

# Analysis of Potential Drug Interactions in Brazilian Mental Health Services: Prevalence and Associated Factors

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## ABSTRACT

**Background:** In the mental health field, the psychotropic polypharmacy is frequently observed, a significant risk factor for the occurrence of drug interactions. **Objective:** Identify potential drug interactions on the prescriptions of mental health services users and describe the associated factors.

**Methods:** A cross-sectional study was conducted in 11 services. Sociodemographic data and information about the use of drug were obtained through interviews of users, analysis of prescriptions and medical charts, using a semi-structured questionnaire. Potential drug interactions were identified using the Micromedex® database, the association with sociodemographic characteristics and aspects related to the medicines prescribed were analyzed using the prevalence ratio. **Results:** The number of medicines prescribed ranged from 0 to 9, with an average of 3.38 (SD=1.76) per user, the most prescribed being haloperidol (12.3%), clonazepam (8.2%) and biperiden (7.9%). The proportion of interactions considering the number of users interviewed was 35.1%. The most frequent between potential interactions were haloperidol and fluoxetine (9.1%); haloperidol and carbamazepine (8.8%); and carbamazepine and chlorpromazine (5.9%). The highest prevalence ratio (PR) for the occurrence of potential interactions was

in women (PR=1.36; 95% CI 1.08:1.71), users who had reported improper medicine use (PR=1.36; 95% CI: 1.07:1.72) and those with more than 5 prescribed medicines (PR=1.87; 95% CI: 1.49:2.33). **Conclusion:** Potential drug interactions were observed in more than one-third of the user's Brazilian mental health services. The profile of interactions detected could guide the pharmacotherapeutic follow-up of priority users, and help the multidisciplinary team identify signs and symptoms that can influence the treatment of users.

**Key words:** Drug interactions, Drug prescriptions, Psychotropic drugs, Mental health, Mental health services.

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## INTRODUCTION

Drug interactions are one of the main problems related to the use of medication.<sup>1</sup> In addition to clinically compromising the patient, interactions are also associated with increased hospitalization time and higher treatment costs.<sup>2</sup> In the mental health field, the use of psychotropic drugs is an important therapeutic resource. Many of these drugs exhibit a narrow therapeutic index, which may be associated with more severe drug interactions.<sup>3</sup> Furthermore, polypharmacy is frequently observed in mental health treatment<sup>4</sup> and is a significant risk factor for the occurrence of drug interactions,<sup>3</sup> demonstrating the need to monitor these occurrences.<sup>5</sup>

Drug interactions that involve psychotropic primarily compromise the metabolism process. Interactions may considerably raise the risk of intoxication, due to the inhibition of some cytochrome P450 isoenzymes, and exacerbate adverse reactions,<sup>6</sup> as occurs in several antipsychotic drugs.<sup>1</sup> Other interactions may trigger a reduction in the plasma concentration of a number of drugs, or even specific syndromes and symptoms.<sup>6</sup> These changes in pharmacokinetic and pharmacodynamics aspects may interfere in the main results that the patient seeks to achieve, namely, symptom elimination, quality of life and disease stabilization.<sup>6</sup>

Drug interaction studies conducted at mental health outpatient facilities are scarce,<sup>7</sup> and most are restricted to a hospital setting,<sup>8</sup> although is an important aspect to consider in therapeutic planning and patient safety.<sup>7</sup> Psychosocial Care Centers (CAPS – from Portuguese Centro de Atenção Psicossocial) are strategic services belonging to the Psychosocial Care Network and the Brazilian health system.<sup>9</sup> Identifying the most frequent

potential interactions may be important in subsidizing clinical practice pharmacovigilance, and planning initiatives to improve patient safety and rational drug use. The aim of the present study was to identify the most frequent potential drug interactions on the prescriptions of CAPS users.

## MATERIALS AND METHODS

A cross-sectional study was conducted with the users of 11 CAPS in the Médio Paraopeba region of Minas Gerais state (MG), Brazil. Eligible CAPS were those located in medium-sized and large cities, with populations of more than 100,000 inhabitants. Participant selection considered a systematic sample of users treated at the services between August 2014 and February 2015, deemed stable by the CAPS team, that is, with no episodes and capable of understanding the researchers' questions. Excluded were users who did not understand the questions, even after the researcher's explanations, thereby characterizing some degree of mental confusion or agitation. The users or their guardians who agreed to participate in the study gave their informed consent. After the interviews were conducted, the medical prescriptions and/or medical records were analyzed.

