ORIGINAL ARTICLE

CONTRAINDICATED AND SERIOUS OUTCOMES IN POTENTIAL DRUG INTERACTIONS PRESENT IN PSYCHOSOCIAL CARE CENTERS MEDICAL PRESCRIPTIONS

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Highlights: (1) All prescriptions analyzed presented potential drug interactions. (2) 3.6-5.4% of the interactions are considered contraindicated and 36-66% are considered serious. (3) A multimodal drug strategy is relevant, however, it requires monitoring.

PRE-PROOF
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ABSTRACT

To evaluate potential drug interactions in medical prescriptions issued at Psychosocial Care Centers. A retrospective, descriptive, documentary, and exploratory cross-sectional study with a quantitative approach, involving one hundred and seventy users from two psychosocial care services, all of whom were continuously using multiple medications. Prescriptions were analyzed to identify potential drug interactions. In all prescriptions evaluated, at least one potentially serious or contraindicated interaction was observed. The most commonly prescribed medications in these services included carbamazepine, sertraline, promethazine, diazepam, clonazepam, haloperidol, levomepromazine, and valproic acid. The frequent use of antipsychotics, anticonvulsants, and antidepressants was associated with an increased risk of clinically significant drug interactions. It is concluded that the use of multiple medications in the treatment of mental disorders is an established clinical practice; however, it is associated with elevated risks. The complex profile of patients receiving care requires an individualized therapeutic approach, taking into account comorbidities, socioeconomic vulnerability, treatment resistance, symptom diversity, potential adverse effects, and drug interactions with other medications and other substances.

Keywords: drug interaction, mental disorder, psychotropic drugs, drugs of abuse.

Introduction

Drug interaction is a clinically significant event in which the pharmacokinetic or pharmacodynamic effects of a drug are modified by the presence of another drug, herbal remedy, food, beverage, psychotropic agent, or other chemical compounds.[1] When two or more medications are administered simultaneously to a patient, they may act independently or interact with each other, increasing or decreasing the therapeutic and/or toxic effect of one or

both drugs.[1-2] These interactions can alter the effectiveness of the treatment, compromising therapeutic goals or, in some cases, causing toxicity.

Furthermore, drug interactions increase the likelihood of adverse effects, undesirable reactions, and toxic symptoms, which can result in serious clinical complications and compromise the patient's quality of life, potentially contributing to non-adherence to pharmacotherapy.[3-4] Interactions can be classified according to their severity, ranging from low to medium to high, depending on the potential clinical impact on the patient. The severity of interactions is evaluated based on the likelihood of adverse effects, the magnitude of the effects, and the possibility of reversibility, which can even contribute to the patient's death.[5-6]

In Psychosocial Care Centers (*Centros de Atenção Psicossocial*, CAPS), the pharmacist plays a fundamental role in promoting the rational use of medications, collaborating directly with patients, their families, and the multidisciplinary healthcare team. The pharmacist is trained to identify inconsistencies in medical prescriptions, especially those related to potentially dangerous drug interactions. This professional can, therefore, prevent or minimize the risk of contraindicated or serious interactions that could compromise the effectiveness and safety of the treatment. Therefore, the objective of this research was to evaluate the potential drug interactions present in the medical prescriptions of users treated at CAPS, to outline the pharmacotherapeutic profile of these patients. The research also aimed to identify the main problems related to medication use, focusing on interactions that may compromise the effectiveness and safety of the pharmacological treatment used.

Methodology

Type of study*:* This is a cross-sectional, retrospective, descriptive, and exploratory study, with a quantitative approach and documentary design.

Collection locus and period*:* Data collection was carried out between January and August 2023, using the medical prescriptions of active users from two Psychosocial Care Centers (CAPS) located in the municipality of Aracaju, state of Sergipe, Brazil: CAPS III Jael Patrício de Lima and CAPS AD III Primavera.

***Data sources**:* Both physical and electronic medical prescriptions were used, accessed through the IDS SAÚDE® system. All service professionals have some level of access to the system, ensuring the completeness of the evaluated clinical records.

***Inclusion criteria**:* All active users of the services during the data collection period were considered eligible. After screening and obtaining consent, 97 users from CAPS AD III Primavera and 73 users from CAPS III Jael Patrício de Lima remained in the sample, totaling 170 participants.

***Consent and ethical considerations**:* All participants, as well as their legal guardians (where applicable), signed the Free and Informed Consent Form (FICF). The study was approved by the Research Ethics Committee of the University Hospital of the Federal University of Sergipe (CAAE: 92400618.4.0000.5546), in accordance with the provisions of Resolution No. 466/2012 of the National Health Council.

***Description of participating services**:* Both CAPS are classified as Type III Psychosocial Care Centers (*Centros de Atenção Psicossocial* – CAPS III), operating on a 24-hour basis, seven days a week, including overnight reception and care. They provide "open-door" services (walk-in or referred demand) and are staffed by a multidisciplinary team composed of: psychiatrist, nurse, pharmacist, psychologist, physical education professional, social worker, workshop facilitator, nursing assistants, and nursing technicians, as well as administrative and cleaning staff.

***Variables and analysis procedures**:* The variables collected were: Patient identification: name, medical prescription number, date of service entry; Sociodemographic data: age, gender, neighborhood of residence; Clinical data: main diagnosis according to the International Classification of Diseases – 11th revision (ICD-11)[7]; Current treatment: medications prescribed at the time of data collection.

