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Potential Psychotropic Drug Interactions among Drug-dependent People

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ABSTRACT

Using psychiatric drugs to treat drug dependence and its comorbidities is very common. The objective of this study was to analyze the interactions between prescribed drugs for patients treated at a specialized mental health-care center for persons who use drugs, located in the state of Santa Catarina, Brazil. A cross-sectional study was conducted on secondary data collected from 2010 to 2018. We reviewed the medical records of patients aged 18 years or older who took psychotropic drugs and had any type of substance dependence. The analysis of psychotropic drug interactions was conducted in three databases: *Medscape, Drug Interactions Checker*, and *Micromedex*. We included 1,022 of the 2,322 patients attending the care center during the study period. Psychotropic drug interactions were found in 779 (76.4%) study participants, and they presented 2,292 (100%) interactions, out of which 136 (6.0%) had minor clinical risk, 537 (23.4%) had moderate risk, and 1,619 (70.6%) had major risk for the patient, totaling 172 incompatible combinations between two psychotropic drugs. Of the total number of interactions, 128 were pharmacokinetic and 44 were pharmacodynamic. The high number of psychotropic drug interactions is a serious public health issue. Psychopharmacological treatment should be carefully addressed to be safe for the patient.

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Drug interactions; drug-related side effects and adverse reactions; substance-related disorders; mental health; pharmacovigilance

Introduction

Use of psychotropic drugs is quite common in health-care centers for the management of various diseases affecting people worldwide (Xavier et al. 2014). Every day, new cases of mental disorders are diagnosed, including depression, anxiety, obsessive-compulsive disorders, self-esteem problems, chronic tiredness, *burnout* syndrome, risky behaviors, and addictive behaviors, such as the consumption of heroin, ecstasy, cocaine, crack, alcohol, and even psychotropic drugs (Takayanagi et al. 2014). The search for effective treatments has led to additional psychiatric medications and services to provide support to people (Perrusi 2015).

In Brazil, the dispensation of psychotropic drugs is regulated by specific laws, although there is little information on use restrictions, such as contraindications, adverse reactions, interactions, warnings, and precautions (Mastroianni, Galduróz, and Carlini 2005). The use of psychotropic drugs and their combinations can result in various problems, such as unwanted drug interactions, adverse reactions, and tolerance (Fernandes et al. 2012). Among the adverse reactions, drug interactions are the most frequent. More than 30% of the adverse reactions are caused by drug interactions, which results in significant morbidity each year (Iyer et al. 2014).

Potential drug–drug interaction (PDDI) is an adverse drug reaction that corresponds to pharmacological responses in which the effects of one or more drugs are altered by the simultaneous or previous administration of other medications (Moura, Acurcio, and Belo 2009). The pharmacological response may be further altered by the concomitant intake of food, drink, or some environmental chemical agent. Drug interactions may be either pharmacokinetics, when the interaction alters the rate or extent of drug absorption, distribution, biotransformation, and excretion, or pharmacodynamic, when it occurs at the site of drug action, involving the mechanisms by which the desired effects proceed in an agonist or antagonistic manner (Ritter et al. 2016).

PDDI involving psychotropic medications are very common (Balen et al. 2017; Correia, Li, and Rocha 2016; Fernandes et al. 2012; Ostermann et al. 2016). Given the above, the aim of this paper was to analyze potential drug interactions between substance misuse and psychotropic drugs to ensure safe treatment of patients with mental disorders and chemical dependence. Safe and effective use of psychotropic drugs provides the person with another form of treatment, other than psychotherapy and psychosocial activities.

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Methods

Study sample

An epidemiological, cross-sectional study was carried out using secondary data. The research was conducted at a Psychosocial Care Center for Alcohol and Other Drugs (known by the Portuguese acronym CAPS AD) located in the state of Santa Catarina, Brazil. This public health-care center treats people who are dependent on alcohol and other drugs, associated or not associated with other mental disorders.

