INTRODUCTION

Since its introduction in the early 60s (1), benzodiazepines (BZDs) have been the most prescribed psychotropic medication worldwide (2), despite their various therapeutic and side effects (2,3). Therapeutic indications for the use of BZDs are diverse and include the treatment of seizures (4), alcohol and barbiturate withdrawal symptoms (5), psychomotor agitation (6), insomnia and other sleep disorders (7), panic disorders (8), social phobia, generalized anxiety disorder (9), and as an adjunctive treatment for both depression and mania (10). Common side effects of BZD are drowsiness associated with incoordination or ataxia, which may lead to car accidents, problems with operating machinery, and, especially among the elderly, falls (11). Memory impairments that are potentially non-reversible have also been observed (3,12). Long-term use of BZDs is related to physical dependence. Discontinuation from chronic BZD use can result in withdrawal syndrome, particularly among the elderly (10). Withdrawal symptoms that have been reported include anxiety, sleep disturbance, irritability, a hand tremor, and rarely, more severe conditions such as seizures and psychosis (13).

Current guidelines such as the National Institute of Health and Care Excellence (NICE) (14) recommend that BZD should be used at the lowest possible dose for the shortest period possible. There are considerable evidence-based concerns regarding the serious adverse consequences of BZD use, such as falls (14), risk of suicide, abuse, dependence (10), and risk of Alzheimer’s disease (15). In a series of pharmacoepidemiological studies conducted by the World Mental Health Survey Initiative (WMHS) (16,17), the use of psychotropic agents was evaluated in the general population. In addition, if a respondent had been diagnosed with a psychiatric disorder in the 12 months preceding the survey, this was recorded (18,19). The observed prevalence of BZD use in the general population ranged between 3.2% and 18.6% (Table 1). These rates were even higher among individuals that had been diagnosed with a psychiatric disorder, with a range between 9.2% and 41.9%.

OBJECTIVES: To report the prevalence and factors associated with the use of benzodiazepines in the general population and those with a mental health condition in the metropolitan area of São Paulo, Brazil.

METHODS: 5,037 individuals from the Sao Paulo Megacity Mental Health Survey data were interviewed using the Composite International Diagnostic Interview, designed to generate DSM-IV diagnoses. Additionally, participants were asked if they had taken any medication in the previous 12 months for the treatment of any mental health condition.

RESULTS: The prevalence of benzodiazepine use ranged from 3.6% in the general population to 7.8% among subjects with a mental health condition. Benzodiazepine use was more prevalent in subjects that had been diagnosed with a mood disorder as opposed to an anxiety disorder (14.7% vs. 8.1%, respectively). Subjects that had been diagnosed with a panic disorder (33.7%) or bipolar I/II (23.3%) reported the highest use. Individuals aged ≥50 years (11.1%), those with two or more disorders (11.2%), those with moderate or severe disorders (10%), and those that used psychiatric services (29.8%) also reported higher use.

CONCLUSION: These findings give an overview of the use of benzodiazepines in the general population, which will be useful in the public health domain. Benzodiazepine use was higher in those with a mental health condition, with people that had a mood disorder being the most vulnerable. Furthermore, females and the elderly had high benzodiazepine use, so careful management in these groups is required.

KEYWORDS: Psychiatry; Pharmacy; Psychotropic Drugs; Hypnotics and Sedatives; Benzodiazepines.

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Benzodiazepine use in Sao Paulo, Brazil

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Methods

Benzodiazepine use in Sao Paulo, Brazil

São Paulo Megacity Mental Health Survey

Data for this report were sourced from the São Paulo Megacity Mental Health Survey (SPMHS). The SPMHS is the Brazilian segment of the World Mental Health Survey Initiative, coordinated by the World Health Organization and Harvard University. It was conducted in more than 28 research centers around the world. The SPMHS is a cross-sectional, population-based study. It was designed to estimate the prevalence of mental health disorders, mental health services, and psychotropic drug utilization in a representative sample of the general population. By design, individuals over 18 years old, living in the São Paulo metropolitan area were interviewed by trained lay interviewers (24).