***Analysis of drug interactions**:* Potential drug interactions were analyzed using the following databases: IBM Micromedex® *Drug Interactions*, Drug Interactions, which classifies

interactions as: “contraindicated” (interaction contraindicated for use), “severe” (the interaction may be fatal and/or require medical intervention to minimize or prevent serious adverse effects), “moderate” (the interaction may result in exacerbation of the patient's condition and/or require a change in therapy) and “low” (the interaction has limited clinical effects. Manifestations may include an increase in the frequency or severity of side effects, but generally do not require a major change in therapy.[8] Drugs.com, used exclusively for analysis of interactions involving the drug levomepromazine, is not covered in the previous database. This platform classifies interactions as: “severe” (highly clinically significant. Avoid combinations; the risk of interaction outweighs the benefit), “moderate” (moderately clinically significant. Generally avoid combinations; use only in special circumstances), “low” (minimally significant. Minimize the risk; evaluate the risk and consider an alternative medication, take steps to mitigate the risk of interaction and/or institute a monitoring plan).[9]

***Data processing**:* The data were manually extracted from medical prescriptions and organized into a spreadsheet using Microsoft Excel® Descriptive statistical analysis (absolute and relative frequencies) was performed to characterize the participants' profile and categorize drug interaction.

Results and Discussion

Sociodemographic data

Distinct characteristics can be observed among the 170 patients included in the research, between those treated in the two services analyzed. At CAPS Jael, 65.75% (n=48) of the users were female, while at CAPS Primavera, the majority of patients (94.8%; n=92) were male. The predominant age range was 30 to 39 years at CAPS Jael and 40 to 49 years at CAPS Primavera (Table 1). The higher number of male patients at CAPS Primavera, which offers services for chemical dependents (AD), is consistent with other studies conducted in institutions in the same state and different regions of Brazil.[10-11] On the other hand, at CAPS Jael, also known as CAPS “Disorder”, the higher prevalence of female users is consistent with findings from national studies, which highlight the greater demand for mental health care by women.[12-13] This female profile at CAPS “Disorder” can, in part, be explained by the higher incidence of mental disorders among women.[14]

Table 1 – Sociodemographic profile of patients from CAPS AD III Primavera (n=97) and from CAPS III Jael Patrício (n=73); Aracaju, SE, Brazil. 2024

Characteristics		**CAPS AD**	**CAPS Jael**
	Variables	**N (%)**	**N (%)**
Gender	Female	5 (5.1)	48 (65.75)
	Male	92 (94.8)	25 (34.25)
Age Group	20 - 29		9 (12.33)
	30 – 39	20 (20.6)	23 (31.5)
	40 – 49	40 (41.2)	20 (27.4)
	50 – 59	28 (28.8)	14 (19.18)
	60 or more	9 (9.2)	7 (9.59)
CID 11*	6C40	44 (45.3)	
	6C4	67 (69.1)	
	6C20	13 (13.4)	23 (31.5)
	6A21		9 (12.3)
	6A6	3 (3.1)	12 (16.4)
	6B00		5 (6.8)
	6D10		14 (19.1)

Source: CAPS AD III Primavera and CAPS III Jael Patrício. Aracaju - SE, 2024. *The number of ICD codes is greater than the number of patients included because a patient may have more than one diagnosis.

It was possible to outline the main diseases and health conditions of the studied population using the International Classification of Diseases, version 11 (ICD-11).[7] The collection and analysis of ICD codes in a population are fundamental to understanding the public health scenario, supporting the formulation of appropriate health policies, and improving health systems, ensuring that the needs of communities are met effectively.[15] In the case of CAPS Jael, 17 different ICD codes were identified in the studied population (n=73), with the following standing out: ICD 6A20, corresponding to schizophrenia, with 31.5% (n=23) of patients; ICD 6D10, related to personality disorders, with 19.1% (n=14); ICD 6A6, indicating

bipolar disorder, with 16.4% (n=12); ICD 6A21, characterizing schizoaffective disorder, with 12.3% (n=9); and ICD 6B00, corresponding to anxiety disorders, with 6.8% (n=5) (Table 1).[7]

At CAPS AD Primavera, 11 ICD codes related to mental and behavioral disorders were identified in the studied population (n=97). The main ICD code was 6C4 and its subclasses, which refer to disorders due to substance use and addictive behaviors, affecting 69.1% (n=67) of patients. Within this category, subclass 6C40, which describes disorders related to alcohol use, was the most prevalent, accounting for 45.3% (n=44) of cases. Furthermore, ICD codes 6A20, corresponding to schizophrenia, were also observed in 13.4% (n=13) of patients, and 6A6, referring to bipolar disorder, in 3.26% (n=3) (Table 1).[7] These diagnoses are indicative of disorders caused by the use of the main drugs of abuse consumed by users treated at the CAPS AD, such as alcohol, tobacco, marijuana, cocaine, and crack. This pattern is similar to that found in another study conducted at the CAPS AD in the municipality of Aracaju.[10]

Most commonly prescribed medications

In CAPS, psychotropic medications are the most frequently prescribed. The average number of medications prescribed per patient ranges from 4 to 6, indicating polypharmacy. All prescriptions analyzed, both at CAPS Jael and CAPS AD, presented one or more potential drug interactions. This complex prescribing pattern, characterized by the use of multiple drugs, reinforces the importance of the continuous presence of qualified professionals, such as pharmacists, to guide the rational use of medications. These professionals must constantly monitor the signs and symptoms of side effects, adverse and toxic reactions, as well as evaluate and classify the degree of potential drug interactions present in prescriptions, thus ensuring the safety and well-being of patients.

