

Gender differences and psychotropic polypharmacy in psychiatric patients in Brazil: a cross-sectional analysis of the PESSOAS Project

Diferenças de gênero e polifarmácia psicotrópica em pacientes psiquiátricos no Brasil: uma análise transversal do Projeto PESSOAS

Diferencias de género y polifarmacia psicotrópica en pacientes psiquiátricos en Brasil: un análisis transversal del Proyecto PESSOAS

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Abstract

We aimed to estimate the prevalence and correlates of psychotropic polypharmacy in Brazilian psychiatric patients by gender. Sociodemographic, behavioral and clinical data were obtained through face-to-face interviews and medical charts of 2,475 patients. Psychotropic polypharmacy was defined as the use of two or more psychotropic drugs and occurred in 85.7% of men (95%CI: 83.6%-87.6%) and 84.9% of women (95%CI: 82.8%-86.8%; $p > 0.05$). The mean number of psychotropic drugs/patient was 2.98 ± 1.23 and most common combinations included antipsychotics. Multivariate analysis showed that for both genders, previous hospitalization, severe mental illness, multiple psychiatric diagnoses and an insufficient number of professionals in the health care unit was associated with psychotropic polypharmacy. However, other correlates such as inpatient care, use of non-psychotropic drugs, living in unstable conditions and current smoking vary among them. Psychotropic polypharmacy was a common practice in this national sample. The results highlighted the need for national guidelines to manage patients with mental illness, considering the difference among genders and disease severity, to reduce the burden of polypharmacy in this population.

Polypharmacy; Psychotropic Drugs; Mental Disorders; Gender and Health

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Introduction

Mental disorders are among the five most important contributors to the global burden of disease and disability. Together with substance use disorders, they account for 7.4% of disability-adjusted life-years lost and were the leading cause of years lived with disability worldwide in 2010¹. In Brazil, the prevalence of at least one lifetime mental disorder was 44.8% in a large metropolitan area, with an estimated lifetime risk at age 75 of 57.7%².

Gender plays a vital role in neurobiological aspects, psychosocial factors, and behavioral patterns in several psychiatric disorders. Gender differences have been reported in the prevalence, type of diagnosis, treatment and behavior among individuals with mental disorders³, with higher prevalence of disorders among boys during childhood and among women during adulthood^{1,4}. Women have a higher prevalence of affective and anxiety disorders while men have higher rates of substance use and antisocial personality disorders^{1,2,5,6,7,8}.

The use of psychotropic medicines has been the main strategy for treatment of these individuals. In Brazil, their utilization appears to be three times higher among women, especially benzodiazepines and antidepressants^{9,10}. Women also seek and use health services more often than men¹⁰. Drug interactions and adverse events commonly occur with these medications, and are responsible for the most common cause of hospitalizations due to adverse drug events¹¹.

Polypharmacy has no uniform definition, and can be classified as the number of medicines taken simultaneously, corresponding to the use of two or more medicines or be evaluated as minor polypharmacy (concurrent use of two to four medicines) and major polypharmacy (concurrent use of five or more medicines)¹². Concerns with polypharmacy include the possibility of cumulative toxicity and worsening adherence by increasing the complexity of treatment^{13,14}. In addition, they increase the costs of therapy with strategies that are not well established in the literature¹⁴.

The prescription of multiple drugs for patients with mental illnesses has been an increasingly common practice without clear clinical effectiveness and with a potential likelihood of adverse drug reactions, despite controversies^{13,15}. Accordingly, the aim of this study was to assess the prevalence and correlates of psychotropic polypharmacy, defined as the use of two or more psychotropic medicines from the same or a different pharmacological class, with emphasis on gender differences, in a national representative sample of psychiatric patients under care in Brazil.

Methods

This study is part of a national multicenter study among psychiatric patients in Brazil, as described in detail in previous publications^{16,17,18}. Briefly, we conducted a multicenter cross-sectional study in 2006 in 11 public psychiatric hospitals and 15 outpatient Psychosocial Care Centers (CAPS). CAPS are public mental health outpatient clinics created to progressively reduce psychiatric hospital care. They provide consultations, therapeutic and creative workshops, physical and recreational activities, art therapy, and medication on a daily basis during week days¹⁹, while hospitals attend patients under closed regimens for an average of 20 days.