Sample

A sample of 5,037 individuals (response rate: 81.3%) were assessed using the Composite International Diagnostic Interview (CIDI), which generates DSM-IV diagnoses. We report on a subsample of 2,935 subjects who were submitted to a more extended version of the interview, which included questions on psychotropic drug use (24).

Data collection

Participants were asked about prescription medicines that they had used in the previous 12 months for emotional issues, nerves, mental health, substance use, energy, concentration, sleep, or stress. According to the Anatomical Therapeutic Chemical (ATC) index 2018 (https://www.whocc.no/atc_ddd_index/), the medicines focused on in this report were anxiolytics (alprazolam, bromazepam, clobazam, clordiazepoxide, clonazolam, diazepam, and lorazepam), hypnotics and sedatives (chloral hydrate, flunitrazepam midazolam, zolpidem), and antiepileptics (clonazepam). The term “benzodiazepines” (BZDs) will be used henceforth to refer to all the above medicines.

Data analysis

The data analysis examined both the prevalence of BZD use in the general population and among individuals who had been diagnosed with a mental health disorder. Few studies have been conducted on the prevalence of BZD use in specific non-developed regions. In Chile, the estimated prevalence of BZD use in the general population was 4% (21) (Table 1). Few studies have been conducted on the prevalence of BZD use in Brazil (20). The relationship between BZD use and mental health disorders in the general population has rarely been investigated (22). The reported prevalence of BZD use over one month in the general population was 2% and 3% in Rio de Janeiro and São Paulo, respectively (23). Among individuals who had been diagnosed with a mental health disorder, the one-month prevalence of BZD use was lower in Rio de Janeiro than in São Paulo (3.4% vs. 7.1%, respectively). However, the methodological differences regarding the period investigated, sample characteristics, and data collection preclude any direct comparisons being made (20). There is a lack of knowledge regarding the use of BZDs over a period longer than 12-months, its monotherapy or polypharmacy patterns, the prevalence of BZD use in specific mental health disorders, and the impact of BZD use on symptom severity, comorbidities, health insurance coverage, and health service use.

Given the scarcity of epidemiological data, we aimed to report the prevalence of BZD use in a representative sample of the general population and those with a mental health condition (diagnosed in the last 12 months) in São Paulo, Brazil. Information about monotherapy and the combined use of BZDs along with its relationship to symptom severity, comorbidities, health insurance coverage, and health service use are also discussed.

Table 1 - Pharmacoepidemiological studies conducted within the World Mental Health survey initiative and other studies in South America.

| Reference | Location | Period       | Names of studies | Sample | Age | Prevalence of use |
|-----------|----------|--------------|-----------------|--------|-----|------------------|
| Alonso et al. (25) | Europe | 2001-2003 | ESEMeD | 21,425 | ≥ 18 | 9.8% 25.5% |
| Bruffaertes et al. (16) | Belgium | 2001-2002 | ESEMeD | 2,419 | ≥ 18 | 12.3% 25.5% |
| Codony et al. (18) | Spain | 2001-2002 | ESEMeD | 5,473 | ≥ 18 | 11.4% 32.7% |
| Campanha et al. (20) | Brazil | 2005-2007 | SPMHS | 2,935 | ≥ 18 | 3.6% 7.8% |
| Gasquet et al. (17) | France | 2001-2003 | ESEMeD | 2,894 | ≥ 18 | 18.6% 41.9% |
| Grinshpoon et al. (19) | Israel | 2003-2004 | INHS | 4,859 | ≥ 21 | 3.2% 9.2% |
| Other studies in South America | | | | | | |
| Rojas et al. (21) | Chile | 1996-1998 | | 3,870 | 16-64 | 04% - |
| Quintana et al. (22) | Rio de Janeiro | 2007-2008 | | 1,208 | ≥ 15 | 1.6% 3.4% |
| Quintana et al. (23) | São Paulo | 2007 | | 2,536 | 15-75 | 2.7% 7.1% |

High consumption of BZD was also observed among females and older people (16,17,18,19,20). However, methodological diversity hampered a direct comparison of the rate of BZD use among participant countries of the WMHS Initiative.
BZDs more often than males (5.5% vs. 1.6%). The use of BZD was also higher among subjects aged over 65, compared to those aged 50-64 and 18-24 years (7.8% vs. 6.1% vs. 1.8%, respectively) (Table 2).