Among the most frequently prescribed medications in the two CAPS analyzed, the following stand out: carbamazepine (n=93), sertraline (n=76), promethazine (n=64), diazepam (n=63), clonazepam (n=61), haloperidol (n=58), levomepromazine (n=40), and valproic acid (n=36) (data not shown). Despite differences in user profiles and diagnoses, no significant variations were observed in prescribed medications between the two services. However, some differences can be noted: at CAPS AD, the most prescribed benzodiazepine is diazepam (n=52), while at CAPS Jael the use of clonazepam predominates (n=29). Similarly, carbamazepine is the most commonly used anticonvulsant at CAPS AD (n=81), while at CAPS Jael, valproic acid

is the most prevalent prescription (n=28). When analyzing prescriptions by therapeutic class, anticonvulsants predominate, including benzodiazepines (n=256), followed by antipsychotics (n=174), antidepressants (n=100), and anticholinergics (n=79).

The anticonvulsants carbamazepine and valproic acid are among the most prescribed medications, not only for their effectiveness in controlling and preventing seizures, but also for their properties as mood stabilizers.[16] Studies indicate their positive effects in the treatment of eating disorders, as well as in reducing impulsive and compulsive behaviors, making them important allies in reducing cravings.[17] Furthermore, these drugs have a low potential for abuse and less interaction with alcohol, characteristics that are especially relevant in the context of treating patients with substance use disorders.[18]

Like anticonvulsants, benzodiazepines such as diazepam and clonazepam also frequently appear in prescriptions, being widely used in the management of seizures associated with alcohol withdrawal syndrome, as well as being indicated in the treatment of anxiety disorders, insomnia, and cocaine withdrawal syndrome, contributing to the reduction of relapse of substance use.[19] However, its clinical use is limited due to the high potential for developing physical dependence and tolerance, effects less observed with the use of anticonvulsants. Another medication widely prescribed by both CAPS is promethazine, an antihistamine with anticholinergic properties, frequently used to mitigate the extrapyramidal side effects induced by antipsychotics.[20] This drug interaction is considered beneficial because, by reducing such adverse effects, promethazine can promote adherence to antipsychotic treatment. Graph 1 shows the distribution of the most prescribed medications by ICD code in the two CAPS.

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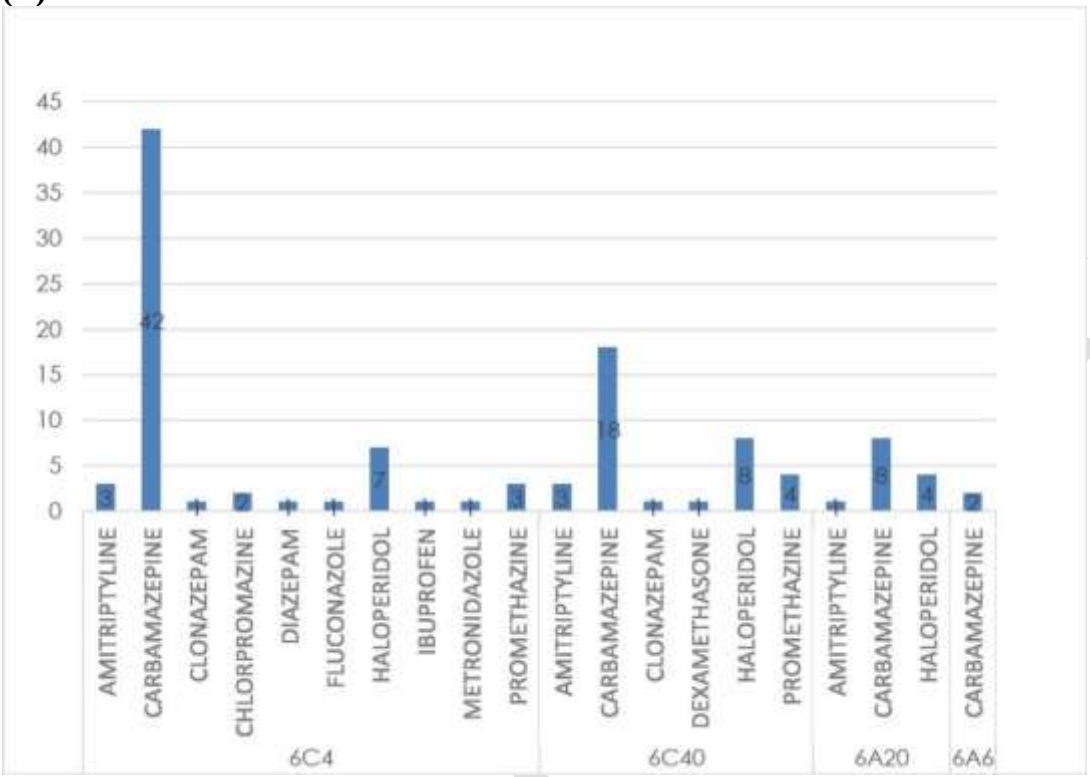
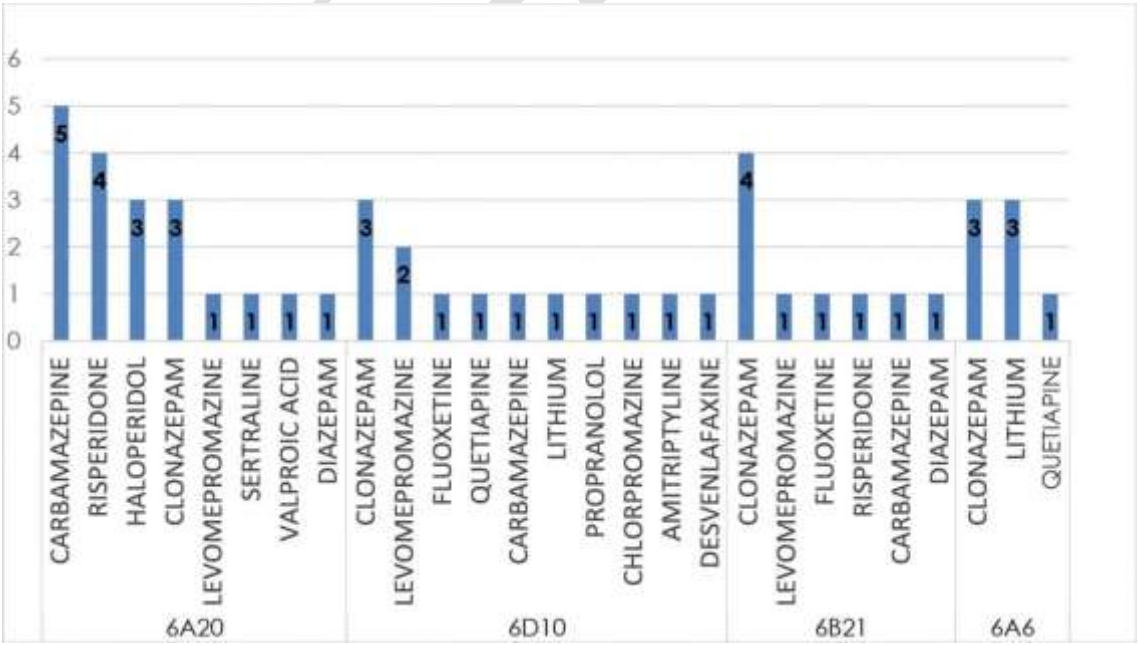
Graph 1 – Most frequently prescribed medications by ICD-11 at (A) CAPS AD III Primavera (N=63) and (B) CAPS III Jael Patrício (n=34); Aracaju, SE, Brazil. 2024