Medications provided at CAPS include at least those of the *Brazilian National List of Essential Medicines* (RENAME in portuguese), while local health services can provide other medications as needed. In 2006, the list included three options of antipsychotic agents (haloperidol, chlorpromazine, lithium carbonate), two anxiolytics, hypnotics and sedatives (diazepam, clonazepam), two antiparkinsonian (biperiden, levodopa+carbidopa), four antidepressants (fluoxetine, amitriptyline, nortriptyline, clomipramine) and four antiepileptics (carbamazepine, valproatesodium, phenytoin and phenobarbital)²⁰. In addition to the list, the provision of medicines in the hospitals depends on each institution's standard practices.

We obtained a two-stage probability sample, proportional to the type of care (inpatient or outpatient) and the national distribution of the reported AIDS cases by region. Eligibility criteria included adult patients (≥ 18 years old) under psychiatric care in hospitals or adult CAPS, who were able to answer the questionnaire and to sign the informed consent, as assessed by a mental health professional interviewer. We obtained demographic, socioeconomic, behavioral, and selected clinical data

through a semi-structured interview. Medical data, including psychiatric diagnoses and prescriptions, was obtained from medical charts. Protocol, questionnaires and procedures were tested in a pilot study, described previously¹⁸.

The project was approved by the participating centers and by the Ethics Research Committee of the Minas Gerais Federal University (COEP/UFMG, Etic 125/05) and the National Ethics Research Committee of the Brazilian Ministry of Health (CONEP 592/2006).

Events and explanatory variables

Psychotropic polypharmacy, the event of interest in this study, was defined as the concurrent use of two or more psychotropic medicines registered in the medical charts at the time of data collection. Patients under psychotropic polypharmacy were compared with patients on monotherapy and those who did not use any medication. For the purposes of this analysis, the potential explanatory variables were grouped into individual and institutional characteristics.

The individual characteristics investigated were: (a) demographic: age (≥ 40 or < 40 years old), marital status (single/divorced/widowed or married/stable union); (b) socioeconomic: education level (≥ 5 or < 5 years of study), place of residence (unstable or stable), health insurance (yes or no), family income in the last month (\leq USD 200 or $>$ USD 200); (c) behavioral: lifetime cigarette smoking (current smokers or ex-smokers or non-smokers), lifetime alcohol or illicit drug use (yes or no); (d) medical information: self-reported previous hospitalization (yes or no), non-psychotropic medicine prescription (yes or no), main psychiatric diagnosis, number of psychiatric diagnoses, non-psychiatric comorbidities and number of non-psychiatric diagnoses. Explanatory characteristics related to the mental health service were type of service setting (psychiatric hospital or CAPS), number of professionals, and availability of medicines in the centers.

Current place of residence was defined as unstable (living in shelters, hostels, hospital or on the streets) and stable (living in a house or apartment). Current smokers were defined as those who reported smoking at least one cigarette per day regardless of the length of smoking period at the time of the interview, and ex-smokers those who used to smoke, but were not smokers at the time of the interview. Lifetime alcohol or illicit drug use was defined as the use of alcohol or any illicit drug regardless of the frequency or dose.

Previous hospitalization was defined as self-reported hospitalization before the date of the interview. The main psychiatric diagnosis was extracted from the patient's chart and described according to the 10th revision of the International Classification of Diseases (ICD-10)²¹. In the case of more than one diagnosis, these were hierarchically classified according to severity, as follows (1) psychotic disorders, depression with psychotic symptoms and bipolar disorder, (2) depression and anxiety, (3) substance use disorder, and (4) other (e.g. dementia, mood disorders and personality and behavior, epilepsy). On account of the small numbers, categories (2), (3) and (4) were grouped together as non-severe mental illness and (1) corresponded to severe mental illness²². Psychotropic medicines were classified according to the Anatomical Therapeutic Chemical (ATC) classification of the World Health Organization²³.

Characteristics related to the services were obtained from the director of each site. The number of professionals was classified as sufficient and insufficient, considering the Brazilian Ministry of Health recommendation to health services operation. Medicines were classified as sufficient or insufficient based on a qualitative assessment and perception of the availability and variability of medicine lists for prescription by health professionals at the service, as described previously¹⁷.

Statistical analysis

A descriptive analysis was carried out followed by bivariate analysis, stratified by gender. Pearson's Chi-square was used to assess statistical differences in proportions. The magnitude of the associations between explanatory variables and psychotropic polypharmacy was estimated by the odds ratio (OR) with a 95% confidence interval (95%CI) and the level of significance considered was 0.05.