Procedures

The target population was composed of participants aged 18 years old and over. A census method was used for the data collection. All medical records with the most recent prescriptions between September 2010 and December 2018 were included in the study. Each medical record contained numerous prescriptions, so we opted for the most recent ones to base our analysis and provide a clinical pharmacy intervention. All data were collected using medical records. Excluded were persons younger than 18 years of age, those who were not prescribed psychotropic drugs, and those who did not take the prescribed psychotropics or who requested psychiatric hospitalization only. Cases where handwriting was illegible in the medical record, and cases that were attended at the care center but did not return for the first appointment with the psychiatrist were also excluded.

Measures

The data collection using documentary research in the medical records was performed in three phases, and preserved the anonymity of the participants. In the first phase, the physical records containing sociodemographic and clinical variables filed at the care center were examined. The collected information encompassed the patient's age at admission (first service), gender, education, hospitalizations, treatment length in months, psychoactive drugs used, chemical dependence, adverse drug reactions reported by the participants, and participation in the activities developed at the care center, called therapeutic workshops.

In the second phase of the study, an analysis of the dosage of the most recent psychotropic drugs prescribed for each patient was made. Psychotropic drug dosages were categorized as "adequate" and "not adequate," according to the patient's diagnosis and profile. A single psychotropic drug that presented inadequate dosage determined the medical record to be inadequate, regardless of how many psychotropic drugs were prescribed. Dosage was defined as inadequate where a psychotropic medication was prescribed without dosage instructions, where the dosage did not accord with patient weight and age, or where the dosage was illegible, written in a non-existent concentration, or given in fractions of a tablet or capsule. Also defined as inadequate were prescriptions with longer duration than indicated (risk of toxicity), with an incorrect drug administration schedule, prescribed using abbreviations or with the observation "if necessary." Last, prescriptions of the same drug more than once, but with equal concentrations and corresponding names (brand, generic, similar, reference), were regarded as inadequate.

In the third phase of the study, psychotropic drug interactions were identified by using *Medscape Drug Interaction Checker, Drug Interactions Checker for Drugs, Food & Alcohol*, and *Micromedex* online databases. These databases provide a list of drugs with information on the therapeutic indication, and drug interactions are identified and classified. In this study, interactions were classified by clinical risk and mechanism of action. The Medscape Drug Interaction Checker ranks the interactions according to the drug mechanism of action, whereas the Drug Interactions Checker for Drugs, Food & Alcohol ranks the interactions according to clinical risks. To confirm the results found in both databases, we consulted the *Micromedex* database, which classifies drug interactions according to clinical risk and mechanism of action.

Regarding clinical risks, based on the Micromedex database and on a previous study (Cruciol-Souza and Thomson 2006), interactions were classified as contraindicated, major, moderate, and minor. Interactions were classified as contraindicated when medicines should not be used concomitantly. Major interactions were those that may be life-threatening and/or require medical intervention to minimize or prevent serious adverse effects. Moderate interactions were those that may result in exacerbation of the patient's condition and/or require a change in therapy. Minor interactions were those that may limit the clinical effects. Manifestations may include an increase in the frequency or severity of side effects, but usually do not require a major change in therapy (Cedraz and Junior 2014). If there was more than one drug interaction in the same participant's medical record, this was determined, as a whole, by the clinical risk found in the interaction of greatest impact to the patient.

As for the mechanism of action, they were classified into pharmacokinetic and pharmacodynamic interactions. When alterations occur because of the interference with drug absorption, distribution, metabolism, and/or excretion, it is said to be a pharmacokinetic interaction. When changes occur in the drug effect because of increased

activity (synergism) or decreased activity and/or activity cancellation (antagonism), it is said to be a pharmacodynamic interaction (Cedraz and Junior 2014). If there was more than one drug interaction with different mechanisms of action in the same medical record of the participant, this, as a whole, was determined by the mechanism of action that was most frequent among all interactions found in the most recent prescribed drugs. If there were only two interactions, it was considered the interaction action mechanism that had the highest clinical risk for the patient. Thus, clinical risks and mechanisms of action were analyzed for each psychotropic drug by reviewing the patient's medical record to identify drug interactions. All study procedures were approved by the Research Ethics Committee of the University of Southern Santa Catarina on October 24, 2018 (Opinion No. 2 979 024).

