drug-drug interactions (DDI). Online drug interaction database programs are used to alert physicians, but there are no internationally recognized standards to define DDI. This study compared the category of potential DDI returned by 6 commercial drug interaction database programs for drug interaction pairs involving drugs commonly prescribed for bipolar disorder.

Methods The category of potential DDI provided by 6 drug interaction database programs (3 subscription, 3 open access) was obtained for 125 drug interaction pairs. The pairs involved 103 drugs (38 psychiatric, 65 nonpsychiatric); 88 pairs included a psychiatric and nonpsychiatric drug; 37 pairs included 2 psychiatric drugs. Every pair contained at least 1 mood stabilizer or antidepressant. The category provided by 6 drug interaction database programs was compared using percent agreement and Fleiss kappa statistic of interrater reliability.

Results For the 125 drug pairs, the overall percent agreement among the 6 drug interaction database programs was 60 %; the Fleiss kappa agreement was slight. For drug interaction pairs with any category rating of severe (contraindicated), the kappa agreement was moderate. For drug interaction pairs with any category rating of major, the kappa agreement was slight.

Conclusion There is poor agreement among drug interaction database programs for the category of potential DDI involving psychiatric drugs. Drug interaction database programs provide valuable information, but the lack of consistency should be recognized as a limitation. When assistance is needed, physicians should check more than 1 drug interaction database program.

Introduction

Drug-drug interactions (DDI) contribute to emergency department visits, hospital admissions, longer hospital stays, and increased costs to society [1]. The consequences of most DDI are less severe, often misinterpreted as reduced efficacy, and are an ongoing challenge in psychiatric practice [2, 3]. Drug interaction database programs are widely recognized as the primary tool to assist physicians in preventing DDI but also demonstrate the need to understand the limitations of automation [4]. There are no internationally recognized standards to define DDI risk [5, 6], and database programs use different methods to search, identify and classify risk [7–9].

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Factors that increase the risk for DDI include older age, polypharmacy, pharmacological properties of drugs, genetic polymorphisms, multimorbidity, and multiple prescribers at different locations [10–14]. Many of these factors are present when treating patients with bipolar disorder. The recurrent, episodic, and heterogeneous nature of bipolar disorder often requires complex treatment regimens for the long-term [15]. Outpatients with bipolar disorder, including the elderly, routinely experience polypharmacy defined as 2 or more psychiatric medications [16–21]. Between 18–36 % of patients with bipolar disorder received 4 or more psychiatric medications [16, 17, 21, 22]. The pharmacological properties of many drugs prescribed for bipolar disorder may contribute to serious DDI [23], including lithium [24, 25], some antiepileptics [26, 27], antipsychotics [28, 29], and antidepressants [28]. There is a high burden of comorbid medical illness in patients with bipolar disorder [30, 31].

We previously investigated the category of potential DDI for drug interaction pairs containing a psychiatric drug and found that the category returned by drug interaction programs often differed [32]. Due to the increased risk for potential DDI in bipolar disorder, this study compared the category of potential DDI returned by 6 drug interaction database programs for drug interaction pairs containing a mood stabilizer or antidepressant. In this study, the mood stabilizer or antidepressant was paired with another psychiatric drug or a nonpsychiatric drug. The drug interaction pairs were checked using 6 drug interaction database programs, 3 subscription and 3 open access services.

Methods

Drug interaction database programs and categories

The 6 drug interaction database programs that were compared included 3 subscription programs: Clinical Pharmacology owned by Elsevier [33], Lexicomp owned by Wolters Kluwer as included in Uptodate [34], and Micromedex owned by IBM [35]. The 3 open access programs included drugs.com owned by the Drugsite Trust [36], Medscape owned by the WebMD Network [37], and Epocrates owned by Athenahealth, Inc [38]. All 6 products are commonly used by clinicians.

