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Article

Potential interactions between psychotropic drugs and alcohol and tobacco dependence

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The aim of this study was to identify and analyze the potential interactions between psychotropic drugs and alcohol and tobacco addiction. A cross-sectional study was carried out on secondary data collection in a Center for Psychosocial Care in Alcohol and Other Drugs. Subjects aged 18 years old and over, with alcohol and tobacco dependence, who were taking psychotherapies were included. Medical records with the most recent prescriptions were reviewed. Potential interactions between psychotropic drugs and alcohol and tobacco were analyzed using the Micromedex database and stratified according to clinical risks and mechanisms of action. The Pearson's Chi-square test was used to find significant associations between the variables of interest. The significance level was set at 5%. Between the 2010–2018 period, 2,322 subjects were treated at the care center. Of these, 1,020 fulfilled the inclusion criteria, out of whom 515 (50.5%) were dependent on alcohol and 310 (30.4%) were dependent on tobacco. We found 1,099 potential interactions between psychotropic drugs and alcohol and 160 potential interactions between psychotropic drugs and tobacco. In relation to alcohol dependence, psychotropic drugs interacted largely with moderate clinical risk, and pharmacokinetic mechanisms of action. In relation to tobacco dependence, high clinical risk interactions and pharmacodynamic mechanisms of action predominated.

Keywords: Alcoholism. Drug interactions. Pharmacoepidemiology. Tobacco use disorder. Substance-related disorders.

INTRODUCTION

Psychopharmacology has brought numerous therapeutic benefits to people with addictive disorders. However, adverse effects, such as tolerance, dependence, weight gain, and memory impairment are observed, especially when using selective serotonin reuptake inhibitor antidepressants, antipsychotics, and benzodiazepines (Santos *et al*., 2016; Weintraub, 2017).

Psychotropic drugs are the most commonly prescribed medications in clinical practice (Guimarães *et al*., 2018). Like any other drug, psychotropic drugs have consequences. Therefore, before using them, the potential risk-benefit ratio must be evaluated, and other resources must be properly explored (Bezerra *et al*., 2016; Frey *et al*., 2018). Adverse drug events include drug adverse reactions and errors (Alvim *et al*., 2015). The World Health Organization defines adverse reaction as any response to a medicine which is noxious and unintended, and which occurs at doses normally used in man for prophylaxis, diagnosis, therapy of diseases or for the modification of physiological functions (Pan American Health Organization, 2005).

Potential Drug-drug interactions are the most frequent adverse events. Over 30% of adverse events are caused by drug-drug interactions, which results in significant morbidity every year (Iyer *et al*., 2014). Drug-drug interactions are adverse drug events corresponding

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to pharmacological responses in which the effects of one or more drugs are changed by simultaneous or previous administration of other medications. The pharmacological response may also be altered by concomitant used of drugs and food, drink or some environmental chemical agent (Moura, Acurcio, Belo, 2009).

Treatment with psychotropic drugs is frequent in the health area for the management of several diseases that affect people, such as in the treatment of additive behaviors, including alcohol, tobacco, and other drugs of abuse (Takayanagi *et al*., 2014). Alcohol dependence is a major public health issue, given its high prevalence and socioeconomic and personal damages (Redonnet *et al*., 2012). Therefore, assessment of alcohol dependence and other psychoactive substances should become an integral part of mental health interventions, especially in patients under psychopharmacological treatment for chemical dependence (Skogen *et al*., 2014).

Smoking prevalence rates and mortality due to tobacco dependence (nicotine) are very high, which is another public health issue (Mirra *et al*., 2010). It is estimated that tobacco smoking is currently responsible for 5 million deaths worldwide each year. Of these, 200,000 deaths per year occur in Brazil (World Health Organization, 2008). Prevention measures should be addressed simultaneously, since tobacco dependence associated with alcohol and other drugs of abuse is increasing persistently (Guerzoni *et al*., 2018; Maideen, 2019). Both alcohol and tobacco are licit psychoactive substances in almost all countries, which contributes to the emergence of different diseases (Rosa *et al*., 2014).