The use of BZD monotherapy was reported in 1.8% of the sample. Antidepressants (1.4%) were the most commonly used psychiatric medication in combination with BZD (Table 3).

Table 2 presents the correlates of BZD use according to the socio-demographic variables, psychiatric diagnoses, comorbidities, symptom severity, use of health services, and the possession of private health insurance coverage.

The use of BZD was higher in those aged between 35-49 years (10.2% vs. 4.7%; OR=2.3; 95%CI=1.4-4.7), and over 50 years (11.1% vs. 4.7%; OR=2.6; 95%CI=1.2-5.3), than those between 18-34 years (4.7%). The use of BZDs was also higher among homemakers, retired subjects, and the unemployed compared to employed individuals (11.8% vs. 10.1% vs. 5.9%, respectively (Table 4).

Concerning psychiatric disorders, individuals diagnosed with a mood disorder (14.7%; OR=5.5; 95%CI=2.5-13), anxiety disorder (8.1%; OR=3.5; 95%CI=1.6-7.8), or substance use disorder (7.9%; OR=2.9; 95%CI=1.5-5.2) were more likely to use BZD than those without these disorders (Table 4).

Psychiatric comorbidities and symptom severity also play a role in the use of BZDs. Although individuals who had been diagnosed with two or more disorders used more BZDs than those with a single diagnosis (11.2% vs. 5.6%; OR=2.1, 95%CI=1-3.3), the likelihood of using BZD was lower in the adjusted model 2 (OR=0.4; 95%CI=0.2-0.9). The likelihood of BZD use was higher among patients with disorders that were considered to be serious or moderate than among those with a mild disorder (10.0% vs. 3.7%; OR = 2.8; 95%CI=1.7-4.8) (Table 4).

There was a trend ($p = 0.0505$) of higher BZD use among individuals who had health insurance coverage than those who did not (10.7% vs. 6.1%; OR=1.9; 95%CI=1.0-3.4). Remarkably, BZD use among individuals who reported using psychiatric services was almost 30 times higher than those who did not (29.8% vs. 1.3%; OR=25.0; 95%CI=13.7-45.6) (Table 4).

BZD use among subjects who had been diagnosed with a mental health disorder was 7.8%. Among the diagnostic classes, mood disorders displayed the highest prevalence of BZD use (14.7%). Participants who had been diagnosed with a panic disorder or bipolar disorder (33.7% and 23.3%, respectively) reported using BZD the most (Table 5).

The likelihood of BZD use was also higher among those with obsessive-compulsive disorder (OR=7.0; 95%CI=1.6-30.0), drug abuse (OR=8.2; 95%CI=1.9-36.4), drug dependence (OR=9.3, 95%CI=1.5-58.8), impulse control disorders (OR=5.6, 95%CI=1.1-27.7), and attention deficit disorder (OR=17.5, 95%CI=2.1-146.8) (Table 5).

Subjects that had not been diagnosed with a mental health disorder reported infrequent BZD use (1.9%). This prevalence was much higher among females than males (OR=13.0; 95%CI=4.1-41.3) (Table 5).

Considering the number of psychotropics used, 3% of subjects that had been diagnosed with a mental health disorder reported using BZD as a monotherapy. This was most frequent in those who had been diagnosed with attention deficit disorder (10.1%). The mean frequency of monotherapy was 2.9% for anxiety disorders, and 9.8% for panic disorders. Lower rates of BZD use were observed among individuals with mood (4%), bipolar I/II (4.5%) or major depressive disorders (4%) (Table 5).

