ABSTRACT
Objectives: In this study we present the development of a database of psychoactive drugs dispensed to patients attended by the Brazilian Public Health System (SUS) in the city of Manhuaçu, Minas Gerais and the pattern of drug prescription in this city.
Methods: 827 patients under psychoactive treatment and attended by SUS were surveyed and information such as gender, degree of education, age, marital status were collected. The collected data were analyzed in order to outline patients’ profile and the dispensing and information was used to access the pattern of psychoactive drug use in the city.
Results: Women accounted for 67.2% of the population and age seemed to influence positively the use of psychoactive drugs. Benzodiazepines and antidepressants were among the most prescribed drugs especially after 20 years of age, while in the younger population the antipsychotics and antiepileptics were the mainly prescribed drugs. Antiepileptics/mood stabilizers seemed to be prescribed mainly to single men and women.
Conclusion: Personal data concerning gender, age and marital status are related with psychoactive drug dispensing. The collected data will serve as support for the performance of pharmacists responsible for dispensing psychoactive drugs in the municipality.
Keywords: Psychotropic Drugs. Drug Utilization. Age Factors. Brazil.

INTRODUCTION
Drugs that act on the central nervous system, designated as psychoactive drugs, are among the earliest pharmacological compounds developed and still among the most widely used worldwide. Moreover, the use of psychoactive drugs has increased in recent decades in many western countries and, even, in some Asiatic countries. This tendency has been attributed to the increased frequency of psychiatric disorders within the population, the introduction of new psychoactive drugs in the pharmaceutical market, and the novel therapeutic indications of old psychoactive drugs.
According to Sinitox (Toxicological and Pharmaceutical National Information System, Brazil), there have been over 112 thousand poisonings registered in Brazil in the year of 2007, of which 30.31% were caused by medications, the main cause of intoxications. Poisoning by psychoactive drugs is especially worrisome, since it can often result in patient's death, accidentally or intentionally.

In this context, the pharmacist-patient relationship is crucial, and pharmacists must act in the documentation of medication history. Pharmaceutical care has the objectives to focus on the patient during the therapeutic intervention, and to promote the rational use of drugs. For that matter, the pharmacist might evaluate the use of drugs and the patients’ profile, generating databases that would ultimately enable the guidance and the dissemination of information about drugs, as well as the promotion of continuing education of health professionals, patients and the community.

Many studies concerning psychoactive drugs prescription and dispensation are available in the literature, and this article contributes to this subject by showing the patterns observed in the city of Manhuaçu, Minas Gerais, Brazil. The central focus of the present work was to generate a database based on information provided by patients using psychoactive drugs, attended by the Brazilian Public Health System (SUS) in the city of Manhuaçu, Minas Gerais, Brazil, and to correlate the collected data with the profile of psychoactive drugs use.

METHODS

In the period of one month, from April to May 2009, 827 patients under psychoactive treatment and attended by SUS were surveyed in the city of Manhuaçu, Minas Gerais, Brazil. The interviews were conducted in a single location during drug dispensation by the pharmacist. Only drugs listed by the Brazilian Standardized Municipal Essential Medicines (REMUME) were provided to the patients included in this study. The instrument used in the interview was a questionnaire with five questions regarding patients’ information, such as gender, degree of education, age, marital status, and psychoactive drugs dispensed. This questionnaire was presented and approved by the Municipal Secretary of Health of Manhuaçu. An original database was generated with the information provided by the patients. The five variables included in the model studied were then coded, based on preliminary analysis: a) gender (male, female), b) age (0-10 years, 11-20 years, 21-30 years, 31-40 years, 41-50 years, more than 50 years), c) education degree (iliterate, primary school, high school, incomplete high school education, graduation degree), d) marital status (single, married, divorced, widowed), e) used psychoactive drug.