The objective of this study was to identify and analyze the potential interactions between psychotropic drugs and alcohol and tobacco addiction, according to the clinical risks for patients and mechanism of action and pharmacokinetic and pharmacodynamic drug-drug interaction. The impact of this study will show alternatives to ensure patient safety using this pharmacological class as a form of treatment for alcohol and tobacco addiction. A safe and effective use of psychotropic drugs will provide an alternative treatment for chemical dependency in addition to psychotherapy and psychosocial activities.

MATERIAL AND METHODS

Study Sample

An epidemiological, cross-sectional study was carried out using secondary data. The research was conducted at a Psychosocial Care Center in Alcohol and Other Drugs (known by the Portuguese acronym CAPS AD) located in southern Brazil. This public health care center is a reference in the treatment of people who are dependent on alcohol and other drugs of abuse, associated or not associated with other mental disorders. The patients are treated by a multidisciplinary team in this care center.

Procedures and inclusion and exclusion criteria

The target population was composed of participants aged 18 years old and over. A census method was used for data collection. All medical records with the most recent prescriptions between September 2010 and December 2018 were included in the study. The medical records and prescriptions that were not legibly or did not have complete data related to the psychopharmacological treatment were excluded from the study. Dependence on illicit drug abuse was not assessed in this study.

Measures

The data collection using documentary research in the medical records was performed in two 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 (psychiatric comorbidities, according to the International Statistical Classification of Diseases and Related Health Problems - ICD). The collected information encompassed patient's age at admission (first service), gender, skin color, treatment length in months, psychotropic drugs used, and chemical dependence.

In the second phase, the possible interactions between psychotropic drugs and alcohol and tobacco were identified, supported by the online *Micromedex* database. This tool categorizes potential drug interactions according to the clinical risk for the patient and the

mechanism of action. Based on a previous study (Cruciol-Souza, Thomson, 2006) and according to the *Micromedex* database, clinical risks were categorized as Contraindicated, Major, Moderate, and Minor. Regarding the mechanism of action, they were categorized into pharmacokinetics and pharmacodynamics.

Analyses

The collected data were entered into the *EpiData* v.3.1 software. Statistical analysis was performed by using the IBM *SPSS* v.21 statistics software (IBM, Armonk, New York, USA). Descriptive epidemiology was used for the presentation of the data. Quantitative variables were expressed as measures of central tendency and dispersion, whereas qualitative variables were expressed as proportions. The Pearson's Chi-square test was used to test significant associations between each independent variable and the outcome studied. The significance level was set at 5%.

Ethical aspects

This study was approved by the Research Ethics Committee of the University of Southern Santa Catarina on October 24, 2018 (Opinion No. 2 979 024).

RESULTS

Within the 2010–2018 period, 2,322 people attending the CAPS AD were scrutinized, of whom 1,302 were excluded from the study for the following 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, which resulted in 1,020 study participants.

Of the total number of participants, the psychiatric comorbidities were the following: 383 (49.2%) had behavior disorders (such as suicidal thoughts and attempts, mood swings, depressing or anxious emotions), 436 (56.0%) had anxiety disorders, 430 (55.2%) had depression, 104 (13.4%) presented schizophrenia, and 182 (23.4%) had bipolar disorders.

The median age of the participants was 34 years (SD = 11.6), ranging from 18 to 75 years. Table I presents the characteristics of the study participants and their association with alcohol and tobacco dependence.

TABLE I - Characteristics of surveyed subjects regarding alcohol and tobacco dependence and its association with demographic and clinical features

Characteristics	Total n (%)	Alcohol dependence n (%)	p-value	Tobacco dependence n (%)	p-value
Gender			0.057		0.266
Male	824 (80.8)	428 (83.1)		244 (78.7)	
Female	196 (19.2)	87 (16.9)		66 (21.3)	
Ages (years)			**<0.001**		0.939
18–24	184 (18.0)	57 (11.1)		52 (16.8)	
25–34	328 (32.2)	146 (28.3)		100 (32.3)	
35–44	253 (24.8)	136 (26.4)		76 (24.5)	
45–59	220 (21.6)	149 (28.9)		71 (22.9)	
>=60	35 (3.4)	27 (5.3)		11 (3.5)	
Ethnicity			0.517		0.866

TABLE I - Characteristics of surveyed subjects regarding alcohol and tobacco dependence and its association with demographic and clinical features

Characteristics	Total n (%)	Alcohol dependence n (%)	p-value	Tobacco dependence n (%)	p-value
White	867 (85.0)	444 (86.2)		266 (85.8)	
Black	110 (10.8)	52 (10.1)		31 (10.0)	
Brown	43 (4.2)	19 (3.7)		13 (4.2)	
Treatment length (months)			**0.005**		0.086
1–6	531 (52.1)	245 (47.5)		146 (47.1)	
7–12	299 (29.3)	157 (30.5)		94 (30.4)	
13–24	131 (12.8)	73 (14.2)		46 (14.8)	
>24	59 (5.8)	40 (7.8)		24 (7.7)	

n: number of participants, %: percentage, p-value: Pearson's Chi-square.