Statistical analysis

The collected data were entered into the EpiData software, version 3.1. Statistical analysis was performed using the SPSS software v.21.0 (IBM Armonk, New York, USA).

Numerical variables were expressed as the mean and standard deviation (SD), and the nominal variables were presented as absolute and proportional values. Prevalence ratios (PR) were calculated for independent variables, and drug interactions found in the medication prescriptions, crude analysis and, subsequently, adjusted for potential confounding variables, using modified Poisson regression models. Confounding factors were selected among variables associated with medication discrepancy, in the bivariate analysis. A P-value <0.05 was considered statistically significant.

Results

There were 2,322 patients treated at the mental health-care center between 2010 and

2018. Of these, 1,302 were excluded from the survey for different reasons: 77 patients did not take the prescribed psychotropics drugs, 165 requested psychiatric hospitalization only, 222 patients were younger than 18 years of age, 409 were not prescribed psychotropic drugs for treatment, and 429 patients were attended at the care center, but did not return for the first appointment with the psychiatrist, resulting in 1,020 final participants in the present study.

The mean age of the study participants was 34 years (range 18–75 years). Average years of schooling was 8 years (range 1–16 years). Of the 1,020 participants surveyed, 517 (50.7%) were referred to psychiatric hospitals by the surveyed mental health-care center.

Adverse reactions to psychotropic drugs were reported by 110 (10.9%) participants to health-care professionals, and noted in their medical records. Among the adverse reactions reported, 42 (4.1%) indicated insomnia, 14 (1.4%) headache, 13 (1.3%) loss of appetite, 9 (0.9%) weight gain, 8 (0.8%) excessive sleepiness, 6 (0.6%) erectile dysfunction, 6 (0.6%) intestinal discomfort, 6 (0.6%) nausea and vomiting, 3 (0.3%) pruritus, and 3 (0.3%) reported weight loss.

Between 2010 and 2018, a total of 3,583 prescriptions were dispensed to the 1,020 surveyed patients. The medications were grouped into pharmacological classes. The dispensation frequency is shown in Figure 1, considering that each patient could take drugs belonging to more than one pharmacological class. Less frequently prescribed drugs were grouped into other drugs, namely: alprazolam, clomipramine, duloxetine, phenobarbital, lamotrigine, nortriptyline, oxcarbazepine, ritalin, and ziprasidone.

Of the 1,020 participants, 613 (60.1%) had inadequately dosed psychotropic drugs according to the criteria adopted in this study to evaluate the dosage of the most recent psychotropic drugs prescribed for each user. In addition, there were psychotropic drug interactions in 779 (76.4%) participants. Assessment of all prescriptions (3,593) for the 1,020 participants in this study revealed a prevalence of 64% interactions of psychotropic drugs taken by each participant, totaling 2,292 drug interactions. For a psychotropic drug interaction to occur, at least two psychotropic drugs must be prescribed. More than one drug interaction was found for each participant's medical record, totaling 2,292 interactions.

In this study, the 779 participants presented 2,292 interactions, of which 136 (6.0%) had minor clinical risk, 537 (23.4%) had moderate risk, and 1,619 (70.6%) had major clinical risk for the patient, totaling 172 different combinations. Of these 172 interactions, 128 were classified as pharmacokinetic and 44 as pharmacodynamic, according to their mechanism of action.

The number of drug interactions found in each participant's medical record ranged from 1 to 40 different drug interactions. Of the total medical records, 326 (32.0%) had one interaction, 126 (12.4%) had two interactions, 123 (12.1%) had three interactions, 64 (6.3%) had four interactions, 31 (3.0%) had six interactions, and 19 (1.9%) had seven interactions. Other interactions in the same participant's medical record accounted for 32.3%. The association between the study participants' sociodemographic and clinical variables and the drug interaction outcome variable is shown in Table 1. It is worth mentioning that a participant may have more than one type of mental disorder, as well as more than one type of substance dependence.