Table 2 - Prevalence of benzodiazepine use in the previous 12 months in the general population according to sex and age. São Paulo Megacity Mental Health Survey (N=2935).

| Sex         | N (%) | SE  | p-value |
|-------------|-------|-----|---------|
| Total       | 162 (3.6) | 0.5 | 0.0004  |
| Female      | 122 (5.5) | 0.4 |         |
| Male        | 40 (1.6)  | 0.3 |         |
| Age         |        |     | 0.0687  |
| 18-24 (N=406) | 09 (1.8) | 0.9 |         |
| 25-34 (N=684) | 18 (2.6) | 0.7 |         |
| 35-49 (N=1,026) | 68 (3.4) | 0.6 |         |
| 50-64 (N=590) | 48 (6.1) | 1.4 |         |
| ≥ 65 (N=229)  | 19 (7.8)  | 3.5 |         |

Table 3 - Prevalence of monotherapy and combined use of benzodiazepines in the previous 12 months in the general population by sex. São Paulo Megacity Mental Health Survey (N=2935).

|                  | N (%) | SE  | OR (95% CI) female/male | $X^2$ | p-value |
|------------------|-------|-----|-------------------------|-------|---------|
| Benzodiazepines  | 162 (3.6) | 0.5 | 3.7 (2.0-6.7) | 18.2  | <0.0001 |
| Monotherapy ²    | 65 (1.8)  | 0.4 | 3.6 (2.0-6.5) | 18.5  | <0.0001 |
| Combined use ³   |       |     |                        |       |         |
| Benzodiazepines + antidepressant | 79 (1.4)  | 0.2 | 6.2 (2.3-16.7) | 13.3  | 0.0003 |
| Benzodiazepines + antipsychotics | 11 (0.2)  | 0.1 | 11.3 (2.7-48.0) | 10.9  | 0.001  |
| Benzodiazepines + mood stabilizer | 20 (0.4)  | 0.1 | 1.5 (0.5-5.2) | 0.5   | 0.4904 |

Weighted proportions. OR, odds ratio; CI, confidence interval. ²At least one psychotropic drug. ³Only benzodiazepines. ⁴Any benzodiazepine drug plus another psychiatric medication. Sex comparison: males were used as the reference group.

**DISCUSSION**

The 12-month prevalence of BZD use in the São Paulo metropolitan area was 3.6%. This rate is similar to that reported in a survey conducted in Rio de Janeiro (22). Similarly, in Chile, about 4% of individuals reported using hypnotics and anxiolytics (21). Conversely, the reported prevalence of BZD use in European countries (9.8% (25), 12.3% (16), 5.5% (19)), and the United States of America (5.2% (26)) is higher.

Even though the methodologies used were different, several studies have reported higher BZD use in Brazil previously. In 1979, the reported use of BZDs in São Paulo was 8.8% (27). Additionally, in 1993, 8.0% used tranquilizers and 1.2% used hypnotics (28). Recent studies have shown that the prevalence of use has indeed decreased to 1.6% and 2.7%, respectively, in Rio de Janeiro (22) and São Paulo (23).

The higher prevalence of BZD use among females may be due to females having a higher rate of mental health disorders, such as anxiety, major depression, and dysthymia (24). This sex difference persists even among individuals with a
psychiatric diagnosis and among those without any psychiatric diagnosis. This suggests that other factors might be involved. Accordingly, the higher use of psychotropic drugs by females could also be explained by treatment-seeking behavior and lower alcohol and psychotropic drug use (25).

People working at home and those with low social functioning, such as retirees and the unemployed, also reported higher BZD use. This is in line with previous reports in Europe (29). In the current study, the use of psychiatric services increased the chance of using BZDs by 30%. Seeking help for emotional problems appears to be associated with the use of BZDs (29).