Multivariate analysis was conducted by logistic regression. Variables with p-values equal to or less than 0.20 in the bivariate analysis were selected to start multivariate modeling. The backward

stepwise procedure was conducted, i.e. modeling, began with all variables (full model) and sequential deleting of each variable. Only variables with p-values equal to or less than 0.05 remained in the final model. Missing data were excluded from analysis. The likelihood ratio test was used to compare models, and fit was evaluated using the Hosmer-Lemeshow test. Statistical analyses were performed using the SAS 9.4 (SAS Inst., Cary, USA) and Stata 13 (StataCorp LP, College Station, USA) softwares.

Results

A total of 2,475 (90%) participants were interviewed. The remaining 10% of the sample (288) did not participate mainly because of refusal (52%). There was no statistically significant difference between participants and non-participants with regard to age, sex, schooling and psychiatric diagnoses.

Among the 2,475 participants, 1,277 (51.6%) were women. Psychotropic medicines were prescribed for 96.0% of the patients with a mean number of 2.98 psychotropic medicines per patient (SD = 1.23; coefficient of variation = 41%, and median = 3.0). Psychotropic polypharmacy occurred in 85.3% of patients (N = 2,111; 95%CI: 83.8%-86.6%), 85.7% among men (95%CI: 83.6%-87.6%) and 84.9% among women (95%CI: 82.8%-86.8%; p > 0.05). Non-psychotropic medicines were also prescribed for 31.8% (95%CI: 30.0%-33.6%) of the patients (Table 1).

Table 1

Description of psychiatric patients studied. PESSOAS Project, Brazil, 2006 (N = 2,475).

Characteristics	Total (N = 2,475)		Men (n = 1,198)		Women (n = 1,277)	
	n *	%	n *	%	n *	%
Mental health service						
Service setting (psychiatric hospital)	898	36.3	537	44.8	361	28.3 **
Socio-demographics						
Age (≥ 40 years)	1,351	54.6	604	50.5	747	58.5 **
Schooling (< 5 years)	1,206	49.8	598	51.2	608	48.5
Marital status (single/divorced/widowed)	1,662	67.2	913	76.3	749	58.7 **
Place of residence (unstable)	306	12.4	199	16.6	107	8.4 **
Health insurance (yes)	256	10.6	112	9.7	144	11.4
Monthly family income (> USD 200)	1,017	64.5	497	70.0	520	60.0 **
Behavior						
Current smokers (yes)	1,298	52.7	761	63.8	537	42.3 **
Ex-smokers (yes)	465	18.9	209	17.5	256	20.2
Ever used alcohol (yes)	1,591	64.7	924	77.5	667	52.7 **
Ever used any illicit drug (yes)	621	25.2	438	36.7	183	14.4 **
Clinical						
Previous hospitalization (yes)	1,434	58.3	790	66.3	644	50.8 **
Psychotropic polypharmacy (≥ 2 medicines)	2,111	85.3	1,027	85.7	1,084	84.9
Non-psychotropic medicines prescribed (yes)	774	31.8	435	36.6	339	27.2 **
Psychiatric diagnosis (ICD-10) [severe mental illness]	1,403	56.7	729	60.9	674	52.8 **
Number of psychiatric diagnoses (> 1)	994	40.2	496	41.4	498	39.0
Number of non-psychiatric diagnoses (> 1)	189	7.8	88	7.6	101	8.1

ICD-10: 10th revision of the International Classification on Diseases ²¹.

* Excluded missing values;

** Statistical significance p < 0.05.

Note: severe mental illness: psychotic disorders, depression with psychotic symptoms and bipolar disorder. Non-severe mental illness: depression and anxiety, substance use disorder, dementia, other.

Considering the mental health service, 36.3% of patients were treated in a psychiatric hospitals, with a greater proportion of men (44.8%; $p < 0.05$). Regarding socio-demographic characteristics, 54.6% were 40 years old or over – with women older than men on average ($p < 0.05$) – and 49.8% of patients had less than five years of schooling. Men were more often single, divorced or widowed (76.3% vs. 58.7%), had an unstable place of residence (16.6% vs. 8.4%), and had family incomes higher than USD 200 in the last month (70% vs. 60%). Only 10.6% of all patients had health insurance.

There was a high prevalence of current smoking and alcohol use among patients (52.7% and 64.7%, respectively) and about a quarter of them declared having used any illicit drug during their lifetime, with men presenting higher rates than women in all of those characteristics.

With respect to clinical characteristics, the majority of patients had been previously hospitalized (58.3%) and had severe mental illness diagnosis (56.7%), both with higher prevalence among men ($p < 0.05$). Moreover, 40.2% of the patients had more than one psychiatric diagnosis, while only 7.8% had more than one non-psychiatric diagnosis (Table 1).