The psychoactive drugs were divided in 7 different classes regarding their clinical use, mechanism of action, chemical class, and the Anatomical Therapeutic Chemical (ATC) classification system, as: Benzodiazepines derivatives (which we will refer to only as "Benzodiazepines"), Antidepressants Non-selective monoamine reuptake inhibitors (which we will refer to as Tricyclic antidepressants due to their structural similarity), Antidepressants selective serotonin reuptake inhibitors (which we will refer to only as the abbreviation SSRIs), Antipsychotics, Anticholinergics, Antiepileptics (which we will refer to as antiepileptics and mood stabilizers, once the latter is a common clinical application for the drugs in this class) and others (Table 1). Data concerning drug dispensation were expressed as absolute number and frequency of dispensation (percentage of people to whom a specific drug has been prescribed). To analyze the trend of increase or decrease in drug prescription varying with patients’ ages the chi-square test for trend was applied. The association of discrete variables (gender, marital status and education) with the dispensation of psychoactive drugs was performed only within the adult population (above 20 years) and was estimated by the chi-square test. The occurrence of polypharmacy (i.e., the use of multiple medications) and the main drug associations were measured by counting and were expressed as absolute values and ratios for each age group. The statistical analyses were performed using the GraphPad Prism 5.0.

RESULTS

The present study was based on the 21 psychoactive drugs provided by SUS database generated in Manhuaçu, Minas Gerais, Brazil. The drugs, their pharmacological classification and the frequency of each one dispensation are shown in Table 1. Initially, tabulations were carried out to estimate the patterns of psychoactive drug use according to gender, age, marital status and education. The studied population (n=827) was constituted 271 men (32.8%) and 556 women (67.2%). The most frequently prescribed drug was clonazepam, which was used by 29.51% of the patients, followed by fluoxetine (25.78%), diazepam (24.54%), amitriptyline (18.07%) and carbamazepine (11.45%).

Data analysis showed higher rates of drugs dispensation to patients older than 50 years (34.2%), followed by the age group ranging from 41 to 50 years (24.6%), 31 to 40 years (20%), 21 to 30 years (12.4%), 11 to 20 years (4.8%) and 0 to 10 years (4.0%). It was observed that in younger patients (age groups between 0 and 10 and between 11 and 20) the class of drugs most commonly prescribed was the antiepileptics and mood stabilizers, especially carbamazepine (Table 2). Patients with more than 21 years old showed an increase in the prescription of benzodiazepines, tricyclic antidepressants and selective serotonin reuptake inhibitors, especially clonazepam, diazepam, amitriptyline and fluoxetine. The use of chi-square test for trend showed a statistically significant trend of increasing in the prescription of benzodiazepines, tricyclic antidepressants and selective serotonin reuptake inhibitors and also a decreasing in the prescription of antiepileptics and antipsychotics with increasing age (Table 2).
was carried out. However, the overall analysis had
drugs. To perform such an analysis, chi-square test
status appeared to influence the use of the studied
antiepileptics/mood stabilizers (Table 3). The marital
anticholinergics drugs, and 13.6% were using
antipsychotics drugs, 2.8% were in use of
Nonetheless, 6.4% of women were taking
drugs was 12.4%, 7.9%, and 28.3%, respectively.
The trend is the exact opposite when the use of
antidepressants, and 14.2% were taking SSRIs. On the other hand,
percentage of men using antipsychotics,
31.1% were in use of SSRIs. On the other hand,
34.1% were in use of SSRIs. On the other hand,
mood stabilizers prescription as only 18.8% of married men used this kind of
drugs, while for other civil statuses this value was
always above 36% (chi-square p<0.01) (Table 3).

Drug combination was also studied. The average number of medications used per patient was 1.52.
The vast majority of patients (62.4%) were in use of
only one product, and just around 10% used more
than 2 drugs combined (Table 4). The most
commonly observed combination of two drugs in
patients younger than 20 years of age was that of
antiepileptic and an antipsychotic. More specifically, the association of
periciazine and carbamazepine was highly
prescribed for children under 10 years old while
association of valproic acid and carbamazepine was
the most frequent in patients between 11 and 20
years old. For patients older than 20 years, the
association of antidepressants (both tricyclic or
SSRIs) with a benzodiazepine was the most
commonly observed psychoactive association
(Table 5).