A surprising finding is the higher use of BZD among those subjects who had been diagnosed with a mood disorder compared to those with an anxiety disorder (14.7% vs 8.1%, respectively), even regarding monotherapy (4.0% vs 2.9%). However, this finding has been reported in a number of studies that have used a similar methodology (16). Sometimes, the use of BZDs among subjects with mood disorders has been comparable (16) or higher than the use of antidepressants (18,29). The non-specific effects of BZD appear to be less harmful than first-line antidepressants, which has prompted some clinicians to prefer BZD (10). In France, the use of hypnotics and anxiolytics was similar for those with depression or an anxiety disorder (43.4% vs 42.5%). This finding reflects the challenges in diagnosing and managing mood disorders in primary care (17).

Table 4 - Correlates of benzodiazepine use in the previous 12 months with sociodemographic variables, mental health disorders, disorder severity, comorbidities, use of health services, and the existence of private health insurance coverage. São Paulo Megacity Mental Health Survey (N=1,271).

| Variable                        | Total sample | N (%) | Model 1 OR (95% CI) | Model 2 OR (95% CI) |
|---------------------------------|--------------|-------|---------------------|---------------------|
| Sex                             |              |       | p-value             | p-value             |
| Female                          | 836          | 85 (8.7) | 1.5 (0.7-3.2)       | 0.3563              |
| Male                            | 435          | 32 (6.2) | 1                   | 0.0418              |
| Age (years)                     |              |        |                     |                     |
| 18-34                           | 481          | 20 (4.7) | 1                   | 0.4799              |
| 35-49                           | 472          | 56 (10.2) | 2.3 (1.1-4.7)       | 0.0197              |
| ≥ 50                            | 318          | 41 (11.1) | 2.6 (1.2-5.3)       | 0.0127              |
| Education (years)               |              |        |                     |                     |
| Low (<4)                        | 346          | 36 (9.5) | 1.3 (0.7-2.4)       | 0.421               |
| Low-average (5-8)               | 330          | 28 (8.6) | 0.9 (0.5-1.8)       | 0.7639              |
| High-average/high (>9)          | 595          | 53 (7.5) | 1                   | 0.3014              |
| Family income                   |              |        |                     |                     |
| Low (<0,5)                      | 344          | 18 (5.5) | 0.5 (0.2-1.0)       | 0.0641              |
| Low-average (0.5-1.0)           | 344          | 34 (7.5) | 0.7 (0.37-1.2)      | 0.1714              |
| High-average (1.0-2.0)          | 292          | 30 (7.6) | 0.7 (0.4-1.3)       | 0.2091              |
| High (>2.0)                     | 291          | 35 (10.9) | 1                   |                     |
| Marital status                  |              |        |                     |                     |
| Married/cohabiting              | 777          | 80 (8.7) | 1                   | 0.2566              |
| Previously married/never married| 494          | 37 (6.7) | 0.8 (0.5-1.2)       | 0.0058              |
| Employment status               |              |        |                     |                     |
| Employed/student                | 729          | 58 (5.9) | 1                   | 0.0014              |
| Homemaker/retired               | 331          | 42 (11.8) | 2.2 (1.4-3.5)       |                     |
| Unemployed                      | 211          | 17 (10.1) | 1.8 (0.8-4.4)       | 0.1839              |
| Anxiety disorder                |              |        |                     |                     |
| No                              | 435          | 28 (7.3) | 1                   |                     |
| Yes                             | 836          | 89 (8.1) | 1.1 (0.7-1.7)       | 0.585               |
| Mood disorder                   |              |        |                     |                     |
| No                              | 704          | 35 (3.2) | 1                   |                     |
| Yes                             | 567          | 82 (14.7) | 5.2 (2.6-10.3)     | 5.7 (2.5-13.0)      |
| SUD*                           |              |        |                     |                     |
| No                              | 1108         | 104 (7.8) | 1                   |                     |
| Yes                             | 163          | 13 (7.9) | 1.0 (0.5-2.1)       | 0.984               |
| ICD*                            |              |        |                     |                     |
| No                              | 1080         | 101 (8.2) | 1                   |                     |
| Yes                             | 191          | 16 (5.8) | 0.7 (0.4-1.3)       | 0.2634              |
| Comorbidity                     |              |        |                     |                     |
| No                              | 731          | 48 (5.6) | 1                   |                     |
| Yes                             | 540          | 69 (11.2) | 2.1 (1.3-3.5)       | 0.0035              |
| Severity                        |              |        |                     |                     |
| Mild                            | 397          | 19 (3.7) | 1                   |                     |
| Serious/Moderate                | 874          | 98 (10.0) | 2.8 (1.7-4.8)       | 0.0001              |
| Service use                     |              |        |                     |                     |
| No                              | 935          | 15 (1.3) | 1                   |                     |
| Yes                             | 336          | 102 (29.8) | 31.2 (19.3-50.4)    | 25.0 (13.7-45.6)    |
| Health insurance                |              |        |                     |                     |
| No                              | 798          | 56 (6.1) | 1                   |                     |
| Yes                             | 473          | 61 (10.7) | 1.9 (1.0-3.4)       | 0.0505              |

