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].
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.

<table>
<thead>
<tr>
<th>Study Category</th>
<th>Clinical pharmacology</th>
<th>Micromedex</th>
<th>Lexicomp</th>
<th>Epocrates</th>
<th>Drugs.com</th>
<th>Medscape</th>
</tr>
</thead>
<tbody>
<tr>
<td>Severe</td>
<td>Level 1. Severe-contraindicated; Severe-avoid</td>
<td>Contraindicated</td>
<td>(X) Avoid combination</td>
<td>Contraindicated</td>
<td>Major-contraindicated</td>
<td>Contraindicated</td>
</tr>
<tr>
<td>Major</td>
<td>Level 2. Major</td>
<td>Major</td>
<td>(D) Consider therapy modification</td>
<td>Avoid/use alternative</td>
<td>Major</td>
<td>Serious-use alternative</td>
</tr>
<tr>
<td>Moderate</td>
<td>Level 3. Moderate</td>
<td>Moderate</td>
<td>(C) Monitor therapy</td>
<td>Monitor/modify treatment</td>
<td>Moderate</td>
<td>Monitor closely</td>
</tr>
<tr>
<td>Minor</td>
<td>Level 4. Minor</td>
<td>Minor</td>
<td>(B) No action needed</td>
<td>Caution advised</td>
<td>Minor</td>
<td>Minor</td>
</tr>
<tr>
<td>None</td>
<td>None</td>
<td>Unknown</td>
<td>(A) No known interaction</td>
<td>No significant interactions found</td>
<td>Unknown</td>
<td>No interactions found</td>
</tr>
<tr>
<td>Missing *</td>
<td>Missing</td>
<td>Missing</td>
<td>Missing</td>
<td>Missing</td>
<td>Missing</td>
<td>Missing</td>
</tr>
</tbody>
</table>

* One drug in pair not in database.
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.

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 [52, 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...
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 prescribed off-label in psychiatry and primary care [82, 83].

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

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