After entering a drug interaction pair, each of the 6 drug interaction database programs returns a category for potential DDI, along with explanatory information and evidence in different formats. The categories returned are similar but have different names. For this analysis, the categories were converted into 6 categories: severe (contraindicated), major, moderate, minor, none, and missing. (▶ **Table 1**). If a drug interaction database program returned more than 1 category of potential DDI for a drug pair, the most serious category was selected. The searching occurred between 10/10/2019 and 10/20/2019.

Drug interaction pairs

The 125 drug interaction pairs that were searched involved 103 drugs: 38 psychiatric drugs and 65 nonpsychiatric drugs. Of the 125 drug interaction pairs, 88 pairs included a psychiatric and nonpsychiatric drug, and 37 included 2 psychiatric drugs. All 125 drug interaction pairs contained at least 1 mood stabilizer (lithium, antiepileptic, or antipsychotic) or antidepressant. Drugs routinely prescribed by psychiatrists were considered psychiatric drugs, although some psychiatric drugs have FDA approval for indications outside of psychiatry. The 125 drug interaction pairs that were searched are listed in **Appendix 1**.

Multiple resources were used to select the 125 drug interaction pairs. These include studies of potential DDI detected in various healthcare settings [11, 39–44], reviews of potential DDI involving psychiatric drugs [23, 27, 28, 45–47], lists of serious drug interactions used in prior testing of drug interaction database programs [48–50], and lists of frequently prescribed drugs [51, 52]. All 125 drug interaction pairs had at least 1 category rating of major from at least one of the 6 drug interaction database programs.

Interrater percent agreement and reliability

Two methods were used to compare agreement in the category provided by the 6 drug interaction database programs: the percent agreement and the Fleiss kappa statistic. For each of the 125 drug interaction pairs, the percent agreement in the category provided by the 6 drug interaction database programs was calculated (the number of ratings that agree divided by the total number of ratings, or 6) [53]. The mean for all 125 drug interaction pairs was then calculated for the overall percent agreement.

▶ **Table 1** Drug interaction categories returned by 6 drug interaction database programs converted to study categories.

Study Category	Database Categories for Each Database					
	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
Missing *	Missing	Missing	Missing	Missing	Missing	Missing

* One drug in pair not in database.

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The Fleiss kappa statistic was also used to summarize agreement among the 6 drug interaction database programs. A Fleiss kappa statistic was calculated for each category of potential DDI, as well as an overall statistic for all category ratings. The Fleiss kappa statistic measures the agreement between raters that is above the level expected by chance, and is suitable for 3 or more raters [54]. A Fleiss kappa value varies from −1.0 (perfect disagreement) to 0 (agreement expected by chance) to 1.0 (perfect agreement). The scale of Landis and Koch was used to interpret the strength of agreement of the Fleiss kappa value. A kappa value of <0.00 is poor agreement, 0.00–0.20 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 is almost perfect agreement [55]. P-values are calculated for the Fleiss kappa, with statistical significance ($p < 0.05$) meaning that rater agreement was not due solely to chance. Although Fleiss kappa is a measure of agreement among raters, high agreement does not always mean the answer is correct, and low agreement does not always mean the answer is incorrect. The R software package "irr" Version 0.84.1 was used for all Fleiss kappa statistic calculations [56].

Results

The overall percent agreement in category provided by the 6 drug interaction programs for the 125 drug interaction pairs was 60 %. There was no difference in percent agreement between drug interaction pairs including a psychiatric and nonpsychiatric drug (60 %) and pairs with 2 psychiatric drugs (59 %). For the 125 drug interaction pairs, the range in category results returned (least to most severe category) is shown in ▶ **Fig. 1**. The drug interaction pairs with the broadest range of categories from the 6 drug interaction programs are shown in ▶ **Tables 2** and ▶ **3**. ▶ **Table 2** shows the drug interaction pairs with at least 1 rating of severe and a range that differed by 2 or more categories (none–severe, minor–severe, moderate–severe). ▶ **Table 3** shows the drug interaction pairs with at least 1 rating of major and a range that differed by 2 or more categories (none–major, minor–major, missing–major).