Weighted proportions. OR, odds ratio; CI, confidence interval. *Substance use disorders. **Impulse control disorders. Model 1: crude. Model 2: All variables were analyzed together.
Table 5 - Twelve-month prevalence of benzodiazepine use according to the DSM-IV/VWMH-CIDI diagnosis by sex. Results from the São Paulo Megacity, São Paulo, Brazil (N=1,271).

| Mental health disorder                              | Total          | At least one BZD | Exclusive use |
|-----------------------------------------------------|----------------|------------------|---------------|
|                                                     | N (%) | SE   | OR (95% CI) | X²    | p-value | N (%) | SE   | OR (95% CI) |
| Anxiety Disorders                                   |       |      |             |       |         |       |      |             |
| Panic disorder                                      | 61    | 17 (33.7) | 1.7 (0.3-10.4) | 0.4    | 0.542   | 04 (9.8) | 4.2   | 0.4 (0.0-3.8) |
| Generalized anxiety disorder                        | 128   | 08 (6.4) | 0.5 (0.1-3.3) | 0.6    | 0.4391  | 03 (4.3) | 3.1   | 0.1 (0.0-1.9) |
| Specific phobia                                     | 471   | 54 (7.7) | 0.8 (0.3-2.3) | 0.2    | 0.6757  | 19 (2.8) | 0.7   | 0.8 (0.2-3.4) |
| Social phobia                                       | 174   | 23 (10.4) | 2.3 (0.6-9.8) | 1.3    | 0.25    | 05 (2.1) | 1.1   | 0.8 (0.1-5.2) |
| Agoraphobia without panic                            | 88    | 16 (13.5) | 9.9 (0.9-104.6) | 3.6    | 0.0573  | 04 (3.9) | 2.2   | 2.3 (0.2-26.5) |
| Post-traumatic stress disorder                      | 80    | 10 (6.6) | 0.7 (0.1-4.7) | 0.18   | 0.6714  | 03 (2.5) | 1.6   | 0.1 (0.0-5.8) |
| Obsessive-compulsive disorder                       | 155   | 19 (8.8) | 7.0 (1.6-30.0) | 6.8    | 0.0094  | 03 (1.4) | 0.8   | 0.4 (0.0-3.2) |
| Adult separation anxiety                            | 95    | 12 (12.6) | 4.3           | -      | -      | 04 (4.2) | 2.4   | -           |
| Any anxiety disorder                                | 836   | 89 (8.1) | 1.1 (0.5-2.52) | 0.0    | 0.8466  | 31 (2.9) | 0.6   | 0.6 (0.2-1.5) |
| Mood Disorders                                       |       |      |             |       |         |       |      |             |
| Major depressive disorder                           | 488   | 62 (13.4) | 2.2           | 1.4 (0-4-2.8) | 0.3 | 0.5879 | 17 (4.0) | 1.0   | 0.9 (0-2.4) |
| Dysthymia                                           | 62    | 09 (11.8) | 2.3           | 2.1 (4-9.5) | 0.8 | 0.3614 | 02 (2.7) | 1.9   | -           |
| Bipolar I and II disorders                          | 73    | 19 (23.3) | 1.4           | 3.6 (0.9-15.1) | 3.1 | 0.6112 | 21 (4.0) | 1.0   | 1.1 (0-3.4) |
| Any mood disorder                                   | 567   | 82 (14.7) | 1.3           | 4.1 (0.7-23.3) | 2.6 | 0.1096 | 04 (2.2) | 1.3   | 0.8 (0-1.0) |
| Substance Use Disorders                             |       |      |             |       |         |       |      |             |
| Alcohol abuse                                       | 134   | 10 (7.8) | 2.0 (0.5-8.05) | 0.9    | 0.3492  | 03 (2.9) | 1.1   | 0.1 (0-1.9) |