(A)



(B)



Source: CAPS AD III Primavera (**A**) and CAPS III Jael Patrício (**B**). Aracaju - SE, 2024.

Drug Interactions Contraindicated and Severe

The drug prescriptions analyzed at the CAPS revealed dozens of drug-drug interactions classified as severe or even contraindicated, according to the IBM Micromedex® Drug Interactions and Drugs.com databases.[8–9] At CAPS AD, approximately 3.6% (n=17) of the interactions identified in the prescriptions are contraindicated (Table 2A), while 36.8% (n=174) are classified as "severe" (Table 2B). At CAPS Jael, 5.4% (n=18) of the interactions are considered contraindicated (Table 2A), and 66% (n=220) are categorized as severe (Table 2B).

Among the interactions classified as contraindicated, antipsychotics represent 4.2% (n=14) of the total identified at CAPS AD, with thioridazine being the main agent involved in these interactions. Similarly, at CAPS Jael, antipsychotics account for 5.4% (n=18) of the contraindicated interactions, again with thioridazine being the main culprit. In addition to antipsychotics, antidepressants also appear among the medications associated with contraindicated interactions (n=100), with fluoxetine and sertraline being the most frequently involved.

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Table 2A – Profile of potential contraindicated drug interactions present in the prescriptions of patients from CAPS AD III Primavera (n=97) and from CAPS III Jael Patrício (n=73); Aracaju, SE, Brazil. 2024. (**See the complete table in Appendix 1**)

Drug Interactions	PRIMAVERA		JAEL		TOTAL	
	N	%	N	%	N	%
Antipsychotics vs. Others						
Thioridazine vs. Promethazine	4	0.7	4	1.2	**8**	**0.9**
Thioridazine vs. Fluoxetine	3	0.5	2	0.6	**5**	**0.5**
Thioridazine vs. Haloperidol	1	0.2	4	1.2	**5**	**0.5**
Thioridazine vs. Sertraline			4	1.2	**4**	**0.4**
Thioridazine vs. Propranolol			2	0.6	**2**	**0.2**
Levomepromazine vs. Quetiapine			2	0.6	**2**	**0.2**
Thioridazine vs. Amitriptyline	1	0.2			**1**	**0.1**
Thioridazine vs. Chlorpromazine	1	0.2			**1**	**0.1**
Ziprasidone vs. Sertraline	1	0.2			**1**	**0.1**
Ziprasidone vs Promethazine	1	0.2			**1**	**0.1**
Haloperidol vs Metoclopramide	1	0.2			**1**	**0.1**
Haloperidol vs Fluconazole	1	0.2			**1**	**0.1**
Antidepressants vs. Others						
Antidepressants vs. Others	1	0.2			**1**	**0.1**
Others						
Ketoconazole vs. Fluconazole	1	0.2			**1**	**0.1**
Ketoconazole vs. Simvastatin	1	0.2			**1**	**0.1**

Source: CAPS AD III Primavera and CAPS III Jael Patrício. Aracaju - SE, 2024.