We also collected educational data from each of the
patients enrolled in this study. The adult population
was divided into 5 groups of schooling with the
following percentages: Illiterate (29.4%), Primary
school (56.2%), High school (10.7%), Incomplete
Graduate Education (2.5%) University Degree
(1.1%). No influence of schooling in drug
dispensation has been detected (chi-square
p>0.05).

DISCUSSION
The present study aimed to determine the profile of
the psychoactive drugs dispensation by SUS in the
Brazilian city of Manhuaçu, Minas Gerais state,
through the development of a database containing
confidential information of patients with psychiatric
and/or neurological disorders. The ultimate benefit
herein intended is to technically overcome a
foremost Public Health issue concerning
pharmaceutical care. This town is located in a
Brazilian region called “Zona da Mata Mineira” and
according to the latest estimates from the Brazilian
Institute of Geography and Statistics (IBGE), the
municipality had in 2009 about 79 thousand
inhabitants.

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Table 1. Psychoactive drugs dispensed at the municipality and their prescription frequency. (n=827).

| Medication                  | N  | %   |
|-----------------------------|----|-----|
| Benzodiazepines             |    |     |
| Clonazepam                  | 245| 29.6|
| Diazepam                    | 212| 26.8|
| Lorazepam                   | 7  | 0.9 |
| Tricyclic Antidepressants   |    |     |
| Amitriptyline               | 150| 18.1|
| Imipramine                  | 13 | 1.6 |
| Clomipramine                | 5  | 0.6 |
| Nortriptyline               | 42 | 5.1 |
| SSRI                        | 214| 25.9|
| Antipsychotics              |    |     |
| Chlorpromazine              | 6  | 0.7 |
| Pentfluoridil               | 1  | 0.1 |
| Sulpiride                   | 5  | 0.6 |
| Thioridazine                | 13 | 1.6 |
| Haloperidil                 | 46 | 5.6 |
| Levomepromazine             | 12 | 1.4 |
| Periciazine                 | 10 | 1.2 |
| Pipotiazine                 | 1  | 0.1 |
| Anticholinergics            |    |     |
| Biperiden                   | 38 | 4.6 |
| Antiepileptics /Mood Stabilizers | | |
| Valproic acid               | 31 | 3.7 |
| Carbamazepine               | 95 | 11.5|
| Lithium Carbonate           | 6  | 0.7 |
| Phenobarbital               | 87 | 10.5|
| Others                      | 2  | 0.2 |
| Promethazine                | 2  | 0.2 |

We also analyzed the profile of drugs prescription
according to patients’ sex and marital status within
our adult (older than 20 years) sample (n=756). It was observed that the use of tricyclic
antidepressants and SSRIs was more frequent in
women when compared to men (chi-square
p<0.001 for both drug groups). 31.1% of adult
women were in use of tricyclic antidepressants, and
34.1% were in use of SSRIs. On the other hand,
only 17.3% of men were using tricyclic
antidepressants, and 14.2% were taking SSRIs.

The present study aimed to determine the profile of
the psychoactive drugs dispensation by SUS in the
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inhabitants.

Table 2. Psychoactive Drugs dispensed at the municipality and the frequency of prescription for the six stipulated age
groups. *p<0.05; **p<0.01; ***p<0.001 (Chi-square for trend).

| Drug Class                          | Age Group | 0 - 10 | 11 - 21 | 21 - 30 | 31 - 40 | 41 - 50 | Above 50 |
|-------------------------------------|-----------|--------|---------|---------|---------|---------|----------|
| Benzodiazepines***                  | 2 (6.1)   | 3 (7.5)| 47 (46.1)| 96 (57.8)| 130 (64.0)| 186 (65.7)|         |
| Tricyclic antidepressants*          | 4 (12.2)  | 6 (15.0)| 16 (17.6)| 50 (30.1)| 72 (35.5)| 71 (25.1)|         |
| SSRIs                               | 0 (0.0)   | 2 (5.0)| 29 (28.4)| 51 (30.7)| 61 (30.5)| 71 (25.1)|         |
| Antipsychotics***                  | 12 (36.4)| 7 (17.5)| 15 (44.7)| 15 (45.0)| 28 (13.6)| 26 (9.2)|         |
| Anticholinergics                    | 1 (3.0)   | 5 (12.5)| 4 (9.4)| 6 (3.6)| 12 (5.9)| 9 (3.2)|         |
| Antiepileptics and mood stabilizers** | 31 (93.9)| 33 (81.5)| 41 (40.2)| 35 (21.1)| 32 (15.8)| 47 (16.6)|         |
In this study, analysis of psychoactive drugs prescriptions in the region of Al-Qassam, Saudi Arabia. In this study, analysis of psychoactive drugs prescriptions in the region of Al-Qassam, Saudi Arabia. In this study, analysis of psychoactive drugs prescriptions in the region of Al-Qassam, Saudi Arabia. In this study, analysis of psychoactive drugs prescriptions in the region of Al-Qassam, Saudi Arabia.