Among the 26 services included, 65.4% were considered to have an insufficient number of professionals (CAPS = 80%; hospitals = 45.5%) and 19.2% to have an insufficient number of mental health medicine available (CAPS = 36.7%; hospitals = 9%) (data not shown in tables).

The ten most commonly prescribed medicines were haloperidol (15.7%), biperiden (10.5%), diazepam (8.9%), chlorpromazine (8.7%), carbamazepine (7.3%), promethazine (6.9%), clonazepam (6.4%), levomepromazine (4.4%), amitriptyline (3.9%), and fluoxetine (3.4%), accounting for about 75% of all prescription medicine records. Considering the second and third levels of the ATC classification system, the most prescribed medicines were psycholeptics (antipsychotic agents = 37%; anxiolytics = 10%; hypnotics and sedatives = 1%), followed by antiepileptics (17%), psychoanaleptics (antidepressants = 12%) and antiparkinsonian (anticholinergic agents = 11%) (data not shown in tables).

The same pattern was observed for patients in psychotropic polypharmacy. Antipsychotics were most often combined with other medicines, either in the same class (37.5%) or with other classes, including antiepileptics (33.7%), anticholinergics (33.3%), anxiolytics (22.2%), antidepressants (17.9%), and to a lesser extent with hypnotics and sedatives (2.4%) (Table 2).

Stratified gender analysis

The bivariate analysis indicated that for both genders, severe mental illness diagnoses were associated with a higher chance of psychotropic polypharmacy, as well as the number of psychiatric diagnoses and inpatient care (i.e., psychiatric hospital), and self-reported previous hospitalization ($p < 0.05$). An insufficient number of professionals in the services was negatively associated with a higher chance of polypharmacy for both genders ($p < 0.05$). Furthermore, for both genders being single, divorced or widowed, and lifetime illicit drug use were associated with higher psychotropic polypharmacy ($p < 0.05$). Having more than five years of schooling and having health insurance were associated with psychotropic polypharmacy among men only. Among women, more than one non-psychiatric diagnosis and reporting current smoking or alcohol use were associated with psychotropic polypharmacy ($p < 0.05$). The prescription of non-psychotropic medicines was positively associated with psychotropic medicines among women, and negatively associated among men ($p < 0.05$) (Table 3).

Multivariate analysis revealed that correlates of polypharmacy differed between men and women. For both genders, patients previously hospitalized, with severe mental illness diagnoses, and with more than one psychiatric diagnosis had a higher chance of psychotropic polypharmacy ($p < 0.05$). Instead, an insufficient number of professionals in the health care unit was negatively associated with psychotropic polypharmacy ($p < 0.05$). Among men, inpatient care was associated with higher psychotropic polypharmacy, while unstable living and the prescription of any non-psychotropic medicines were negatively associated with psychotropic polypharmacy ($p < 0.05$). Finally, among women, the prescription of non-psychotropic medicines and lifetime cigarette smoking were associated with a higher chance of psychotropic polypharmacy ($p < 0.05$) (Table 4).

Table 2

Description of the combinations of psychotropic medicines prescribed according to the ATC classification. PESSOAS Project, Brazil, 2006 (n = 2,111).

ATC classification (3rd level) combination	n *	%
Same class combination		
Antipsychotics	792	37.5
Antiepileptics	207	9.8
Antidepressants	74	3.5
Anxiolytics	2	0.1
Anticholinergics	1	0.0
Different classes combination		
Antipsychotics + Antiepileptics	712	33.7
Antipsychotics + Anticholinergics	703	33.3
Antipsychotics + Anxiolytics	469	22.2
Antipsychotics + Antidepressants	377	17.9
Antiepileptics + Antidepressants	313	14.8
Antiepileptics + Anticholinergics	288	13.6
Antidepressants + Anxiolytics	253	12.0
Anxiolytics + Anticholinergics	204	9.7
Antiepileptics + Anxiolytics	197	9.3
Anticholinergics + Antidepressants	142	6.7
Antipsychotics + Hypnotics and sedatives	50	2.4
Antidepressants + Hypnotics and sedatives	27	1.3
Antiepileptics + Hypnotics and sedatives	25	1.2
Anxiolytics + Hypnotics and sedatives	22	1.0
Anticholinergics + Hypnotics and sedatives	17	0.8

ATC: Anatomical Therapeutic Chemical classification system ²³.

* Included only patients on psychotropic polypharmacy (≥ 2 medicines prescribed).

Table 3

Bivariate analysis of psychotropic polypharmacy, stratified by gender, among patients with mental disorders. PESSOAS Project, Brazil, 2006 (N = 2,475).