Regarding the frequency of drug interactions, of the 779 study participants, 660 (84.7%) had interactions with major

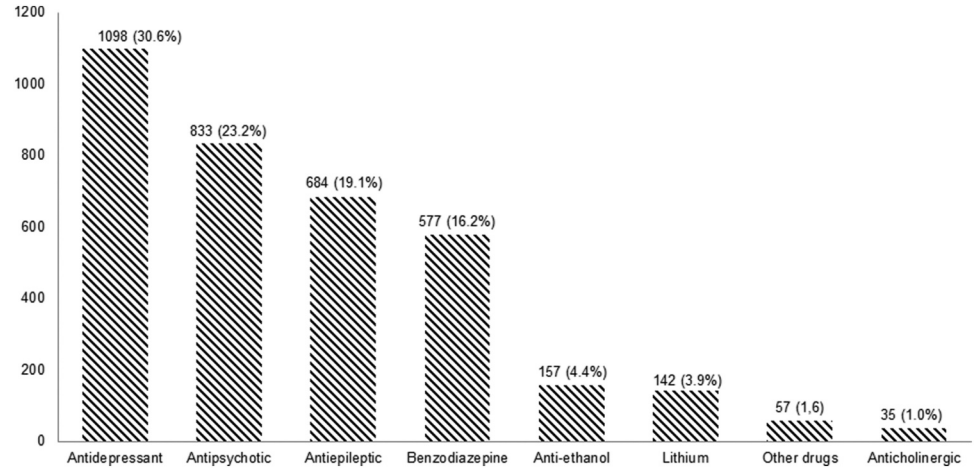

Figure 1.

Table 1. General and clinical characteristics of the 779 study participants and their statistical association with drug interactions.

		Drug interactions			
Characteristics	Total n (%)	Crude PR	P-value	Adjusted PR	P-value***
Gender					
Male	617 (79.2)	1.07 (1.01–1.12)	**0.014**	1.06 (1.01–1.12)	**0.024**
Female	162 (20.8)	1.00		1.00	
Age (years)					
18–24	143 (18.4)	0.97 (0.86–1.10)	0.665		
25–34	242 (31.1)	1.00 (0.89–1.13)	0.948		
35–44	199 (25.5)	0.97 (0.85–1.09)	0.571		
45–59	169 (21.7)	0.98 (0.97–1.11)	0.747		
≥60	26 (3.3)	1.00			
Treatment length (months)					
1–6	381 (48.9)	1.18 (1.10–1.27)	**<0.001**	1.15 (1.07–1.24)	**<0.001**
7–12	236 (30.3)	1.12 (1.04–1.20)	**0.005**	1.11 (1.02–1.19)	**0.010**
13–24	108 (13.9)	1.08 (1.00–1.18)	0.066	1.09 (1.00–1.18)	0.058
>24	54 (6.9)	1.00		1.00	
Therapeutic Workshop					
Yes	405 (52.0)	0.93 (0.89–0.96)	**<0.001**	0.95 (0.91–0.99)	**0.008**
No	374 (48.0)	1.00			
Substance dependence					
Alcohol	384 (49.3)	1.03 (0.99–1.07)	0.169		
Cocaine	528 (67.8)	1.00 (0.95–1.04)	0.871		
Crack	485 (62.3)	0.99 (0.94–1.03)	0.486		
Ecstasy	51 (6.5)	1.00 (0.92–1.09)	0.960		
LSD*	62 (8.0)	1.00 (0.92–1.08)	0.970		
Marijuana	445 (57.1)	0.97 (0.93–1.01)	0.187		
Morphine	19 (2.4)	0.92 (0.81–1.04)	0.188		
Nicotine	253 (32.5)	0.94 (0.90–0.98)	**0.007**	0.96 (0.91–0.99)	**0.042**
Solvents	90 (11.6)	0.98 (0.92–1.05)	0.606		
Mental disorders					
Behavior disorder	383 (49.2)	1.01 (0.97–1.05)	0.693		
Anxiety disorder	436 (56.0)	0.97 (0.93–1.01)	0.117		
Depression	430 (55.2)	0.93 (0.90–0.97)	**0.002**	0.97 (0.93–1.01)	0.154
Schizophrenia	104 (13.4)	0.96 (0.90–1.02)	0.230		
Bipolar disorder	182 (23.4)	0.96 (0.91–1.01)	0.083		