An interesting example that illustrates this fact may be in conflict with data collected in different regions. Indeed, these antidepressant drugs have been listed, along with benzodiazepines, as one of the most widely used drugs in the previous cited epidemiological studies conducted in Brazil, which have stated that benzodiazepines are among the most used psychoactive drugs in the country. Two antidepressant drugs - a tricyclic antidepressant and a SSRI - were also on the list of the most frequently prescribed drugs in our study. According to epidemiological studies, depression is a common psychiatric disorder - as anxiety and depression - are more frequent diagnosed in women than in men.

The analysis of data collected between the months of April and May, 2009 showed that most of the prescribed psychoactive drugs were clonazepam, fluoxetine, diazepam, amitriptyline, carbamazepine and phenobarbital. According to epidemiological studies, depression is a common psychiatric disorder - as anxiety and depression - are more frequent diagnosed in women than in men.

Table 3. Psychoactive Drugs dispensed in the unit and the frequency of prescribing according to sex and marital status in adults (Above 20 years).

| Sex and Marital status | BDZ | Tricyclic | SSRI | Antipsych. | Anticholin. | Antiepileptics |
|------------------------|-----|-----------|------|------------|------------|---------------|
| Women                  | 306 (57.9) | 164 (31.1) | 180 (34.1) | 34 (6.4) | 15 (2.8) | 72 (13.6) |
| Single                 | 52 (63.4)  | 24 (29.2)  | 24 (29.3) | 10 (12.2) | 4 (4.8)  | 19 (23.2) |
| Married                | 183 (55.4) | 109 (34.6) | 117 (34.8) | 18 (5.4) | 9 (2.6)  | 43 (12.8) |
| Widowed                | 32 (69.3)  | 17 (31.5)  | 24 (44.4) | 1 (1.9)   | 1 (1.8)  | 6 (11.1)  |
| Widowed                | 39 (68.4)  | 14 (24.6)  | 15 (26.3) | 5 (8.8)   | 1 (1.7)  | 4 (7.0)   |
| Men                    | 126 (55.8) | 39 (17.3)  | 32 (14.2) | 28 (12.4) | 18 (7.9) | 64 (28.3) |
| Single                 | 39 (49.4)  | 12 (15.2)  | 9 (11.4)  | 17 (21.5) | 10 (12.6) | 30 (38.0) |
| Married                | 72 (61.5)  | 25 (21.3)  | 21 (17.9) | 10 (8.5)  | 6 (5.1)  | 22 (18.8)**|
| Widowed                | 10 (55.6)  | 2 (6.5)    | 1 (5.6)   | 2 (11.1)  | 7 (38.9) | 7 (41.7)  |
| Widowed                | 5 (41.7)   | 1 (8.3)    | 0 (0.0)   | 0 (0.0)   | 5 (41.7) |

Table 4. Number of drugs per prescription in each of the six stipulated age groups.