Regarding interactions classified as severe at the CAPS AD, antipsychotics stand out, accounting for 28.2% (n=174) of the total. Among these, haloperidol appears most frequently (n=124), followed by levomepromazine (n=81) and chlorpromazine (n=67). At the CAPS Jael, the predominance of antipsychotics is also evident, being responsible for 42% (n=140) of severe interactions. In this study, haloperidol again leads, with 15.5% (n=52) of the interactions, followed by lithium (8%, n=26) and quetiapine (7%, n=24), as shown in Table 2B. Overall, antipsychotics were widely involved in the severe interactions identified, especially haloperidol and levomepromazine, both known for their risk of QT interval prolongation. This effect is potentiated when combined with other substances with the same risk, such as cocaine and thioridazine.[21]

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Table 2B – Profile of potential severe drug interactions present in the prescriptions of patients (n=97) from CAPS AD III Primavera and (n=73) from CAPS III Jael Patrício; Aracaju, SE, Brazil. 2024. (**See the complete table in Appendix 1**)

Drug Interactions	PRIMAVERA		JAEL		TOTAL	
	N	%	N	%	N	%
Antipsychotics vs. Others						
Haloperidol vs. Promethazine	29	4.9	20	6.0	**49**	**5.3**
Haloperidol vs. Sertraline	20	3.4	6	1.8	**26**	**2.8**
Haloperidol vs. Clonazepam	10	1.7	8	2.4	**18**	**2.0**
Chlorpromazine vs. Carbamazepine	18	3.1			**18**	**2.0**
Haloperidol vs. Levomepromazine	11	1.9	4	1.2	**15**	**1.6**
Chlorpromazine vs. Sertraline	13	2.2	2	0.6	**15**	**1.6**
Lithium vs. Sertraline	5	0.9	8	2.4	**13**	**1.4**
Lithium vs. Promethazine	3	0.5	8	2.4	**11**	**1.2**
Risperidone vs. Sertraline	3	0.5	8	2.4	**11**	**1.2**
Haloperidol vs. Lithium	4	0.7	6	1.8	**10**	**1.1**
Chlorpromazine vs. Promethazine	10	1.7			**10**	**1.1**
Quetiapine vs. Clonazepam			10	3.0	**10**	**1.1**
Chlorpromazine vs. Clonazepam	9	1.5			**9**	**1.0**
Thioridazine vs. Carbamazepine	5	0.9	4	1.2	**9**	**1.0**
Haloperidol vs. Chlorpromazine	8	1.4			**8**	**0.9**
Olanzapine vs. Clonazepam			6	1.8	**6**	**0.7**
Olanzapine vs. Promethazine			6	1.8	**6**	**0.7**
Chlorpromazine vs. Amitriptyline	5	0.9			**5**	**0.5**
Thioridazine vs. Clonazepam	2	0.3	2	0.6	**4**	**0.4**
Thioridazine vs. Sertraline			4	1.2	**4**	**0.4**
Olanzapine vs. Diazepam			4	1.2	**4**	**0.4**
Quetiapine vs. Promethazine			4	1.2	**4**	**0.4**
Quetiapine vs. Venlafaxine			4	1.2	**4**	**0.4**
Haloperidol vs. Olanzapine			4	1.2	**4**	**0.4**
Haloperidol vs.Risperidone			4	1.2	**4**	**0.4**
Venlafaxine vs. Warfarin			4	1.2	**4**	**0.4**
Risperidone vs. Lithium	2	0.3	2	0.6	**4**	**0.4**
Haloperidol vs. Amitriptyline	3	0.5			**3**	**0.3**
Lithium vs. Ibuprofen	3	0.5			**3**	**0.3**
Risperidone vs. Olanzapine			2	0.6	**2**	**0.2**

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Risperidone vs. Amitriptyline			2	0.6	**2**	**0.2**
Quetiapine vs. Pregabalin			2	0.6	**2**	**0.2**
Quetiapine vs. Fluoxetine			2	0.6	**2**	**0.2**
Quetiapine vs. Sertraline			2	0.6	**2**	**0.2**
Lithium vs. Desvenlafaxine			2	0.6	**2**	**0.2**
Lithium vs. Amitriptyline	2	0.3			**2**	**0.2**
Ziprasidone vs. Carbamazepine	1	0.2			**1**	**0.1**
Chlorpromazine vs. Risperidone	1	0.2			**1**	**0.1**
Chlorpromazine vs. Fluoxetine	1	0.2			**1**	**0.1**
Levomepromazine vs. Metoclopramide	1	0.2			**1**	**0.1**
Levomepromazine vs. Thioridazine	1	0.2			**1**	**0.1**
Levomepromazine vs. Topimarate	1	0.2			**1**	**0.1**
Levomepromazine vs. Ziprasidone	1	0.2			**1**	**0.1**
Haloperidol vs. Azithromycin	1	0.2			**1**	**0.1**
Haloperidol vs. Ketoconazole	1	0.2			**1**	**0.1**
Anticonvulsants vs. Others						
Carbamazepine vs. Sertraline	43	7.4	10	3.0	**53**	**5.7**
Clonazepam vs. Promethazine	16	2.7	24	7.1	**40**	**4.3**
Carbamazepine vs. Clonazepam	27	4.6	6	1.8	**33**	**3.6**
Valproic Acid vs. Clonazepam			20	6.0	**20**	**2.2**
Carbamazepine vs. Ketoconazole	3	0.5			**3**	**0.3**
Phenobarbital vs. Diazepam	3	0.5			**3**	**0.3**
Clonazepam vs. Pregabalin			2	0.6	**2**	**0.2**
Valproic Acid vs. Carvedilol			2	0.6	**2**	**0.2**
Valproic Acid vs. Warfarin			2	0.6	**2**	**0.2**
Carbamazepine vs. Dexamethasone	2	0.3			**2**	**0.2**
Carbamazepine vs. Loratadine	2	0.3			**2**	**0.2**
Clonazepam vs. Diazepam	2	0.3			**2**	**0.2**
Carbamazepine vs. Fluconazole	2	0.3			**2**	**0.2**
Phenytoin vs. Sertraline	2	0.3			**2**	**0.2**
Carbamazepine vs. Medroxyprogesterone	1	0.2			**1**	**0.1**
Carbamazepine vs. Fluoxetine	1	0.2			**1**	**0.1**
Carbamazepine vs. Phenytoin	1	0.2			**1**	**0.1**
Clonazepam vs. Ketoconazole	1	0.2			**1**	**0.1**
Phenobarbital vs. Clonazepam	1	0.2			**1**	**0.1**
Phenytoin vs. Diazepam	1	0.2			**1**	**0.1**