*Behavior changes do not include a specific psychiatric diagnosis, but include suicidal thoughts and attempts, mood swings, exaggerated, depressed, or anxious emotions.
**LSD: lysergic acid diethylamide;
***Poisson regression with a robust error variance.
PR = prevalence ratio

clinical risk, 88 (11.3%) with moderate clinical risk, and 31 (4.0%) with minor clinical risk. No interactions classified as contraindicated were found in the participants' records. Regarding the mechanism of action, 531 (68.2%) records of participants had pharmacokinetic interactions and 248 (31.8%) had pharmacodynamic interactions.

The flowchart in Figure 2 shows the classification of the data obtained for the outcomes of interest.

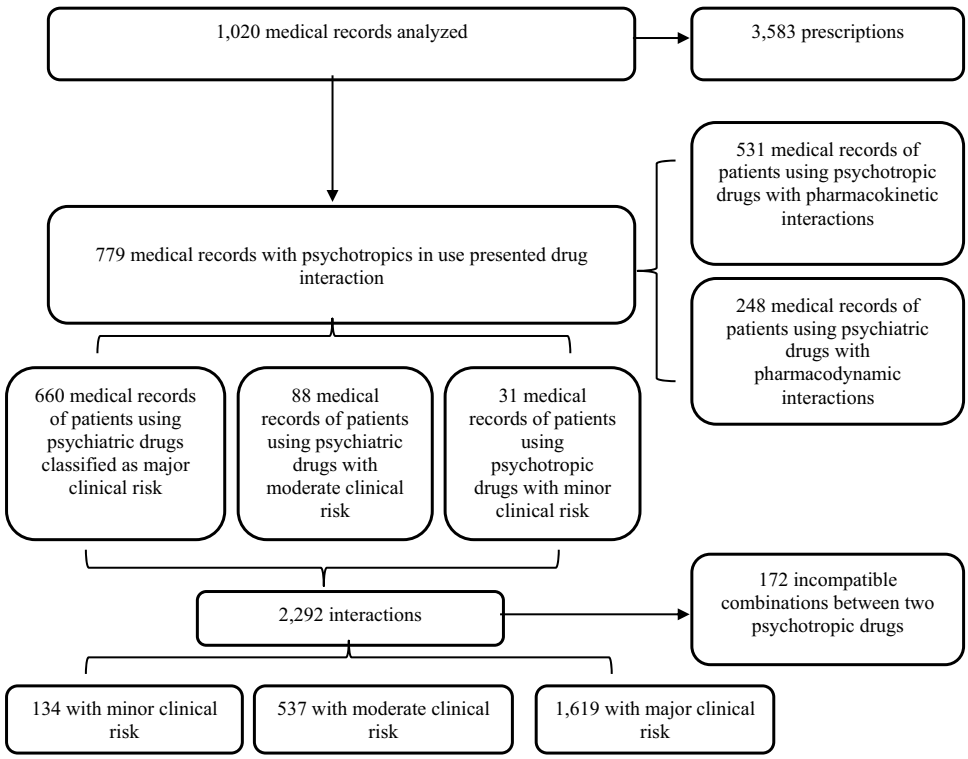

Figure 2. Flowchart of data obtained from medical records of the study participants.

Table 2 presents the frequency distribution of the 1,619 interactions with major clinical risk for the participant. Drug interaction frequency lower than four was grouped as other interactions.

Discussion

In this study, drug interactions had a high prevalence and revealed a positive association with male subjects. A shorter length of treatment with psychotropic drugs was a risk factor for developing drug interactions, whereas participation in behavioral therapies was a protective factor. The frequency of interactions between different psychotropic drug classes was shown according to the clinical risk to the patient and the interaction mechanism of action, which makes this research one of the first studies to explicitly reveal which psychotropic drugs are being prescribed concurrently and in an inadequate manner.