Characteristics	Men (n = 1,198)				Women (n = 1,277)			
	Total	OR	95%CI	p-value	Total	OR	95%CI	p-value
Mental health service								
Service setting								
Psychiatric hospital	537	1.65	1.18-2.32	0.003 *	361	3.97	2.46-6.42	< 0.001 *
CAPS	661	1.00			916	1.00		
Number of professionals								
Insufficient	743	0.57	0.39-0.80	0.001*	355	0.62	0.42-0.90	0.011 *
Sufficient	455	1.00			922	1.00		
Number of medicines								
Insufficient	189	1.05	0.67-1.65	0.825	329	0.82	0.58-1.16	0.262
Sufficient	1,009	1.00			948	1.00		

(continues)

Table 3 (continued)

Characteristics	Men (n = 1,198)				Women (n = 1,277)			
	Total	OR	95%CI	p-value	Total	OR	95%CI	p-value
Socio-demographics								
Age (years)								
≥ 40	604	0.79	0.57-1.09	0.150	747	1.28	0.94-1.74	0.117
< 40	593	1.00			530	1.00		
Schooling (years)								
< 5	598	0.67	0.48-0.94	0.019 *	608	0.82	0.61-1.12	0.219
≥ 5	569	1.00			645	1.00		
Marital status								
Single/Divorced/Widowed	913	1.44	1.01-2.07	0.043*	749	1.65	1.21-2.24	0.001*
Married/Stable union	284	1.00			528	1.00		
Place of residence								
Unstable	199	0.71	0.47-1.06	0.094	107	1.45	0.78-2.70	0.237
Stable	997	1.00			1168	1.00		
Health insurance								
Yes	112	2.02	1.00-4.07	0.046 *	144	0.65	0.42-1.00	0.050
No	1,042	1.00			1,117	1.00		
Monthly family income (USD)								
> 200	497	1.11	0.70-1.77	0.664	520	0.72	0.50-1.05	0.088
≤ 200	213	1.00			346	1.00		
Behavior								
Smoking								
Current smoker	761	1.24	0.89-1.74	0.195	537	2.00	1.43-2.80	< 0.001 *
Ex-smoker	209	0.95	0.62-1.44	0.795	256	1.10	0.75-1.63	0.621
Non-smoker	222	1.00			476	1.00		
Alcohol use (ever)								
Yes	924	1.24	0.85-1.80	0.262	667	1.44	1.05-1.96	0.021*
No	269	1.00			598	1.00		
Any illicit drug use (ever)								
Yes	438	1.75	1.22-2.51	0.002 *	183	3.47	1.80-6.69	< 0.001 *
No	755	1.00			1,090	1.00		
Clinical								
Self-reported previous hospitalization								
Yes	790	1.91	1.38-2.65	< 0.001 *	644	4.71	3.26-6.78	< 0.001 *
No	402	1.00			623	1.00		
Non psychotropic medicines prescribed								
Yes	435	0.70	0.51-0.98	0.037 *	339	2.78	1.76-4.39	< 0.001 *
No	753	1.00			909	1.00		
Psychiatric diagnosis (ICD-10)								
Severe mental illness	729	2.74	1.96-3.81	< 0.001 *	674	5.20	3.61-7.50	0.000 *
Non-severe mental illness	469	1.00			603	1.00		
Number of psychiatric diagnoses								
> 1	496	1.74	1.23-2.47	0.002 *	498	4.95	3.22-7.62	< 0.001 *
≤ 1	702	1.00			779	1.00		
Number of non-psychiatric diagnoses								
> 1	88	0.73	0.41-1.29	0.273	101	3.47	1.39-8.67	0.005 *
≤ 1	1,077	1.00			1,148	1.00		

95%CI: 95% confidence interval; CAPS: Psychosocial Care Centers; ICD-10: 10th revision of the International Classification of Diseases ²¹; OR: odds ratio.

* Statistical significance $p < 0.05$.

Note: excluded missing values. Severe mental illness: psychotic disorders, depression with psychotic symptoms and bipolar disorder. Non-severe mental illness: depression and anxiety, substance use disorder, dementia, other.

Table 4

Multivariate analysis of psychotropic polypharmacy, stratified by sex, among patients with mental disorders. PESSOAS Project, Brazil, 2006 (N = 2,245).