Clonazepam vs. Ketoconazole	1	0.2			**1**	**0.1**
Diazepam vs. Metoclopramide	1	0.2			**1**	**0.1**
Antidepressants vs. Others						
Sertraline vs. Promethazine	22	3.8	14	4.2	**36**	**3.9**
Sertraline vs. Amitriptyline	8	1.4	2	0.6	**10**	**1.1**
Sertraline vs. Ibuprofen	8	1.4			**8**	**0.9**
Amitriptyline vs. Promethazine	4	0.7			**4**	**0.4**
Fluoxetine vs. Promethazine	1	0.2	2	0.6	**3**	**0.3**
Sertraline vs. Ketoconazole	2	0.3			**2**	**0.2**
Sertraline vs. Metronidazole	2	0.3			**2**	**0.2**
Amitriptyline vs. Salbutamol	2	0.3			**2**	**0.2**
Amitriptyline vs. Fluconazole	2	0.3			**2**	**0.2**
Amitriptyline vs. Ibuprofen	1	0.2			**1**	**0.1**
Amitriptyline vs. Ketoconazole	1	0.2			**1**	**0.1**
Amitriptyline vs. Metronidazole	1	0.2			**1**	**0.1**
Sertraline vs. Azithromycin	1	0.2			**1**	**0.1**
Sertraline vs. Diclofenac	1	0.2			**1**	**0.1**
Sertraline vs. Fluconazole	1	0.2			**1**	**0.1**
Anticholinergics vs. Others						
Promethazine vs. Pregabalin			4	1.2	**4**	**0.4**
Promethazine vs. Ketoconazole	1	0.2			**1**	**0.1**
Promethazine vs. Fluconazole	1	0.2			**1**	**0.1**
Promethazine vs. Metoclopramide	1	0.2			**1**	**0.1**
Others						
Ketoconazole vs. Dexamethasone	1	0.2			**1**	**0.1**
Ketoconazole vs. Omeprazole	1	0.2			**1**	**0.1**
Metronidazole vs. Fluconazole	1	0.2			**1**	**0.1**
Losartan vs. Captopril	1	0.2			**1**	**0.1**
Amlodipine vs. Simvastatin	1	0.2			**1**	**0.1**
Ibuprofen vs. Diclofenac	1	0.2			**1**	**0.1**
Simvastatin vs. Multivitamin	1	0.2			**1**	**0.1**

Source: CAPS AD III Primavera and CAPS III Jael Patrício. Aracaju - SE, 2024.

Drug Interactions with Antipsychotics

The interaction between antipsychotics appears in 1% (n=8) of the contraindicated interactions and in 5.5% (n=50) of the interactions classified as severe in the two CAPS

analyzed. This type of interaction is especially concerning because it can worsen QT interval prolongation, requiring caution, particularly in patients with other risk factors for this alteration.[21] Furthermore, combining two or more antipsychotics in the same prescription can significantly increase the risk of adverse effects such as drowsiness, dizziness, weight gain, and metabolic changes. From a clinical standpoint, the concomitant use of multiple antipsychotics has been associated with several disadvantages, including a higher frequency and severity of side effects, reduced adherence to treatment, an increased risk of drug interactions, and a greater likelihood of administration errors due to the complexity of the therapeutic regimen.[22]

The interaction between promethazine and antipsychotics is a relevant clinical concern, especially due to the effects that both drugs exert on the central nervous system. Promethazine, due to its anticholinergic properties, can cause symptoms such as dry mouth, blurred vision, constipation, and urinary retention. Similarly, several antipsychotics also have anticholinergic effects, which increase the risks when used in combination. This risk is particularly significant in the case of antipsychotics such as clozapine, chlorpromazine, and thioridazine, which, when combined with promethazine, can increase the incidence of drowsiness, dizziness, and reduced concentration. These effects are related to the additive action of these substances on histamine H1 receptors, potentiating sedation and other adverse effects.[23]

Sedation is frequently used in psychiatric practice as a therapeutic resource for controlling symptoms such as psychomotor agitation, aggression, and delusions, aiming at stabilizing the clinical picture.[20] However, its use requires caution, especially when it involves drug combinations with significant sedative and anticholinergic potential. Promethazine, for example, has anticholinergic properties that, when combined with antipsychotics such as clozapine, chlorpromazine, and thioridazine, or even with tricyclic antidepressants such as amitriptyline, can intensify adverse cognitive and peripheral effects. Among the associated risks, the following stand out: impairments to cognition and memory, peripheral antimuscarinic effects such as constipation, urinary retention, and blurred vision, as well as the possibility of exacerbation of tardive dyskinesia and cholinergic rebound after abrupt withdrawal of these agents.[24]

Additionally, although sedation may be beneficial in certain clinical contexts, its excessive use may assume an institutionalizing character, promoting disproportionate control over the patient's behavior and compromising their autonomy and critical judgment.[25]

Therefore, it is essential that the use of sedative agents be carefully evaluated, always seeking a balance between therapeutic benefits and respect for the patient's dignity and freedom. Insomnia, in turn, is a symptom frequently reported in psychiatric contexts and is often difficult to manage clinically, which may contribute to the tendency towards the expanded use of sedative medications.