The sociodemographic profile found for the participants of this study was similar to that of other studies conducted on different drug using populations and/or patients with mental disorders. A predominance of males in mental health-care centers has been reported in other studies (Araujo et al. 2012; Castro Neto, Silva, and Figueiroa 2016; Conceição et al. 2018; Faria and Schneider 2009). Men, as compared to women, may more often distrust the efficacy of psychotherapy and take more than one psychotropic drug to treat their condition (Moura et al. 2016; Neto et al. 2015), which may explain why drug interactions are positively associated with male gender in this study.

In this study, the shorter the treatment length of participants using psychotropic drugs, the greater the risk of developing a drug interaction. When a person begins treatment for substance addiction or any mental disorder, he or she is often already using other previously prescribed psychotropic drugs, and it is known that no prescribed psychotropic drug should be abruptly withdrawn from the patient's therapy regimen. In addition, another explanation is that at the beginning of treatment there are more indications of different psychotropic drugs to properly analyze how the patient will react to each psychotropic drug, and thus choose the one that the patient has most likely adaptation to.

The main drug interactions in this study were categorized as major clinical risk for the patient, which brings up clinical concerns, as these potential drug interactions may develop serious adverse effects attributed to pharmacokinetic or pharmacodynamic activity (Balen et al. 2017). Pharmacokinetic interactions tend to develop liver damage, such as the interference of the drug's first-pass metabolism, toxicity, and kidney failure, because these interactions promote alterations in the absorption, distribution, biotransformation, or excretion of the drug (Cruciol-Souza and Thomson 2006). Pharmacodynamic interactions are more

Table 2. Frequency of drug interactions between psychoactive drugs with major clinical risk and their mechanisms of action.

Interactions	n	MA	Interactions	n	MA	Interactions	n	MA
Carbamazepine+Fluoxetine	88	C	Amitriptyline+Imipramine	18	C	Bromazepam+Methotrimeprazine	7	C
Carbamazepine+Chlorpromazine	76	C	Chlorpromazine+Haloperidol	17	D	Carbamazepine+Trazodone	7	C
Chlorpromazine+Fluoxetine	70	C	Fluoxetine+Paroxetine	17	C	Diazepam+Phenytoin	7	C
Fluoxetine+Risperidone	50	C	Fluoxetine+Sertraline	16	D	Fluoxetine+Olanzapine	7	C
Methotrimeprazine+Lithium	48	D	Bupropion+Imipramine	15	D	Amitriptyline+Paroxetine	6	D
Chlorpromazine+Risperidone	46	C	Lithium+Paroxetine	15	C	Bromazepam+Clonazepam	6	C
Fluoxetine+Lithium	45	D	Fluoxetine+Haloperidol	14	C	Bupropion+Sertraline	6	D
Amitriptyline+Fluoxetine	42	C	Amitriptyline+Lithium	13	D	Carbamazepine+Olanzapine	6	C
Citalopram+Fluoxetine	38	C	Haloperidol+Risperidone	12	C	Clonazepam+Zolpidem	6	D
Citalopram+Risperidone	36	C	Citalopram+Paroxetine	11	C	Fluoxetine+Trazodone	6	C
Amitriptyline+Citalopram	35	C	Methotrimeprazine+Sertraline	11	C	Fluoxetine+Venlafaxine	6	D
Carbamazepine+Clonazepam	33	C	Phenytoin+Risperidone	10	C	Paroxetine+Sertraline	6	D
Lithium+Risperidone	33	D	Amitriptyline+Bupropion	9	D	Amitriptyline+Quetiapine	5	C
Chlorpromazine+Lithium	32	D	Chlorpromazine+Zolpidem	9	C	Bupropion+Escitalopram	5	D
Fluoxetine+Imipramine	30	C	Haloperidol+Lithium	9	C	Bupropion+Phenytoin	5	C
Chlorpromazine+Imipramine	28	C	Imipramine+Paroxetine	9	D	Bupropion+Venlafaxine	5	C
Paroxetine+Risperidone	28	C	Methotrimeprazine+Zolpidem	9	C	Carbamazepine+Escitalopram	5	C
Bupropion+Carbamazepine	26	C	Paroxetine+Trazodone	9	C	Carbamazepine+Quetiapine	5	C
Amitriptlyne+Risperidone	25	C	Paroxetine+Venlafaxine	9	D	Citalopram+Sertraline	5	C
Risperidone+Sertraline	25	C	Amitriptyline+Haloperidol	8	C	Escitalopram+Risperidone	5	C
Amitriptyline+Chlorpromazine	24	C	Amitriptyline+Sertraline	8	D	Bromazepam+Topiramate	4	C
Imipramine+Risperidone	24	C	Amitriptyline+Venlafaxine	8	C	Bupropion+Haloperidol	4	D
Carbamazepine+Sertraline	22	D	Bromazepam+Diazepam	8	C	Citalopram+Escitalopram	4	D
Citalopram+Lithium	22	D	Bupropion+Paroxetine	8	D	Citalopram+Haloperidol Decanoate	4	C
Bupropion+Fluoxetine	21	D	Carbamazepine+Phenytoin	8	C	Chlorpromazine+Quetiapine	4	D
Citalopram+Topiramate	21	C	Chlorpromazine+Sertraline	8	C	Chlorpromazine+Trazodone	4	C
Imipramine+Lithium	21	D	Diazepam+Zolpidem	8	C	Escitalopram+Quetiapine	4	D
Bupropion+Citalopram	20	D	Imipramine+Sertraline	8	D	Haloperidol+Imipramine	4	C
Bupropion+Risperidone	20	D	Topiramate+Zolpidem	8	C	Haloperidol Decanoate+Paroxetine	4	D
Citalopram+Chlorpromazine	20	C	Bromazepam+Chlorpromazine	7	C	Lithium+Olanzapine	4	D
						Other drug interactions	95	C/D