Among the 1,020 participants, 515 (50.5%) were dependent on alcohol, 310 (30.4%) were dependent on tobacco, and 238 (46.2%) were dependent on both drugs. Given the fact that more than one psychotropic drug was prescribed in the medical records for each patient with alcohol or tobacco dependence, we found 1,099 (215.5%) potential interactions between psychotropic drugs and alcohol and 160 (51.6%) potential interactions between psychotropic drugs and tobacco. Table II shows the frequency of the prescriptions with potential drug interactions between psychotropic drugs and alcohol and tobacco, stratified according to clinical risks and mechanisms of action.

TABLE II - Frequency of prescriptions with drug interactions between psychotropics drugs and alcohol and tobacco

Psychotropic drug	Prescriptions with alcohol interactions n (%)	Clinical Risk*	Mechanism of action*	Possible outcome*	Management*
Amitriptyline	69 (6.3)	Moderate	C	Additive impairment of motor skills.	Dosage adjustments
Bupropion	51 (4.6)	Major	C	Additive CNS depression.	Avoid alcohol during treatment
Bromazepam	15 (1.4)	Major	C	Additive CNS depression.	Avoid alcohol during treatment
Citalopram	86 (7.8)	Moderate	C	Liver damage. Additive CNS depression.	Avoid or limit consumption of alcohol
Clonazepam	66 (6.0)	Major	C	Increase sedation	Avoid alcohol during benzodiazepine therapy
Chlorpromazine	129 (11.7)	Moderate	C	Either increases toxicity of the other by pharmacodynamic synergism	Avoid alcohol during treatment
Diazepam	189 (17.2)	Moderate	C	Increase sedation	Avoid alcohol during benzodiazepine therapy

TABLE II - Frequency of prescriptions with drug interactions between psychotropics drugs and alcohol and tobacco

Psychotropic drug	Prescriptions with alcohol interactions n (%)	Clinical Risk*	Mechanism of action*	Possible outcome*	Management*
Disulfiram	81 (7.4)	Contraindicated	C	Liver damage. Increase the level or effect of ethanol by affecting hepatic enzyme CYP2E1 metabolism. Disulfiram increases toxicity of ethanol by decreasing metabolism. Enhanced CNS & cardiac toxicity	Should be avoided
Escitalopram	10 (1.0)	Moderate	D	Additive CNS depression and/or impairment of judgment, thinking, and psychomotor skills.	Avoid or limit consumption of alcohol
Imipramine	60 (5.4)	Moderate	D	Toxicity. Increase sedation	Alcoholics who have undergone detoxification should be monitored for decreased therapy efficacy
Lorazepam	15 (1.4)	Moderate	D	Increase sedation	Avoid alcohol during benzodiazepine therapy
Methotrimeprazine	116 (10.5)	Moderate	D	Additive CNS depression and psychomotor impairment	Avoid alcohol during treatment
Olanzapine	05 (0.4)	Moderate	D	Either increases toxicity of the other by pharmacodynamic synergism. Additive CNS depression	Patients receiving CNS-active agents should be advised to avoid or limit consumption of alcohol
Paroxetine	38 (3.4)	Minor	D	Additive CNS depression and/ or impairment of judgment, thinking, and psychomotor skills	Avoid alcohol during treatment
Phenytoin	14 (1.3)	Moderate	D	Decreased phenytoin levels may be seen with chronic alcohol ingestion	Monitor symptoms of toxicity, drowsiness, visual disturbances, change in mental status, nausea, or ataxia
Quetiapine	12 (1.1)	Moderate	D	Either increases toxicity of the other by pharmacodynamic synergism. Additive CNS depression.	Avoid alcohol during treatment
Sertraline	41 (3.7)	Moderate	D	Liver damage. Additive CNS depression and/or impairment of judgment, thinking, and psychomotor skills	Avoid or limit consumption of alcohol
Topiramate	59 (5.4)	Contraindicated	D	Increase sedation. Dizziness or drowsiness. Excessive somnolence and other forms of nervous system depression.	The patient should be informed to avoid alcohol or to use caution if these agents are co-administered, especially if performing hazardous tasks such as driving or operating machinery
Venlafaxine	21 (2.0)	Minor	D	Additive CNS depression and/or impairment of judgment, thinking, and psychomotor skills.	Avoid alcohol during treatment
Zolpidem	22 (2.0)	Major	D	Either increases effects of the other by pharmacodynamic synergism. Additive CNS depression.	Avoid or limit consumption of alcohol