| Number of drugs | Number (%) of drugs per prescription in each age group. |
|-----------------|----------------------------------------------------------|
| 0 – 10           | 18 (54.6) 27 (87.5) 65 (65.7) 101 (60.9) 120 (58.1) 185 (65.3) 516 (62.4) |
| 11 – 21          | 13 (39.4) 8 (20.0) 25 (24.5) 48 (28.9) 54 (26.6) 78 (27.6) 226 (27.3) |
| 21 – 30          | 3 (3.0) 4 (10.0) 7 (6.9) 14 (8.4) 17 (8.4) 12 (4.2) 55 (6.6) |
| 31 – 40          | 1 (3.0) 2 (2.5) 4 (9.9) 3 (1.8) 7 (3.4) 7 (2.5) 24 (2.9) |
| 41 – 50          | 0 (0.0) 0 (0.0) 0 (0.0) 0 (0.0) 0 (0.0) 0 (0.0) 1 (0.5) |
| Above 50         | 0 (0.0) 0 (0.0) 0 (0.0) 0 (0.0) 0 (0.0) 0 (0.0) 2 (0.3) |

Table 5. Most commonly prescribed drug associations in each of the six stipulated age groups and their frequency.

| Drug Combination per age group | N   | %    |
|-------------------------------|-----|------|
| Clonazepam + Fluoxetine       | 10  | 9.8  |
| Diazepam + Fluoxetine         | 4   | 3.9  |
| Valproic Acid + Carbamazepine | 4   | 3.9  |
| Amitriptyline +Clonazepam     | 13  | 7.8  |
| Fluoxetine + Clonazepam       | 18  | 10.8 |
| Carbamazepine + Phenobarbital | 6   | 3.6  |
| Amitriptyline + Diazepam      | 12  | 5.9  |
| Diazepam + Fluoxetine         | 25  | 12.3 |
| Amitriptyline + Diazepam      | 11  | 5.4  |
| Above 50 years old            |     |      |
| Amitriptyline + Diazepam      | 22  | 7.8  |
| Clonazepam + Fluoxetine       | 15  | 5.3  |
| Diazepam + Fluoxetine         | 19  | 6.7  |
nearly twice as common in women than in men and this disparity is considered as a fact by the World Health Organization (WHO). Therefore, the prevalent dispensation of antidepressants drugs for women over men found in the city of Manhuaçu corroborated with national and international statistics concerning depression care. Even though there have not been published data, at least to our knowledge, reporting gender differences regarding the overall prevalence of less common mental illnesses, such as schizophrenia and bipolar disorder, we have observed a higher frequency of antiepileptic and mood stabilizer drugs dispensation to men than to women in Manhuaçu. It is possible that the observed profile reflects a peculiarity of the studied region or might even be a result of the extensive use of antidepressants by women, which could influence the overall statistical analysis. Concerning the higher prescription of biperiden to men when compared to women in Manhuaçu, one might predict that this fact results from the higher risk of male to develop Parkinson’s disease, as well as the earlier development of the pathology symptoms. Finally, regarding the marital status, the only statistically significant result in our study was the lower use of antiepileptics and mood stabilizers by married men when compared to other civil statuses, and also the higher use of these classes of medications by single women when compared to women who were married at the time of the questionnaire application or before it. It is noteworthy that the epidemiological literature often identifies a lower prevalence of mental disorders among married individuals as well as greater use of psychoactive drugs in single, divorced or widowed subjects.