Drug Interactions with Anticonvulsants

Anticonvulsants represent a significant portion of drug interactions classified as severe in the two CAPS analyzed: 27% (n=156) in CAPS AD and 29% (n=100) in CAPS Jael. Among these, clonazepam stands out, responsible for 11.6% (n=67) of severe interactions in CAPS AD and 23% (n=78) in CAPS Jael. Carbamazepine also plays a significant role, accounting for 18.3% (n=106) of severe interactions in CAPS AD and 5.9% (n=20) in CAPS Jael. Some anticonvulsants, such as carbamazepine itself, can reduce plasma levels of certain antipsychotics through pharmacokinetic interactions, compromising their therapeutic efficacy. In these cases, dose adjustments may be necessary for both antipsychotics and anticonvulsants to minimize adverse effects and maintain treatment effectiveness.[26]

Carbamazepine, being one of the most frequently prescribed medications in CAPS, is also among the drugs with the highest number of identified drug interactions. Although it is a potent inducer of cytochrome P450 enzymes (particularly isoforms 1A2, 2C9, and 3A4), most interactions associated with this medication are classified as moderate in severity. One example is the interaction with haloperidol, whose clearance can be increased by approximately 32%, resulting in a variable reduction in its plasma levels. Similarly, the interaction between carbamazepine and omeprazole can lead to a decrease in serum concentrations of the latter, due to the induction of its oxidative metabolism. However, it is important to highlight that, despite these interactions being pharmacologically plausible, the available clinical evidence is still limited.[27]

In interactions involving decreased plasma drug levels, as occurs with carbamazepine, it is essential to evaluate the potential impact of this alteration on the efficacy and safety of the treatment. In these situations, it may be necessary to adjust the doses of one or both drugs involved to ensure that co-administration maintains therapeutic efficacy and minimizes risks to the patient. This requires rigorous clinical monitoring, including evaluation of therapeutic

response, surveillance for possible adverse effects, and, when indicated, measurement of plasma drug levels.[28] In this context, the interaction between carbamazepine and sertraline is considered serious due to their additive effects on 5-HT2 serotonergic receptors. This combination can increase the risk of serotonin syndrome, a potentially fatal condition caused by excess serotonin in the central nervous system. This syndrome encompasses cognitive (confusion, agitation), autonomic (hypertension, tachycardia, hyperthermia), and somatic (tremors, hyperreflexia) manifestations, and can progress to coma and death.[2,29]

The literature also highlights a complex relationship between serotonin and seizures: in general, high serotonin levels exert an inhibitory effect on seizure activity, while low levels may promote their occurrence.[30] However, considering that carbamazepine is a potent hepatic enzyme inducer, it is possible to speculate that its use may reduce serotonin concentration in the CNS, which theoretically would decrease the risk of serotonin syndrome, although this hypothesis requires clinical confirmation. Another serious interaction involving carbamazepine occurs with antipsychotics such as chlorpromazine. The simultaneous administration of liquid carbamazepine suspension with liquid forms of chlorpromazine or thioridazine is not recommended, as precipitation of the mixture may occur, resulting in a drastic reduction in the bioavailability of the drugs.[8]

Drug Interactions with Antidepressants

The role of antidepressants in the context of drug interactions cannot be overlooked, since, in addition to contraindicated interactions, these drugs are also frequently involved in interactions classified as severe. In the CAPS AD, antidepressants account for 27% (n=155) of severe drug interactions, while in the CAPS Disorder they represent 18% (n=62). Of particular note are sertraline, responsible for 23% (n=131) of severe interactions at CAPS AD and 17% (n=56) at CAPS Jael, as well as amitriptyline, with 5% (n=29) at CAPS AD and 1% (n=4) at CAPS Jael (Table 2B). Interactions between antidepressants and antipsychotics are common, since these drug classes are frequently prescribed together in the treatment of various psychiatric disorders.[31] One of the most relevant interactions concerns QT interval prolongation, an additive effect observed in combinations such as haloperidol with sertraline, increasing the risk of potentially fatal cardiac arrhythmias.[29] The literature already extensively documents the risks associated with QT interval prolonging drugs.[21]

In the case of tricyclic antidepressants, such as amitriptyline, the risks are even greater due to the blockade of multiple receptors, such as histamine H1, α1-adrenergic, and muscarinic cholinergic receptors, which, in combination with antipsychotics, can intensify adverse effects such as dry mouth, orthostatic hypotension, drowsiness, constipation, and weight gain.[32] Selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs) are associated with additive effects related to 5-HT2 receptor agonism, with an increased risk of serotonin syndrome, a potentially severe condition that can progress to coma and death.[33] Another aspect that deserves attention is the ability of some antidepressants to lower the seizure threshold. A meta-analysis of observational studies concluded that both SSRIs and SNRIs are associated with an increased risk of seizures, especially when prescribed in conjunction with anticonvulsants, which requires additional care in the management of these patients.[34]

Safety and prescription of multiple medications

The prescription of multiple medications in the treatment of mental disorders has become increasingly common.[22] However, this practice is associated with several potential risks. The complex profile of users served in CAPS requires diverse therapeutic approaches that consider comorbidities, treatment resistance, socioeconomic conditions, a variety of symptoms, potential side effects, adverse reactions, as well as drug interactions and interactions with other psychoactive substances. Additionally, the multimodal strategy, which seeks to target different neurotransmitters as therapeutic targets, is widely recognized by psychiatrists as a relevant and effective approach.[22] The Table Appendix 1 presents detailed data on all drug interactions identified in the study, providing comprehensive information on their frequency, percentage of occurrence, and degree of severity.