Characteristics	Men * (n = 1,078)		Women ** (n = 1,167)	
	OR (95%CI)	p-value	OR (95%CI)	p-value
Mental health service				
Service setting (psychiatric hospital)	2.00 (1.23-3.24)	0.005 ***	-	-
Number of professionals (insufficient)	0.61 (0.39-0.96)	0.033 ***	0.61 (0.38-0.97)	0.035 ***
Socio-demographics				
Place of residence (unstable)	0.50 (0.30-0.83)	0.007 ***	-	-
Behavior				
Current smoker (yes)	-	-	1.91 (1.27-2.87)	0.002 ***
Ex-smoker (yes)	-	-	1.54 (0.96-2.45)	0.072
Clinical				
Self-reported previous hospitalization (yes)	1.59 (1.10-2.29)	0.014 ***	2.56 (1.68-3.89)	< 0.001 ***
Psychiatric diagnosis (severe mental illness)	2.61 (1.81-3.77)	< 0.001 ***	2.91 (1.93-4.39)	< 0.001 ***
Number of psychiatric diagnoses (> 1)	1.56 (1.07-2.27)	0.022 ***	3.90 (2.48-6.12)	< 0.001 ***
Non psychotropic medicines prescribed (yes)	0.58 (0.38-0.86)	0.009 ***	1.96 (1.19-3.18)	0.008 ***

* Hosmer-Lemeshow test: $\chi^2 = 10.71$; df = 8; p = 0.219;

** Hosmer-Lemeshow test: $\chi^2 = 6.45$; df = 8; p = 0.597;

*** Statistical significance p < 0.05.

Note: excluded missing values. Severe mental illness: psychotic disorders, depression with psychotic symptoms and bipolar disorder. Non-severe mental illness: depression and anxiety, substance use disorder, dementia, other.

Discussion

The use of psychotropic medicines and the occurrence of psychotropic polypharmacy were common therapeutic approaches in this nationwide sample of patients with mental illness in Brazil. The proportion of polypharmacy in this population was high and similar among genders, despite the fact that factors independently associated with psychotropic polypharmacy varied among them.

Cross-sectional studies have shown that the use of psychotropic medicines is quite common in the general population. In Brazil, the prevalence of psychotropic use ranged from 6.5% to 13.3%^{9,10,24}, with an emphasis on the use of antidepressants, which were more common among women⁹. In addition, only 16% of patients with a mental disorder were treated with psychotropic agents⁹, contrasting with the high rate of prescriptions of these medicines in our study (96%). These differences may be due to the population, since our sample contains more severe cases than in the general population, and also due to the source of information obtained about the use of medicines (self-reported vs. medical chart register) and the diagnoses evaluated (self-reported vs. medical chart as registered by physicians). Moreover, the difficulty of general practitioners to diagnose and treat patients with mental disorders in primary care settings and barriers of access to specialized health services²⁵ may also help to explain these differences.

Studies have shown that psychotropic polypharmacy among patients with psychiatric disorders varies from 10% to 93%^{13,26,27,28,29,30}, in line with the psychotropic polypharmacy prevalence of 85.3% in our national sample. A trend of enhancing polypharmacy among psychiatric patients has been observed, with a decline in monotherapy strategy over the years from 47.8% in the 1970s, to 19.6% in the 1990s³¹. This can also be observed in the mean number of psychotropic medications prescribed per individual. A combined analysis of 28 studies involving 23,428 patients showed a mean of 2.47 (1.5 to 4.0) psychotropic medicines/institutionalized patient³¹. In recent studies this number is even higher (2.8)²⁸, as was observed in our study (2.98).

Regarding risk factors relating to psychotic polypharmacy, we found that severe mental illness diagnoses were associated with psychotic polypharmacy for both men and women and almost 60% of the patients had severe mental illness diagnosis. The literature describes primary psychiatric diagnosis as one of the most important factors associated with psychotropic polypharmacy: patients with severe mental illnesses such as schizophrenia, depression with psychotic symptoms, and bipolar disorders are at greater risk of polypharmacy and increased use of psychotropic medicines ^{13,26,30,32,33}.

Patients with multiple psychiatric diagnoses also had increased chances of polypharmacy. These findings are corroborated by other studies, which pointed to an association between polypharmacy and markers of more severe illness, such as the number of psychiatric diagnoses ¹⁵, non-psychiatric comorbidities ¹², and previous hospitalization ³⁴. This could partially be explained by actual need of different drugs or monotherapy-refractory conditions that require changes in prescription regimens. Furthermore, similar to other countries, the reduction in the number of psychiatric hospital beds in Brazil may have resulted in discharge of patients with clinically severe conditions, meaning there is a greater need of medicalization in order to facilitate social interaction ^{13,31}, despite the lack of evidence to support these inferences ²⁷.