| Alcohol dependence                                  | 64    | 07 (13.2) | 2.1           | 3.6 (1.5-58.8) | 5.6 | 0.0176 | 01 (2.6) | 2.6   | -           |
| Drug abuse                                          | 31    | 03 (6.6) | 8.2 (1.9-36.4) | 7.8    | 0.0054  | 01 (2.4) | 2.2   | -           |
| Drug dependence                                     | 21    | 03 (11.7) | 9.3           | 3.6 (0.9-15.1) | 3.1 | 0.7068 | 04 (2.2) | 1.3   | 0.8 (0-1.0) |
| Any substance use disorder                          | 163   | 13 (7.9) | 2.5           | 7.5 (1.4-90.6) | 5.2 | 0.1376 | 01 (2.6) | 2.6   | -           |
| Impulse-control Disorders                            |       |      |             |       |         |       |      |             |
| Attention deficit disorder                          | 45    | 07 (13.3) | 3.1           | 6.0    | 0.0083  | 03 (10.1) | 5.8   | 11.3 (1.4-90.6) |
| Oppositional-defiant disorder                       | 20    | 01 (3.8) | 3.8           | 1.5    | 0.0096  | 03 (1.2) | 0.7   | 2.3 (0-3.0) |
| Conduct disorder                                    | 17    | 03 (15.9) | 9.3           | 4.1    | 0.0032  | 10 (2.4) | 8.0   | -           |
| Intermittent explosive disorder                     | 137   | 10 (4.6) | 3.6           | 1.5    | 0.0032  | 06 (2.9) | 1.1   | 4.2 (0-5.7) |
| Any impulse-control disorder                        | 191   | 16 (8.4) | 3.6           | 6.1    | 0.0032  | 10 (2.4) | 8.0   | -           |
| Any 12-month Disorder                               |       |      |             |       |         |       |      |             |
| Any 12-month Disorder                               | 1271  | 117 (7.8) | 1.5           | 0.9    | 0.3563  | 40 (2.7) | 0.4   | 0.8 (0.4-1.8) |
| 0 Disorders                                         | 1664  | 45 (1.9) | 3.0           | 13.0 (4-143.3) | 19.0 | 0.0001 | 25 (1.4) | 0.6   | 20.9 (5-81.9) |
| 1 Disorder                                          | 731   | 48 (5.6) | 1.2           | 4.1 (0-143.3) | 19.0 | 0.0001 | 20 (2.2) | 0.5   | 0.6 (0-2.8) |
| 2 Disorders                                         | 262   | 19 (6.1) | 1.2           | 0.8    | 0.8004  | 08 (2.6) | 1.0   | 1.4 (0-2.9) |
| 3 + Disorders                                       | 278   | 50 (16.3) | 3.0           | 10.4 (0-143.3) | 19.0 | 0.0001 | 12 (4.6) | 1.4   | 1.1 (0-2.5) |
| Severity                                            |       |      |             |       |         |       |      |             |
| Serious                                              | 465   | 77 (15.3) | 1.3           | 0.4    | 0.5226  | -     | -    | -           |
| Moderate                                             | 409   | 21 (4.2) | 1.5           | 0.2    | 0.3438  | -     | -    | -           |
| Mild                                                | 397   | 19 (3.7) | 0.8           | 0.2    | 0.9999  | -     | -    | -           |
| None                                                | 1664  | 45 (1.9) | 0.8           | 3.0    | 0.0032  | -     | -    | -           |