For the 125 drug interaction pairs, the overall Fleiss kappa statistic was 0.142 (slight agreement) as shown in ▶ **Table 4**. The Fleiss kappa statistic for drug interaction pairs with any category rating of severe was 0.426 (moderate agreement) and 0.068 (slight agreement) for pairs with any category rating of major.

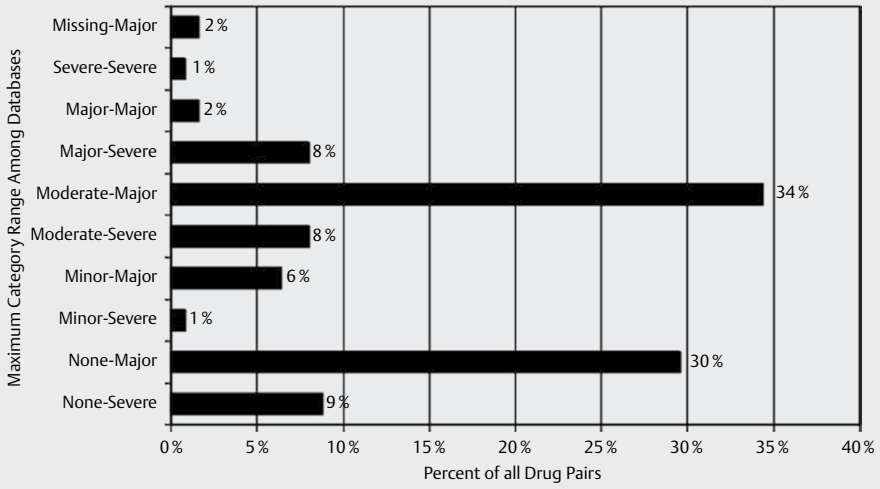
Disagreement in the category of potential DDI occurred even for well-documented DDI, such as between selective serotonin reuptake inhibitors (SSRI) and monoamine oxidase inhibitors (MAOI) [57]. There was 83 % agreement for citalopram + selegiline (5 severe, 1 major), 67 % agreement for sertraline + rasagiline (2 severe, 4 major), and 100 % agreement for escitalopram + tranylcypromine (6 severe).

Drug interaction database programs are updated periodically. Of the 125 drug interaction pairs, 33 were used in our previous analysis in 2018 [32]. For these 33 drug interaction pairs, a total of 21 (11 %) category changes across the 6 drug interaction database programs were found. Of the 21 changes, 8 (38 %) ratings increased in severity and 13 (62 %) decreased in severity.

The web sites for all 6 drug interaction database programs include detailed disclaimers and terms of use statements, which stipulate that the information provided is intended only to supplement and assist the physician and not as a replacement for professional knowledge and judgement. All 6 companies provide information on an "as is" basis and assume no responsibility or liability.

Discussion

The category of potential DDI returned by the 6 drug interaction programs for the 125 drug interaction pairs, all with at least 1 rating of major, often did not agree. The overall interrater reliability was slight, and only moderate for potential DDI in the severe (contraindicated) category. Poor agreement between drug interaction database programs is well documented [58–60], including in studies of psychiatric and antiepileptic drugs that involve potential DDI rated major or severe [32, 61–64]. Potential DDI are challenging to define and detect [5–7, 14], and both polypharmacy and biologics further increase the methodological complexity [65–67]. Experts



▶ **Fig. 1** Maximum category range of potential DDI from the 6 drug interaction database programs for the 125 drug interaction pairs.

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▶ **Table 2** Drug interaction pairs with at least one severe rating and a range that differed by 2 or more categories.