n: number of prescriptions; MA: mechanism of action; C: pharmacokinetics; D: pharmacodynamics, (n = 1,619 medical prescriptions).

prone to lead the patient to death, as they occur at the sites of action of the drugs, by potentiating or reducing the effect of one of the drugs (Cedraz and Junior 2014; Ritter et al. 2016).

Biperiden, indicated for the treatment of extrapyramidal effects secondary to antipsychotic use, was the only prescribed anticholinergic drug found in this study. The use of biperiden is common in patients on antipsychotics, as is the case with risperidone, although concomitant use of biperiden and risperidone increases plasma concentrations of the 9-hydroxyrisperidone metabolite, and may cause side effects. Biperiden is recommended only after the onset of an extrapyramidal effect, its use is provisional (Schoretsanitis et al. 2016), and the duration of use should be reviewed during treatment.

Therapeutic workshops, also known as behavioral therapies, were protective against the development of drug interactions. These behavioral therapies are considered non-pharmacological group interventions aimed at subjective expression, social reintegration, autonomy, citizenship, reduction of psychopathological symptoms, and decline of harmful effects (Souza and Pinheiro 2012). This practice is not only developed in Brazil, but also in the United States, where it is considered the most important therapeutic resource for community services (Johnson, Gibbons, and Crits-Christoph 2011; Nascimento and Marques 2019).

Although substance dependence was not associated with psychotropic drug interactions, except for nicotine, which was a protective factor, there was no scientific basis for such an association. However, one of the possible causes for nicotine to act as a protection against the development of drug interactions would be that these study participants did not use many psychotropic drugs of different classes. According to the *Micromedex* database, alcohol and nicotine interact with various psychotropic drugs, especially benzodiazepines and antidepressants (Redonnet et al. 2012). It is quite common for persons with alcohol dependence to use several psychopharmacological classes due to anxiety, stress, depression, and other behavior changes (Dawson et al. 2015). In this study, however, participants who were dependent on nicotine used fewer pharmacological classes of psychotropics. Therefore, when compared to other drugs of abuse, nicotine was considered a protective factor, given that in the case of other drugs of abuse, there was a greater diversity in the prescription of psychotropic classes, and consequently, a larger number of drug interactions.

A high prevalence of drug interactions was found in this study. Several antipsychotic medications had unwanted drug interactions with antidepressants and other psychotropic drugs, causing dizziness, toxicity, tolerance, memory impairment, insomnia, and liver and kidney damage (Kishimoto et al. 2013; Santos et al. 2016). In a study

conducted at a specialized mental health-care center, out of 131 prescriptions, there was drug interaction with only one psychotropic drug in 38 prescriptions, with two psychotropic drugs in 42 prescriptions, with three psychotropic drugs in 38 prescriptions, and with four or more psychotropic drugs in 13 prescriptions. All reviewed prescriptions showed drug interactions, and most of them could lead to a severe adverse reaction (Fernandes et al. 2012).