The sociodemographic characteristics of users, prescribed drugs and reports on inappropriate use of medicines use were described using measures of central tendency, dispersion and proportion. The units of analysis were the patient, the medicine and the drug interaction. The medicines were classified according to the Anatomical Therapeutic

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Chemical Classification System (ATC) and grouped under the third level to establish the main classes prescribed at these services. Interactions were identified using the Micromedex® database. Potential interactions with clinical relevance were determined, that is, those with excellent or good quality documentation and considered major, moderate or contraindicated.

The association between the occurrence of a potential drug interaction, sociodemographic characteristics and aspects related to the medicines prescribed were analyzed using the prevalence ratio, considering a 95% confidence interval. The programs used in statistical analyses were IBM SPSS Statistics version 19.0 and Microsoft Excel.

The study was approved by the Research Ethics Committee of the Federal University of Minas Gerais under protocol number 1160959 and CAAE 26041113.6.0000.5149. Patients were invited to participate in the study by signing the Free and Informed Consent Term (TCLE) of the research, according to Brazilian ethical legislation. The responsible for the user could sign the TCLE and participate concurrently in the interview with the user.

## RESULTS

A total of 467 users were interviewed. The CAPS users were mostly male (63.17%), single (67.75%), with a predominant age group between 25 and 59 years (65.59%), the mean age of participants was 34 years (SD=16.54). Educational level was concentrated in the initial years of the graded school (51.49%), those who worked, generally exercised occupations with low level of qualification (34.74%).

The number of medicines prescribed at the CAPS ranges from 0 to 9, with an average of 3.38 medicines (SD=1.76) per user, the most prescribed being haloperidol (12.3%), clonazepam (8.2%), biperiden (7.9%), diazepam (7.3%) and valproic acid (6.4%) (Table 1). The most frequently prescribed classes of drugs, in accordance with the third ATC classification level, were antipsychotics (37.5%), antiepileptics (21.5%) and antidepressants (11.9%).

The occurrence of potential drug interactions in the 391 (83.7%) users that were prescribed 2 or more medicines was investigated and 164 (41.9%) displayed between 1 and 8 potential interactions, with a mean value of 0.78 (SD=1.26) interactions per user. The proportion of interactions considering the number of users interviewed was 35.1%. Of the 306

potential interactions identified, 155 (50.6%) were classified as severe, 150 (49.0%) moderate and only one (0.3%) was contraindicated. With respect to the quality of the interaction documents, most were classified by the Micromedex® database as good (n=270; 88.7%), 24 (7.8%) excellent and 12 (3.9%) were not classified due to being manually extracted on the platform.

Fifty-one different combinations of potential interactions were identified in this study, the most frequent between haloperidol and fluoxetine (9.1%); haloperidol and carbamazepine (8.8%); and carbamazepine and chlorpromazine (5.9%) (Table 2). The highest prevalence ratio (PR) for the occurrence of potential interactions was in women (PR=1.36; 95% CI 1.08:1.71), users who had reported improper medicine use (PR=1.36; 95% CI 1.07:1.72), those with more than 5 prescribed medicines (PR=1.87; 95% CI 1.49:2.33), and individuals whose prescription contained antidepressants (PR=1.71; 95% CI 1.36-2.15), antipsychotics (PR=1.72; 95% CI 1.17:2.54) or antiepileptics (PR=1.81; 95% CI 1.34:2.44). The economically active age group, that is, aged between 20 and 59 years, was a protective factor for the occurrence of potential drug interactions (PR=0.50; 95% CI 0.32:0.78).

## DISCUSSION

The prevalence of potential drug interactions in this study was 35.1%, a value similar to that found in a number of general hospitals in Brazil, whose prevalence varied from 22<sup>3</sup> to 37%.<sup>2</sup> This value, however, was lower than those reported in studies conducted at basic care facilities (48.7%),<sup>10</sup> even when the focus was on treating mental disorders (58.4%).<sup>7</sup> The prevalence of potential interactions was higher than a study with patients with schizophrenia using antipsychotics (23%),<sup>1</sup> but lower compared to another study with the same population that included in their investigation besides the medicines for the treatment of mental disorders, antihypertensive drugs in use by the patients (65%).<sup>11</sup> Given the wide variation in the prevalence of interactions, even between general and psychiatric hospitals,<sup>8</sup> results should be compared with caution, including the analysis of different CAPS modalities, since they treat populations and clinical conditions differently.