	Drug Pair	% Agreement	All Database Categories
None to Severe Range			
	amitriptyline + potassium chloride	50 %	3 severe, 3 none
	citalopram + metoclopramide	33 %	1 severe, 2 major, 1 moderate, 1 minor, 1 none
	divalproex + lesinurad	33 %	1 severe, 1 major, 2 moderate, 2 none
	haloperidol + potassium chloride	67 %	2 severe, 4 none
	olanzapine + alprazolam	50 %	1 severe, 3 moderate, 1 minor, 1 none
	olanzapine + potassium chloride	50 %	3 severe, 3 none
	quetiapine + revefenacin	50 %	1 severe, 1 major, 1 moderate, 3 none
	sertraline + disulfiram	50 %	2 severe, 1 major, 3 none
	venlafaxine + quinidine	33 %	1 severe, 2 major, 1 minor, 2 none
	ziprasidone + atomoxetine	50 %	1 severe, 1 major, 1 moderate, 3 none
	ziprasidone + tamoxifen	50 %	2 severe, 1 major, 3 none
Minor to Severe Range			
	ziprasidone + amitriptyline	33 %	2 severe, 2 major, 1 moderate, 1 minor
Moderate to Severe Range			
	aripiprazole + ketoconazole	50 %	1 severe, 3 major, 2 moderate
	citalopram + amiodarone	67 %	1 severe, 4 major, 1 moderate
	citalopram + dofetilide	67 %	1 severe, 4 major, 1 moderate
	escitalopram + fluconazole	67 %	1 severe, 1 major, 4 moderate
	lurasidone + atazanavir	67 %	1 severe, 4 major, 1 moderate
	olanzapine + lorazepam	50 %	1 severe, 3 major, 2 moderate
	quetiapine + ziprasidone	50 %	3 severe, 2 major, 1 moderate
	quetiapine + dronedarone	67 %	4 severe, 1 major, 1 moderate
	quetiapine + sotalol	67 %	1 severe, 4 major, 1 moderate
	ziprasidone + hydroxyzine	50 %	2 severe, 3 major, 1 moderate

disagree on search strategies, resources for seeking evidence, and processes to rank evidence and classify potential DDI [7, 9]. Drug interaction database programs use various information sources and have inconsistent criteria to define severity [5–9, 59, 68]. These inconsistencies in evidence and classification criteria may lead to large discrepancies in the category of potential DDI returned [63, 68], as found in the current study. Until there are standardized measures to evaluate and classify evidence, clinicians should expect different products to provide different results. It is important that clinicians recognize this limitation of drug interaction database programs and, as noted in prior research, consult more than 1 source as needed [32, 63, 69].

When treating patients taking polypharmacy for years, such as those with bipolar disorder, the risk of clinically significant DDI is recurrent. The physician must interpret the potential DDI category from a drug interaction database program for the individual patient, despite many challenges. Information in the EMR is often incorrect. For example, the medication list in the EMR is often inaccurate [70, 71], with at least 1 medication discrepancy found for 85 % of 438 patients at a psychiatric clinic [72]. Both clinical and mental health data, including diagnoses, may be missing from the EMR [73–75] such that both psychiatrists and general doctors are prescribing with an incomplete understanding of the patient history.

Many challenges are related to polypharmacy. Patients taking polypharmacy usually have a unique drug regimen, resulting in more possible drug interaction pairs than ever could be studied clinically [67]. In a study of 353 patients with a stable treatment regimen for bipolar disorder, 231 patients took a unique medication regimen when considering only the psychiatric drugs [16]. A larger number of psychiatric drugs was associated with irregularity in the daily dosage taken of mood stabilizers and antidepressants in patients with bipolar disorder [76, 77]. Since many patients with bipolar disorder are partially adherent or nonadherent, drug concentrations in the blood may not be at therapeutic levels [78]. In a study of 115 highly selected, adherent patients from a psychiatric clinic, who took at least 5 psychiatric and nonpsychiatric drugs, the concentration of 41 % of drugs was below and 6 % above the specific blood reference range for each drug, and 13 % of detected drugs were not in the EMR [79].