Furthermore, considering the profile of the users, many of whom present with increased risk of suicide, rigorous monitoring of access to and rational use of pharmacotherapy becomes even more urgent. This is a responsibility shared by the entire mental health team, with particular emphasis on the role of the pharmacist, who can contribute significantly through guidance on the safe and appropriate use of medications.[35] In this context, one of the pharmacist's clinical responsibilities is to order laboratory tests as part of the drug therapy monitoring service. This practice may include measuring plasma drug concentrations,

evaluating renal or hepatic function, and other relevant tests, to ensure the safety, efficacy, and individualization of treatment.[28]

Within the context of the Brazilian Unified Health System (*Sistema Único de Saúde*, SUS), where therapeutic options can be limited due to a lack of standardization and the unavailability of certain non-subsidized medications, the issue of treatment availability and accessibility becomes particularly relevant. This limitation represents an additional challenge for mental health professionals working in CAPS, who often have to deal with a restricted therapeutic arsenal when faced with complex clinical conditions. Given this reality, the multidisciplinary CAPS' team must adopt alternative strategies to manage the adverse effects of available medications. Such strategies may include guiding patients on self-care practices that help mitigate risks, as well as implementing more frequent and individualized monitoring, especially for those using potentially harmful pharmacological combinations. Patients concomitantly using antidepressants and antipsychotics, for example, should be carefully monitored for side effects such as mood swings, symptoms consistent with serotonin syndrome, and other adverse events. Whenever possible, prescription of drug combinations with the lowest potential for interaction should be prioritized. Alternatively, other therapeutic options should be considered, if available, that offer greater pharmacological safety and a lower risk of undesirable effects.

This study has several limitations, notably its cross-sectional design, the fact that the sample was restricted to a single local setting, and the reliance on records completed by third parties in the medical prescriptions. Furthermore, participants were not evaluated for possible adverse events resulting from drug interactions identified in the prescriptions or from associated comorbidities. It is important to note that the scarcity of information in medical prescriptions is often related to patients' own lack of knowledge about their pharmacotherapy. The lack of frequent contact with family members, who in many cases are primarily responsible for administering medications, also contributes to this informational gap. In several cases, collecting reliable data on medication use requires additional home visits, which increases the challenges and the time needed for medication reconciliation. This scenario is aggravated by the fact that some users have fragile or broken family ties, further hindering the obtaining of accurate information about their ongoing treatment. This situation highlights the need to adopt

specific strategies to deal with complex cases in order to ensure the effectiveness of the medication reconciliation process in the CAPS context.

Conclusion

Data analysis reveals a significant recurrence of potential drug interactions in prescriptions from CAPS, highlighting the importance of understanding the severity of these interactions and their clinical impact on users. Therefore, it is necessary to expand the knowledge of the multidisciplinary team on this topic, as well as to have a qualified professional, such as a clinical pharmacist, for a thorough analysis of prescriptions, focusing on personalized care and patient safety. Within SUS, there are restrictions on access to psychotropic medications, with a predominance of first-generation drugs. This limitation contributes to an increased risk of drug interactions, adverse effects, and side effects, since these medications have a greater propensity to cause these outcomes.

Among the potential interactions identified, the presence of at least two drugs with the potential to prolong the QT interval stands out, an event considered to be of relevant clinical severity. Although these combinations do not always result in additive QT interval prolongations, specific interactions, such as between haloperidol, levomepromazine, and thioridazine, especially when associated with risk factors such as the use of psychoactive substances (cocaine, crack, and amphetamine derivatives), can induce this outcome. Managing the additive effects of medications requires the pharmacist's continuous presence in order to ensure more appropriate management of pharmacotherapy, provide technical guidance to the healthcare team, and conduct health education initiatives for patients and their caregivers. These measures are essential for minimizing the risks associated with polypharmacy and promoting treatment adherence.

Caring for individuals who use psychoactive substances, in turn, demands an even more comprehensive approach, including an understanding of co-prescriptions and their potential drug interactions. To this end, mental health service teams must be familiar with the clinical and psychosocial profile of these users, developing specific and individualized intervention strategies. However, the reality of the services is challenging. In many CAPS, there is only one pharmacist available, usually working only one shift and with predominantly technical-managerial responsibilities, which substantially limits clinical-assistance activities. This

workload overload prevents detailed analysis of prescriptions, compromising the safety of the pharmacological care offered.

Given this scenario, it becomes imperative to adopt multifaceted measures to reduce the risks associated with potential drug interactions. This includes strengthening multidisciplinary care, expanding the presence and role of pharmacists in services, and encouraging the qualified completion of forms requesting the inclusion of medications in the Municipal List of Essential Medicines (*Relação Municipal de Medicamentos Essenciais*, REMUME), thus expanding access to more appropriate therapies. The analyzed data also point to a trend towards the medicalization of CAPS users, with a high prevalence of potentially severe or contraindicated drug interactions, especially between antipsychotics, antidepressants, and anticonvulsants. As next steps, systematic screening for medication-related problems is recommended, with the aim of outlining the clinical profile of users and strengthening the clinical role of the pharmacist as an essential part of the mental health team.

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CONTRAINDICATED AND SERIOUS OUTCOMES IN POTENTIAL DRUG INTERACTIONS PRESENT IN PSYCHOSOCIAL CARE CENTERS MEDICAL PRESCRIPTIONS

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