The most frequent interactions involved fluoxetine, haloperidol and carbamazepine, the last two also recurring in interactions detected at basic care facilities that treat mental disorders.<sup>12</sup> The frequent use of haloperidol in this and other studies underscores the important role of

**Table 1: Medicines more prescribed in Psychosocial Care Centers users in the Médio Paraopeba region, Minas Gerais, Brazil 2014-2015.**

Medicamento	ATC class	Prescription frequency n(%)
haloperidol	Antipsychotics (N05A)	193 (12.3)
clonazepam	Antiepileptics (N03A)	128 (8.2)
biperiden	Anticholinergic Agents (N04A)	124 (7.9)
diazepam	Anxiolytics (N05B)	114 (7.3)
valproic acid	Antiepileptics (N03A)	101 (6.4)
chlorpromazine	Antipsychotics (N05A)	95 (6.1)
levomepromazine	Antipsychotics (N05A)	88 (5.6)
carbamazepine	Antiepileptics (N03A)	80 (5.1)
fluoxetine	Antidepressants (N06A)	69 (4.4)
Vitamin B-complex	Vitamin b-complex, incl. combinations(A11E)	63 (4.0)
risperidone	Antipsychotics (N05A)	61 (3.9)
thiamine	Vitamin B1 (A11D)	55 (3.5)
lithium	Antipsychotics (N05A)	52 (3.3)

ATC: Anatomical Therapeutic Chemical Classification System.

**Table 2: Potential drug-drug interactions most frequent in Psychosocial Care Centers users in the Médio Paraopeba region, Minas Gerais, Brazil 2014-2015.**

Interactions	N(%)	Potential adverse effect	Severity	Clinical Management
fluoxetine/haloperidol	9.15	Concurrent use may result in increased haloperidol exposure and risk of haloperidol toxicity; increased risk of QT prolongation and torsades de pointes.	Major	Monitor patients closely for any signs of toxicity
carbamazepine/haloperidol	8.82	Concurrent use may result in decreased haloperidol concentrations.	Moderate	Monitor the patient for a decreased clinical response to haloperidol when carbamazepine is added to the drug therapy.
carbamazepine/chlorpromazine	5.88	The combination of these drugs in liquid form may result in the formation of a precipitate.	Major	Avoid concomitant use of carbamazepine suspension and a liquid thioridazine or other liquid medications or diluents should not be administered simultaneously.
lithium/haloperidol	5.56	Concurrent use of may result in weakness, dyskinesias, increased extrapyramidal symptoms, encephalopathy, and brain damage.	Major	Monitor patients closely for any signs of toxicity or extrapyramidal symptoms, especially if high doses of DOPamine-2 antagonists, particularly haloperidol, and lithium are used. Serum lithium levels should be monitored periodically. Some clinicians advocate maintaining levels in the low therapeutic range.
amitriptyline/diazepam	4.90	Concurrent use may result in psychomotor deficits (decreased reaction time, decreased vigilance).	Moderate	Patients should be warned that they may experience additive psychomotor impairment that may affect driving or other tasks requiring complex motor skills.
lithium /fluoxetine	4.90	Concurrent use may result in possible increased lithium concentrations and/or an increased risk of SSRI-related serotonin syndrome (hypertension, hyperthermia, myoclonus, mental status changes).	Moderate	Monitor patients on concurrent lithium and selective serotonin reuptake inhibitor therapy for increased plasma concentrations of lithium. In addition, monitor patients for signs and symptoms associated with serotonin syndrome (hypertension, hyperthermia, myoclonus, mental status changes).
carbamazepine/fluoxetine	4.58	Concurrent use may result in increased carbamazepine exposure and increased risk of toxicity.	Major	If coadministering, closely monitor carbamazepine levels and adjust the carbamazepine dosage as needed.
carbamazepine/clonazepam	4.25	Concurrent use may result in reduced plasma levels of clonazepam.	Major	Clonazepam levels should be monitored whenever carbamazepine is added or withdrawn from therapy, or when the carbamazepine dose is changed. Also monitor the patient for seizure control.
valproic acid/carbamazepine	4.25	Concurrent use may result in carbamazepine toxicity (ataxia, nystagmus, diplopia, headache, vomiting, apnea, seizures, coma) and/or decreased valproic acid effectiveness.	Moderate	Monitor patients for signs of carbamazepine toxicity such as nausea, vomiting, drowsiness, and ataxia when valproic acid is added. Serum carbamazepine concentrations should also be measured, though clinicians should be aware of the increase in the concentration of the active metabolite, carbamazepine-epoxide, which is not routinely measured, but does contribute to the efficacy and toxicity of the drug. If carbamazepine is added to valproic acid therapy, monitor valproic acid levels; increased valproic acid dosage may be required.
carbamazepine/risperidone	3.92	Concurrent use may result in reduced risperidone and 9-OH-risperidone exposure.	Moderate	Monitor therapeutic efficacy of risperidone, higher doses may be necessary. It also may be necessary to decrease the risperidone dose with discontinuation of carbamazepine.