DDI involving 2 psychiatric drugs may be difficult to detect and be misinterpreted as toxicity or reduced efficacy [2, 80]. For example, an added drug may gradually increase the serum concentration and unwanted side effects of an ongoing drug, with the DDI misinterpreted as an adverse reaction. Alternatively, an added drug may decrease the serum concentration of an ongoing drug, so the patient appears treatment resistant. Off-label prescribing is associated with adverse events [81], and many psychiatric drugs are prescribed off-label in psychiatry and primary care [82, 83].

Other challenges relate to the implementation of drug interaction database programs. Changes to the prescribing workflow may be cumbersome [84, 85]. Alert fatigue remains a major issue as the majority of DDI alerts are overridden [86, 87]. Physicians often feel that most DDI alerts do not require action or are clinically insignificant, or that the risk for an individual patient is lower than shown

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▶ **Table 3** Drug interaction pairs with at least one major rating and a range that differed by 2 or more categories

	Drug Pair	% Agreement	All Database Categories
None to Major Range			
	aripiprazole + escitalopram	50%	1 major, 3 moderate, 1 minor, 1 none
	aripiprazole + topiramate	67%	1 major, 4 moderate, 1 none
	asenapine + dofetilide	67%	4 major, 1 moderate, 1 none
	asenapine + zonisamide	33%	1 major, 2 moderate, 1 minor, 2 none
	carbamazepine + atorvastatin	50%	2 major, 3 moderate, 1 none
	carbamazepine + dexamethasone	50%	2 major, 3 moderate, 1 none
	carbamazepine + diazepam	50%	2 major, 3 moderate, 1 none
	cariprazine + bupropion	33%	2 major, 2 moderate, 2 none
	cariprazine + topiramate	33%	2 major, 1 moderate, 1 minor, 2 none
	citalopram + atomoxetine	33%	1 major, 2 moderate, 1 minor, 2 none
	citalopram + efavirenz	67%	4 major, 1 moderate, 1 none
	citalopram + fingolimod	50%	3 major, 1 moderate, 2 none
	clozapine + cyclophosphamide	33%	2 major, 2 moderate, 2 none
	clozapine + adalimumab	83%	1 major, 5 none
	clozapine + lenalidomide	33%	2 major, 2 moderate, 2 none
	divalproex + topiramate	67%	1 major, 4 moderate, 1 none
	escitalopram + enoxaparin	50%	3 major, 2 moderate, 1 none
	escitalopram + pimavanserin	50%	3 major, 1 minor, 2 none
	escitalopram + valbenazine	67%	1 major, 1 minor, 4 none
	haloperidol + valbenazine	67%	1 major, 1 moderate, 4 none
	lamotrigine + buprenorphine	50%	2 major, 1 moderate, 3 none
	lithium + amiodarone	50%	2 major, 1 moderate, 3 none
	lithium + quetiapine	50%	1 major, 3 moderate, 2 none
	lithium + sumatriptan	33%	2 major, 2 moderate, 1 minor, 1 none
	olanzapine + donepezil	50%	1 major, 3 moderate, 2 none
	olanzapine + escitalopram	50%	1 major, 3 moderate, 1 minor, 1 none
	perphenazine + bupropion	50%	3 major, 2 moderate, 1 none
	quetiapine + fluvoxamine	50%	1 major, 3 moderate, 1 minor, 1 none
	quetiapine + zolpidem	50%	1 major, 3 moderate, 2 none
	risperidone + ondansetron	50%	3 major, 2 moderate, 1 none
	sertraline + clarithromycin	50%	3 major, 1 moderate, 1 minor, 1 none
	venlafaxine + bupropion	50%	3 major, 1 moderate, 2 none
	venlafaxine + vemurafenib	50%	3 major, 3 none
	ziprasidone + furosemide	50%	1 major, 3 moderate, 2 none
	ziprasidone + pramipexole	50%	3 major, 2 moderate, 1 none
	ziprasidone + zonisamide	33%	1 major, 2 moderate, 1 minor, 2 none
	ziprasidone + hydrochlorothiazide	50%	1 major, 3 moderate, 2 none
Minor to Major Range			
	citalopram + aspirin	67%	1 major, 4 moderate, 1 minor
	fluoxetine + donepezil	50%	1 major, 2 moderate, 3 minor
	lithium + sertraline	50%	3 major, 2 moderate, 1 minor
	olanzapine + ciprofloxacin	67%	1 major, 4 moderate, 1 minor
	quetiapine + ciprofloxacin	50%	2 major, 3 moderate, 1 minor
	quetiapine + escitalopram	50%	3 major, 2 moderate, 1 minor
	sertraline + aspirin	67%	1 major, 4 moderate, 1 minor
	sertraline + warfarin	50%	2 major, 3 moderate, 1 minor
Missing to Major Range			
	cariprazine + boceprevir	50%	3 major, 1 none, 2 missing
	cariprazine + iohexol	33%	2 major, 2 none, 2 missing