Weighted proportions. OR, odds ratio; CI, confidence interval. Sex comparison: males were used as the reference group.
There was also increased use of BZDs in patients with more severe psychiatric disorders. One explanation for this could be the prescribing habits of clinicians. Usually, clinicians might include an addictive medication, such as BZD, for non-responders to treat residual symptoms such as insomnia and anxiety.

BZD is not considered to be the first-line treatment for most anxiety disorders, such as generalized anxiety disorder, phobias, and post-traumatic stress disorder, with antidepressants and antiepileptic drugs, usually prescribed (14). Nevertheless, the use of BZDs was also higher (18,25,29) or similar to the use of antidepressants among individuals with an anxiety disorder (16). It appears that in Brazil, patients are not receiving the most appropriate treatment option (22) because the use of BZD as a monotherapy was higher than that of other classes of psychotropic medications among subjects who had been diagnosed with an anxiety disorder. General practitioners issued 46.9% of the BZD prescriptions (28). Other specialists, such as cardiologists (15.3%) and neurologists (4.5%), issued more tranquilizer prescriptions than psychiatrists (11.7%).

The reported higher use of BZD in the elderly is in line with the patterns observed in most studies conducted in the United States of America (26), Canada (30), and Europe (25). In a systematic review (31) on inappropriate prescriptions for long-term BZD use and analogous non-BZD z-drugs, psychological dependence, absence of social support, ignorance about treatment options, withdrawal symptoms, and unfamiliarity with the potential side effects were the main drivers that perpetuate their use. Additionally, previous use was one of the main factors associated with the likelihood of BZD use among older patients (32). People from older cohorts that have been extensively exposed to BZD in their youth may become addicted (32), and become chronic users (32). Other factors included chronic illness, stress, pain, and insomnia (26). The higher BZD use in older cohorts is concerning due to older individuals being more at risk of falls (33,34,35), associated with healthcare utilization and decline in functional status (36). The causative effect of BZD on the risk of dementia is also a major concern (37). The decline in functional status (36). The causative effect of BZD concerning due to older individuals being more at risk of Alzheimer’s disease (38,15), without stringent confirmation (39).

Taken together, our data and the existing literature must be urgently reviewed by governments, policymakers, and medical societies. There is some consensus that BZD should be discontinued in subjects aged 65 years or older. The most recommended deprescribing strategy for long-term BZD and Z-drug use is pharmacologic interventions. Multidisciplinary reduction of BZD and Z-drug exposure with the addition of alternative pharmacological therapies, psychological therapies (anxiety management, stress management, and psychotherapy), mixed programs (psychological therapy, gradual dose reduction, and usual care), and psychological education are some of the recommended approaches. These interventions present numerous, heterogeneous, and poorly described results, suggesting that studies are needed on how to best deprescribe BZD and Z-drugs in the future (40).

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Campanha AM was responsible for the conception, draft, statistics, critical intellectual contribution. Ravagnani B was responsible for the draft and critical intellectual contribution. Milhoarana IA was responsible for the statistics and critical intellectual contribution. Bernik MA was responsible for the conception, draft and critical intellectual contribution. Viana MC was responsible for the data acquisition and critical intellectual contribution. Wang YP was responsible for the draft and critical intellectual contribution. Andrade LA was responsible for the conception, data acquisition, statistics and critical intellectual contribution.
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