We observed an independent association between psychotropic polypharmacy and current cigarette smoking among women only. Studies in the general population have shown the association between smoking and the simultaneous use of four or more medicines ³⁵ and also with psychotropic medicines ²⁴. In addition, previous studies among psychiatric patients indicate an association between current smoking and substance use disorder diagnoses, but not with ex-smokers ³⁶. Current smokers with substance use disorder diagnoses may be more refractory to smoking cessation and potentially in need of more adjuvant therapy. Whether this is only the case among women needs further investigation and studies are needed to clarify this association.

Among men, being currently hospitalized was associated with higher psychotropic polypharmacy, while having an unstable place of residence (living in shelters, hostels, streets, hospital), as well as having a prescription for non-psychotropic medicines were associated with less psychotropic polypharmacy. We did not find any study that considered these two treatment settings (hospital and CAPS). However, a Brazilian study conducted in 2005 found that elderly patients with length of hospitalization of between 12 and 35 months had less polypharmacy than newly institutionalized patients, probably because at the time of admission these patients had greater severity and instability of the disease ³⁷. Minor antipsychotic polypharmacy in hospitalized and homeless patients occurred in in-patient facilities in Italy in 2002-2003 ²⁶. These studies are consistent with our findings, in which patients in current treatment at the hospitals, with greater severity of illness, showed greater polypharmacy, while those living in unstable conditions had lower polypharmacy.

In our study, the most prescribed medicines were haloperidol, biperiden, diazepam, and chlorpromazine, as reported in East Asia for schizophrenic patients ²⁷. Antipsychotics were the most prescribed medicines (37%) and the most commonly used combinations involved these agents, as observed in other studies ^{13,28,30}. However, antipsychotic polypharmacy is quite controversial in the literature. It has been associated with higher prescriptions of adjunctive medications such as anticholinergic and anti-parkinsonian medicines ^{26,27}; higher daily dosages and higher rates of adverse events ¹⁴.

The negative association between insufficiency of psychiatric professionals and lower polypharmacy deserves attention. It should be noted that proper diagnostic assessment and the need for psychotropic prescription is better ascertained by trained psychiatric professionals. It is likely that this association is only a marker for a lack of psychiatrists, thus patients are not being evaluated for the use of psychotropic medicines. We should also note that the variable 'insufficient availability of medicines' was also found to be in the same direction in the univariate analysis, though it was not statistically significant.

Regarding the availability of psychotropic medicines, in 80.8% of the Brazilian psychiatric services this availability was considered sufficient. However, for most services (92.3%) the standardized medicine list included mainly first generation antipsychotic agents (e.g. haloperidol, chlorpromazine, lithium carbonate) ¹⁷. According to a recent Chinese study, the reduced availability of therapeutic classes can potentially be associated with polypharmacy utilization ³⁸. The updated RENAME did not include antipsychotic agents, but did include two anti-parkinson drugs (cabergoline and

levodopa+benserazide) and one hypnotics and sedative – midazolam. Alternatively, second-generation antipsychotics (clozapine, risperidone, olanzapine, quetiapine, and ziprasidone), other anti-parkinson drugs (amantadine, bromocriptine, entacapone, pramipexole, selegiline, tolcapone), other antiepileptics (ethosumide, gabapentin, lamotrigine, primidone, topiramate, trihexyphenidyl, vigabatrin) and the anxiolytic clobazam are provided by the Brazilian Unified National Health System (SUS) through the specialized component of pharmaceuticals in line with specific criteria ³⁹.

Another barrier to the quality of care in mental health that can contribute to the occurrence of psychotropic polypharmacy is the lack of a national guidelines for prescribing practices in psychiatric care, considering the medicine-based evidence principles. These guidelines should address when polypharmacy is appropriated, for example, in short periods to control the exacerbation of symptoms, to prevent adverse events after increasing the dose of a single agent, or in patients that have been refractory to monotherapy ^{26,40,41}. Case management, continuing education, treatment algorithms, reminders and feedbacks, and pharmaceutical care are other approaches that can be used to avoid inappropriate psychotropic prescribing ⁴¹.

Some limitations of the study should be pointed out. We were not able to address polypharmacy with regard to its duration and reasons for using more than one medication, and this should be further explored in future studies. The definition of psychotropic polypharmacy as the use of two or more psychotropic medicines led to a high rate of this event in this population, and therefore, the effect size of the associated factors may be potentially overestimated by the use of logistic regression. Psychiatric diagnoses were collected from medical charts and there was a limit of seven psychiatric medications that could be collected. Also, because the sample size was not a priori calculated to study polypharmacy stratified by gender, we may have had limited power to detect differences among selected variables with small numbers in both groups. Finally, the study design limits the establishment of direct causality. The associations observed are only indicators of potential causal effect and they may contain residual confounding due to unmeasured variables. In addition, due to the scarcity of literature in the field regarding this population, comparisons are limited and other studies are needed to confirm these findings.