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▶ **Table 4** Fleiss kappa interrater agreement among the 6 drug interaction database programs for 125 drug interaction pairs.

Category	Kappa	P-value	Strength of Agreement*
Severe	0.426	<0.001	Moderate
Major	0.068	0.003	Slight
Minor	0.015	0.511	Slight
None	0.188	<0.001	Slight
Missing	0.196	<0.001	Slight
Overall	0.142	<0.001	Slight

* Landis and Koch 1977.

[87, 88]. Some physicians feel the DDI information provided by the drug interaction database program is incorrect, including half of 118 psychiatrists surveyed [89]. For example, in this study the category of potential DDI for 3 drug pairs containing an SSRI and MAOI was rated major, rather than severe, in 5 of 18 ratings (27.8 %). Alert override may become a habitual behavior, such that an alert acts as a cue that automatically triggers an override response [90]. Automation bias may also occur, with some prescribers becoming over-reliant on the drug interaction database program to detect potential DDI at the exclusion of clinical judgement [91].

Drug interaction database programs provide a large amount of information and are an important and helpful tool. Physicians see patients by specialty and may only have a limited knowledge of DDI [92, 93]. Realistically, it is not possible for a physician to accurately identify all potentially serious DDI. In 2019, the FDA Orange Book of all drugs approved as safe and effective has 3959 entries [94], while the FDA Purple Book of biologics and biosimilars has 29 entries [95]. Additionally, classification of potential DDI is an ongoing process, as shown by the category change in 11 % of the drug interaction pairs investigated a year ago [32]. However, the lack of consistency in results from drug interaction programs in this study and many prior studies should be recognized as a limitation of this technology. If the physician requires assistance in determining potential DDI, more than 1 database product should be checked. Given that most physicians have continual Internet access, physicians can easily obtain multiple independent opinions from more than 1 product. If questions remain after the use of another product, a human expert should be consulted. Routine use of drug interaction database programs underscores the importance of clinical judgement and expertise. The prescriber must recognize when to ask for assistance from a human expert.

There are limitations to this analysis. The results could change after drug interaction database programs are updated and if different drug interaction pairs were searched. There was no attempt to assess or compare the accuracy of the category of potential DDI or to investigate the methodology used to define DDI risk. Other features of the drug interaction database programs including ease of use, quality of information display, integration with the EMR, and impacts on physician workflow were not evaluated. Supplements are commonly used by patients with bipolar disorder [96], but drug interactions with supplements, alcohol, food, smoking, and illegal drugs were not considered. Legal issues related to DDI [97] and the use of psychiatric drugs purchased online from rogue pharmacies were not discussed [98, 99].

Physicians should understand the limitations as well as the capabilities of technology products that impact medical decision making. Ultimately, physician judgement will determine if there is a potential DDI for the individual patient, often requiring a nuanced interpretation of many complex factors. All physicians recognize that drugs have limitations including adverse reactions and DDI. Likewise, physicians should recognize that technology has limitations, and an important limitation of drug interaction database programs is the lack of consistency. When a physician needs assistance from a drug interaction database program, more than 1 program should be checked.

Conflict of interest

The authors declare that they have no conflict of interest.

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