this drug in antipsychotic polytherapy, as well as concerns regarding its prescription patterns in the treatment of mental health.<sup>13</sup> Identifying the main potential interactions at the CAPS is important in guiding the multidisciplinary team, and monitoring the signs, symptoms and toxic effects of drug interactions on priority groups of users, until their inclusion in all the services.

Analysis of potential drug interactions should be part of therapeutic planning for CAPS users, especially those at greater risk of polytherapy,<sup>3</sup> children and the elderly.<sup>5</sup> A study in Australia showed that the identification of drug interactions by pharmacists was one of the most common interventions in psychiatric hospitals,<sup>14</sup> in contrast to the situation of the CAPS in this region.<sup>15</sup> Moreover, in mental health, identifying severe interactions that pose a health risk should be only one of the aspects investigated, since establishing the clinical relevance of interactions for these users may also be crucial. Exacerbating a side effect that poses no serious health risk but affects the routine and behavior of the user, could be clinically significant and may negatively affect adherence to therapy, a frequent and relevant problem for these users.<sup>12</sup>

The clinical management to be carried out for more frequent interactions are related to the monitoring of serum levels of the drugs and mainly to the occurrence of typical symptoms of intoxication by one of the medicines. The Serotonin syndrome is a potentially lethal condition that can be caused by interactions with medications in the treatment of mental disorders and requires the attention of health professional.<sup>16</sup> It is observed that the performance of the pharmacist in these services, informing and alerting about drug interactions is very important in the education of professionals and patients.<sup>17</sup> The pharmacist may alert you to unexpected symptoms and adverse effects, the clinical practice may help minimize adverse drug reactions, avoiding the administration of more drugs with potential side effects.<sup>17</sup>

This is a pioneering study in reporting interactions detected in CAPS users, a recent service offered by the Brazilian health system. The results may lead to new studies and guide the prioritization of interventions in CAPS aimed at patient safety and other aspects that may interfere with the adherence and follow-up of pharmacotherapy.

### Limitations of the study

This is a cross-sectional study, so more studies are necessary for other periods to confirm the profile of potential interactions. Analysis of the potential interactions was limited to a non-random sample and was restricted to drugs prescribed by CAPS, which suggests that this value is underestimated. The potential drug interactions do not necessarily reflect the actual occurrence of interactions in clinical practice but provide important information to minimize the risk of interactions and ensure the efficacy and safety of the proposed therapy.

### CONCLUSION

The result highlights the occurrence of potential drug interactions in more than one-third of the users of these services, which should be

investigated in future studies, considering dosage, drug use duration, diagnosis and other factors that are important for the occurrence of high-risk drug interactions. CAPS users often undergo polytherapy and are exposed to drugs with a significant potential for interactions. The profile of interactions detected could guide the pharmacotherapeutic follow-up of priority users, and help the multidisciplinary team identify signs and symptoms that can influence the clinical status and treatment of CAPS users.

### CONFLICT OF INTEREST

The authors report no conflict of interest.

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