TABLE II - Frequency of prescriptions with drug interactions between psychotropics drugs and alcohol and tobacco

Psychotropic drug	Prescriptions with alcohol interactions n (%)	Clinical Risk*	Mechanism of action*	Possible outcome*	Management*
Psychotropic drug	**Prescriptions with tobacco interactions n (%)**	**Clinical Risk***	**Mechanism of action***	**Possible outcome***	**Management***
Amitriptyline	37 (23.1)	Major	D	Toxicity	Dosage adjustments
Chlorpromazine	76 (47.5)	Moderate	C	Kidney failure. Toxicity	Dosage adjustments
Haloperidol	16 (10.0)	Major	D	Toxicity or reducing the effect of the drug	Dosage adjustments
Haloperidol decanoate	03 (1.9)	Major	D	Toxicity or potentiating the effect of the drug	Dosage adjustments
Imipramine	24 (15.0)	Major	D	Toxicity	
Olanzapine	04 (2.5)	Major	D	Potentiating the effect of the drug	Dosage adjustments

n: number of prescriptions, %: percentage, C: Pharmacokinetic; D: Pharmacodynamic
*** According to the *Micromedex* and *Medscape* databases**

DISCUSSION

One of the characteristics of the surveyed subjects was the association between alcohol dependence and length of treatment at the care center. The longer the treatment at the care center, the lower the number of alcohol dependents. This finding emphasizes the importance of the activities carried out at mental health services, known as Therapeutic Workshops. These activities are considered as group interventions, aiming at subjective expression, social reintegration, autonomy, citizenship, reduction of psychopathological symptoms, and preventing harm to dependents (Silva, Abbad, Montezano, 2019). This method is not only developed in Brazil, but also in the United States where it is one of the most important therapeutic resources used in community services, including mental health, pharmaceutical care, and chemical dependency (Johnson, Gibbons, Crits-Christoph, 2011).

The age of alcohol dependents was another aspect that deserved attention. The more advanced the age, the higher the number of alcohol dependents. This finding was similar to those found in other studies with different populations in Brazil (Munhoz *et al*., 2017) as well as in other countries, such as Australia (Livingston, Dietze, 2016) and the United States (Dawson *et al*., 2015).

Of the 1,099 potential interactions between psychotropic drugs and alcohol, 20 psychotropic drugs interacting with alcohol were listed. Of these, disulfiram should be mentioned since it is a medication used to treat alcohol dependence, even though it is totally contraindicated for patients who have relapses during the treatment period. Naltrexone (Guerzoni *et al*., 2018) would be a pharmacological alternative to treat alcohol dependence, given that it neither interacts with alcohol, nor with other psychotropics drugs. However, naltrexone is much more expensive than disulfiram, which is why the latter is most commonly prescribed at the public health settings.

Twelve out of the 20 psychotropic drugs interacting with alcohol had a moderate clinical risk to the patient, which is worrisome. Moderate-risk drug interaction may exacerbate the patient's condition and/or require a therapy change (Cedraz, Junior, 2014). Only two psychotropic drugs had a low interaction risk, which requires caution, since they may limit the clinical effects.

Clinical manifestations may include an increase in the frequency or severity of side effects, but generally does not require a major change in therapy (Alvim *et al*., 2015; Antonelli *et al*., 2017; Cruciol-Souza, Thomson, 2006).