Antidepressants had a large number of interactions with other psychotropic drugs, related to prescribing frequency. Roughead, Mcdermott, and Gilbert (2007) highlighted the need for continuous pharmacovigilance on the use of psychotropic drug combinations in face of the increasing use of antidepressants and a high level of potentially preventable interactions. Benzodiazepines, antidepressants, and antipsychotics pose risk of drug interaction when combined with more than one drug of the same class, or when an association of different drug classes occurs. These three psychopharmacological classes, in particular, are commonly used for severely ill patients. At the same time, these drugs should be carefully selected as these patients are at high risk of undesirable drug interactions. Phenytoin and Topiramate are two antiepileptic medications that showed interactions with other psychiatric drugs of major clinical risk to the patient in this study. Interactions between antiepileptics and psychotropic drugs usually involve second- and third-generation antiepileptics. In general, they are pharmacokinetic interactions, as antiepileptics are minimally bound to blood albumin (as is the case with Topiramate) and are mainly renally excreted or metabolized by cytochrome P450 (Landmark and Patsalos 2010). Nevertheless, a recent systematic review (Leon and Spina 2018) has stated that there is little description of pharmacodynamic interactions between antiepileptics and other psychotropic drugs. In their review, they mentioned pharmacodynamic interactions between antiepileptics with 20 antidepressants and 17 antipsychotics, 4 with benzodiazepines, and 5 with lithium. In this study, lithium carbonate was a psychopharmaceutical drug that presented major clinical risk interactions, and pharmacokinetic and pharmacodynamic mechanism of action with other psychotropic drugs. Promoting the rational use of psychotropic drugs remains a challenge worldwide. In Australia, for example, there are several studies on the use of psychotropic drugs, including antidepressants, benzodiazepines, and antipsychotics. Inadequate and high-rate home-use psychotropics for elderly Australians have been reported over the past 20 years, and this problem remains unresolved. When and how the increase in prescription of psychotropic drugs began is still unclear (Westbury et al. 2018). Lurie and Lee (1991) have contextualized the issue and alerted physicians to detect rare adverse drug reactions by monitoring actual drug use, assessing optimal dosage patterns, detecting drug interactions, and monitoring therapeutic reasons for the use among special populations, such as drug addicts. Furthermore, they should detect the trend for abuse of psychiatric drugs, identify overdose characteristics of psychiatric drugs, and additional indications, such as integrative and complementary practices.

Some study limitations should be considered. Medical records do not always a detailed report of the diagnosis and treatment was provided. Even though information is filled in by healthcare professionals, not all information is written down in the patient's record, especially when it comes to health professionals who work at the Brazil's Unified Health System (SUS), where demand is high and resources are scarce for completion of the medical records with all information. Studies with a longitudinal design that allow patients to be followed may address this limitation. Furthermore, our analysis of the prescriptions did not consider the patient's clinical condition and the reasons for the physician's decision to prescribe particular medications.

This study presented alternatives for identifying drug interactions between adverse reactions, and demonstrated their impact related to the difficulty healthcare professionals encounter in dealing with psychotropic drugs. It is important to go beyond the identification of the patient's clinical profile, and acquire knowledge of pharmacology, pharmacokinetics, and pharmacodynamics in order to promote the rational use of psychotropic drugs. That is the most effective way to identify potential drug interactions, as well as to properly manage potential adverse drug reactions that may be triggered by the use of several psychotropic drugs. The implementation of clinical pharmacy services in outpatient clinics, hospitals, and mental health-care centers can be considered the most effective alternative to avoid adverse reactions, including drug interactions, because the clinical pharmacist is qualified for such practice. In addition, pharmacists are ready to assist the entire multidisciplinary team involved in the treatment of patients with mental disorders or substance dependence, and provide pharmacological treatment.

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