We have also observed that the number of patients receiving psychotherapy is directly influenced by patients’ age, which is consistent with the literature. According to some statistical studies, the use of such drugs increases dramatically with aging, and this trend is also observed specifically for psychoactive drugs, with a slight drop after 75 or 80 years of life. These observations raise a relevant but yet controversial discussion. Despite the higher use of psychoactive drugs by the elderly, epidemiological data indicate a lower prevalence of mental disorders in these patients, and they are generally more prone to adverse reactions due to changes in drug pharmacokinetics, cognitive and visual problems, several concomitant diseases and the simultaneous use of many drugs. The extent to which the prescription of psychoactive drugs to elderly patients is relevant is polemical and raised deep discussions. The age of the patient also appeared to be associated with the class of drug prescribed. As described in the results section, there have been increases in the prescription of benzodiazepines, tricyclic antidepressants and SSRIs versus decreases in the prescription of antiepileptics and antipsychotics drugs with patients’ aging (Table 2). These phenomena were expected, given the fact that benzodiazepine and SSRIs are not recommended for children. In addition, although it is not yet a consensus, anxiety disorders and depression - the diseases most widely treated with these drugs - seem to increase with age. The decrease in the percentage of patients treated with antiepileptics or antipsychotics drugs in aged patients might also be explained by the increasing cases of depression-related problems with age. Another aspect likely associated with these observations is the precocity of the first signs and symptoms of schizophrenia and other psychotic disorders, the same being applied to the first seizure notification, and the control of the conditions in aged individuals. It has been well established that multiple drug prescription directly correlates with a higher incidence of medication side effects and adverse reactions. Therefore, not exclusively drug prescription might be rational, but should also predict patients’ benefits over risks of such therapeutical strategies. We have noted that the average of psychoactive drugs dispensation in Manhuaçu was 1.52 per patient, ranging from 1 to 6 drugs dispensed per individual, and although the vast majority of patients (62.4%) were using only one medication, the prescription of multiple psychoactive drugs have been also identified in a significant percentage of patients (38.6%) (Table 4). The combination of drugs is often necessary to control some of the mental illness, and such situations require special attention from health professionals as it exposes the individuals to secondary complications due to the medication adverse reactions or ineffective treatment. Data summarized in Table 5 shows the main drug associations observed in each patients’ age group prescribed by SUS health professional in Manhuaçu. In patients younger than 20 years, it has been observed a high frequency of carbamazepine prescription combined with another antiepileptic or a neuroleptic compound. In children under 10 years old, pericazine was the most prescribed drug in combination with carbamazepine, but we have also observed the prescription of carbamazepine in combination with valproic acid or phenobarbital. The association of valproic acid and carbamazepine was the most frequent drug combination regimen prescribed for patients between 11 and 20 years of age. It is known that carbamazepine induces not exclusively its own metabolism, but also the metabolism of other substances as valproate, so that the combination of these two drugs requires special attention, especially in younger individuals. In the population over 20 years old, it has been noted that the association of an antidepressant and a benzodiazepine has become the most commonly prescribed regimen. This association is very frequently used in the treatment of depression and anxiety disorders, and, despite not having available the patients’ diagnosis information, we can suppose that the patients using this drug association in Manhuaçu are under treatment for one of these diseases.

Other less commonly observed drug associations in Manhuaçu deserve special attention due to potential important medication interactions, such as might be observed with the concomitant use of two benzodiazepines and in the association of phenobarbital and valproic acid. Valproic acid is known to inhibit the metabolism of phenobarbital,
and concomitant use of these two drugs can cause barbiturate intoxication. Association of lithium carbonate and haloperidol was observed in one patient. A close monitoring of this patient is a crucial procedure to assure a good individual health being, specifically to the possible development acute neurotoxicity. In addition to the aforementioned requirements, other potentially dangerous therapeutic regimens have been identified in Manhuacu Public Health Care System, such as the combination of clomipramine or fluoxetine with carbamazepine and also the association between antidepressants and clomipramine. Combination of fluoxetine and carbamazepine was shown to reduced serum carbamazepine concentrations and serotonin syndrome has been reported with co-administration of these drugs. Carbamazepine is a potent inducer of Cytochrome P450 3A4 (CYP3A4) enzyme and other oxidative enzyme system in the liver, and it may also increase glucurononyltransferase activity, which influences the metabolism of several drug classes, including tricyclic antidepressants, such as clomipramine, and the co-administration of carbamazepine and clomipramine demands precaution.

CONCLUSIONS
We herein present an analysis of the profile of psychoactive drugs dispensation by SUS in the city of Manhuacu, Minas Gerais, Brazil, designed through the generation of a correlated database platform. We report here some trends in prescription and use of these medications in the Brazilian region, many of them found in similar studies made in other national and international locations. Most importantly, data shown intend to technically support the rational use of psychoactive drugs, as they will to provide deeper scientific background to pharmaceutical care. It is worthwhile pointing out that the generated database will be continually updated to enable the effective monitoring of patients attended by SUS in Manhuacu, and more broadly in the global Brazilian Health Care System.

CONFLICT OF INTEREST
The authors declare no conflict of interests.

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