Assessment of the mechanisms of action of the interactions between psychotropic drugs and alcohol revealed that 19 were pharmacokinetic interactions, which again is worrisome, since pharmacokinetic interactions occur due to interference in the absorption, distribution, metabolism and/or excretion of the drug (Antonelli *et al*., 2017; Cruciol-Souza, Thomson, 2006; Guerzoni *et al*., 2018; Iyer *et al*., 2014; Stanciu *et al*., 2017).

Six psychotropic drugs were listed among the interactions between psychotropic drugs and tobacco, five of which presented a high clinical risk for the patient. High drug interactions may lead to the risk of death and/or require medical intervention to prevent or minimize serious adverse effects (Cedraz, Junior, 2014; Frey *et al*., 2018; Maideen, 2019).

As for the mechanisms of action, the interactions between psychotropic drugs and tobacco were different from those found in the interactions between psychotropic drugs and alcohol. There were five pharmacodynamic interactions, which is when there are effect modifications due to increased drug metabolism activity (synergism) or reduction or reversal (antagonism) of the effects (Bezerra *et al*., 2016; Cedraz, Junior, 2014; Johnson, Gibbons, Crits-Christoph, 2011).

Care and counseling about the proper use of psychotropic drugs are the most important therapeutic methods in community services. Group drug monitoring is the main treatment modality used to treat drug dependence in community treatment settings in the United States (Almeida *et al*., 2018; Johnson, Gibbons, Crits-Christoph, 2011; Stanciu *et al*., 2017).

The participants' abstinence status was not assessed in this study. However, it is known that the person with nicotine withdrawal has common symptoms similar to those of potential drug interactions, such as dizziness, nausea, increased heart rate, irritability, insomnia, increased appetite and difficulty concentrating (McLaughlin, Dani, Biasi, 2015). Among people with alcohol withdrawal, signs of activation of the autonomic nervous system, such as tachycardia, excessive sweating, tremors, in addition to uncontrolled activity of the central nervous system, are frequent symptoms (Becker, 2008). Contrastingly, a recent study (Voskoboinik *et al*., 2020) shows that alcohol abstinence reduces arrhythmia recurrences in patients with atrial fibrillation who drink regularly.

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, Thomson 2006). Pharmacodynamic interactions are more 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 (Bezerra *et al*., 2016; Cedraz, Junior, 2014; Johnson, Gibbons, Crits-Christoph, 2011).

Many drug associations bring benefits to psychopharmacological treatment, or are helpful in cases of dependence on alcohol or tobacco, and the clinical risk of drug interaction often prevails (Guerzoni *et al*., 2018; Maideen, 2019). Topiramate in the dosage range of 75-300 mg per day can be considered as a first-line treatment option for alcohol dependence (Guglielmo *et al*., 2015); however, according to the Micromedex and Medscape databases, topiramate is contraindicated during alcohol ingestion, and this may raise doubts, considering that an alcohol-dependent person may have relapses during treatment. The same observation is valid for the use of haloperidol and other antipsychotic drugs in tobacco-dependent people, even though further research is needed to determine the clinical associations between these drugs (Wehring *et al*., 2017).

This study emphasized the importance of training in the safe and effective use of psychotropics drugs, given the insufficient training provided during undergraduate and postgraduate programs. Continuing professional development should also review this issue. The use of databases, such as *Micromedex* or *Medscape*, allows for mental health professionals and those working with patients with alcohol and other drug dependence to identify and categorize drug-drug interactions according to clinical risks and mechanisms of action.

This study presented alternatives for identifying drug interactions between adverse events, 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.

Limitations

The data presented here should be analyzed considering some limitations: because it is a study on medical records, often not all information is jotted down to complete the patient care. This study presented potential drug interactions. Further studies are needed to monitor those surveyed to identify drug interactions. Although the information is filled out by health professionals, not all information is always written. Further studies with another epidemiological design, with patient follow-up, may be an alternative to address this limitation. For this reason, it is important to carry out longitudinal studies to evaluate this aspect. The fact that the outcomes obtained are not being compared to other databases (overlapping results) requires a further discussion of the results considering this aspect. A significant discrepancy has been observed in the classification of the severity of Drug-Drug Interaction on different databases. There are always concerns about information quality and effectiveness. Dependence on illicit drug abuse was not assessed in this study, since information on drug interactions with different types of drugs is scarce in the databases.

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