Conclusion

In this nationwide sample of psychiatric patients, psychotropic medicine utilization and psychotropic polypharmacy were common practices, with differences in the set of associated factors among genders. There is a need for developing national guidelines to manage patients with mental illness, which should consider the role of gender and disease severity. Other strategies such as case management, continuing education and pharmaceutical care can also contribute to the reduction of the burden of polypharmacy in this population.

Contributors

J. O. Costa carried out the data analysis and interpretation, critical revision of relevant content and approval of final version for publication, as well as overseeing all stages of the research to guarantee the precision and integrity of all elements of the study. M. G. B. Ceccato carried out the data interpretation, write-up of the article and approval of final version for publication, as well as overseeing all stages of the research to guarantee the precision and integrity of all elements of the study. A. P. S. Melo contributed towards the data analysis and interpretation, article write-up and approval of the final version for publication. F. A. Acurcio contributed towards the project design, critical revision of relevant content and approval of the final version for publication. M. D. C. Guimarães contributed towards the project design, data analysis and interpretation, critical revision of relevant content and approval of the final version for publication.

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Conflict of interest

The authors declare no conflict of interests.

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Resumo

Os autores tiveram como objetivo estimar a prevalência da polifarmácia psicotrópica e fatores associados entre pacientes psiquiátricos brasileiros, segundo o gênero. Foram obtidos dados sociodemográficos, comportamentais e clínicos por meio de entrevistas presenciais e prontuários médicos de 2.475 pacientes. A polifarmácia psicotrópica foi definida como o uso de dois ou mais medicamentos psicotrópicos, e foi constatada em 85,7% dos homens (IC95%: 83,6%-87,6%) e 84,9% das mulheres (IC95%: 82,8%-86,8%; $p > 0,05$). A média de medicamentos psicotrópicos por paciente foi $2,98 \pm 1,23$, e as combinações mais comuns incluíam os antipsicóticos. A análise multivariada mostrou que, para ambos os gêneros, internação hospitalar prévia, doença psiquiátrica grave, múltiplos diagnósticos psiquiátricos e número insuficiente de profissionais na unidade de saúde foram associados à polifarmácia psicotrópica. Entretanto, fatores como cuidados hospitalares, uso de drogas não-psicotrópicas, condições de vida instáveis e tabagismo atual variaram de acordo com o gênero. A polifarmácia psicotrópica foi uma prática comum nessa amostra nacional. Os resultados evidenciam a necessidade de diretrizes nacionais para o manejo de pacientes com transtornos mentais, considerando a diferença entre gêneros e a gravidade da doença, para reduzir a carga da polifarmácia nessa população de pacientes.

Polimedicação; Psicotrópicos; Transtornos Mentais; Gênero e Saúde

Resumen

El objetivo de los autores fue estimar la prevalencia de la polifarmacia psicotrópica y factores asociados entre pacientes psiquiátricos brasileños, según con el género. Se obtuvieron datos sociodemográficos, comportamentales y clínicos, a través de entrevistas presenciales y registros médicos de 2.475 pacientes. La polifarmacia psicotrópica se definió como el uso de dos o más medicamentos psicotrópicos, y fue constatada en un 85,7% de los hombres (IC95%: 83,6%-87,6%) y en un 84,9% de las mujeres (IC95%: 82,8%-86,8%; $p > 0,05$). La media de medicamentos psicotrópicos por paciente fue de $2,98 \pm 1,23$, y las combinaciones más comunes incluían los antipsicóticos. El análisis multivariado mostró que, para ambos géneros, el internamiento hospitalario previo, enfermedad psiquiátrica grave, múltiples diagnósticos psiquiátricos, y número insuficiente de profesionales en la unidad de salud, estuvieron asociados a la polifarmacia psicotrópica. Asimismo, otros correlatos, tales como cuidados hospitalarios, uso de medicamentos no-psicotrópicos, condiciones de vida inestables y tabaquismo actual variaron de acuerdo con el género. La polifarmacia psicotrópica fue una práctica común en esa muestra nacional. Los resultados destacan la necesidad de directrices nacionales para cuidar de pacientes con trastornos mentales, considerando la diferencia entre géneros y la gravedad de la enfermedad, para reducir la carga de la polifarmacia en esa población de pacientes.

Polifarmacia; Psicotrópicos; Trastornos Mentales; Género y Salud

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