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Consumption of the benzodiazepine clonazepam (Rivotril®) in Rio de Janeiro State, Brazil, 2009-2013: an ecological study

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Abstract *This descriptive, ecological study of clonazepam consumption in Rio de Janeiro State (RJ) estimated use prevalence from 2009 to 2013 using data from the National Controlled Product Management System operated by Brazil's health surveillance agency, Anvisa. Consumption was measured by total population and by population over 18 years old, using the standardised Daily Defined Doses of 8 mg (anticonvulsant) and 1 mg (sedative-hypnotic). The municipalities of the Rio de Janeiro Metropolitan Region were grouped by Human Development Index (HDI) and GINI index, subjected to cluster analysis and ranked by clonazepam consumption. From 2009 to 2013, consumption in the state rose from 0.35 to 1.97 DDD/1000 population, but the figures are higher for individuals over 18 years of age. A DDD of 1 mg instead of 8mg returns consumption in 2013 of 21 DDD/1000 population over 18 years of age. Consumption in 2013 was highest – 3.38 and 4.52 DDD, respectively – in Rio de Janeiro and Niterói, which have the highest HDIs. This suggests that up to 2% of the adult population uses clonazepam, possibly as a sedative-hypnotic. This broad use and use outside therapeutic indications deserves attention, given clonazepam's potential for abuse and adverse reactions.*

Key words *Prescription drug misuse, Benzodiazepines, Clonazepam, Mental health, Pharmacoepidemiology*

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Introduction

Benzodiazepines act as sedatives, hypnotics, muscle relaxants and anticonvulsants and are especially useful in treating acute anxiety and transient insomnia. There is concern over their chronic use and related risk of harmful effects, dependence, withdrawal syndrome and adverse reactions[1]. Benzodiazepine-related chemical dependency – resulting from tolerance and evidenced by pronounced seeking behaviour – recommends suspending use, which is usually not simple. The withdrawal syndrome, which ensues in at least one third of long-term users, can include insomnia, psychological and physical manifestations of anxiety, depression, distorted or augmented sense perceptions, muscle pains and spasms, agitation, torpor, loss of appetite, psychosis, delirium and epileptic attacks and can last weeks or months[2]. Discontinuation can involve strategies ranging from counselling, meetings, care programmes with doctors or psychologists, through to drug therapy or group psychotherapy[3].

The main adverse reactions to benzodiazepines can compromise mental and motor functions, impair cognition and motor performance, may have severe consequences and affect particularly older adults. They include cognitive dysfunction, risk of which is 50% higher among users than non-users[4]; falls, which occur five times more often among users with postural hypotension than non-users[5]; hip fractures, particularly during the early weeks of use[6]; and motor vehicle traffic accidents[7].

The high frequency of benzodiazepine use finds few parallels among commonly used therapeutic products, whether in European countries[8] or the USA, where their non-medical use generates major demand for emergency care[9] and increasing overdose mortality[10]. In Australia, they were prescribed to 3% of the adult population in the 1990s[11], while 20% of the population of Uruguay has consumed some type of tranquilizer or hypnotic at some time in life[12]. In Brazil, the panorama is no different[13-16].

One important representative of the benzodiazepine class is clonazepam, which is considered a potent drug with a long half-life, hence the concerns over its prolonged use and potential for abuse[17]. In Uruguay, 28% of agents involved in intoxications were benzodiazepines, with clonazepam among the most implicated[18]. In the USA, clonazepam ranked third in total Medicare appointments at which benzodiazepines were prescribed, the number having doubled between 2005 and 2009[19].

In Brazil, clonazepam caught the attention of both mainstream media and health professionals after ANVISA released figures showing that, of all industrialised and compounded formulations subject to special control, it was the active ingredient most consumed nationwide between 2007 and 2010[20,21] .

Pharmaceutical specialities containing clonazepam are registered with ANVISA with therapeutic indications for epileptic disorder, anxiety disorders and mood disorders, in the form of tablets, sublingual tablets and oral solution[22]. Clonazepam forms part of Brazil's national therapeutic formulary and is subject to special control. The reference product is Rivotril®, manufactured by Roche, and 23 generics and 6 similars are registered[23].

Given the scarcity of studies of clonazepam consumption, it was thus considered timely to address the problem of the sale and consumption of products containing this active ingredient in Rio de Janeiro State. The aim is to estimate use prevalence from information offered by ANVISA. It is also intended to explore possible explanations for the differences found among municipalities in the state.

Methods

This study applied a descriptive, ecological approach to quantifying clonazepam consumption by the population of Rio de Janeiro State between 2009 and 2013, drawing on the ANVISA administrative data base. Purchases were taken as proxy for consumption, even considering that not all products purchased may actually have been used and that the ANVISA system does not contemplate information on products consumed in hospitals, in the public health system or distributed by non-governmental organisations.

Information source, study population and indicators

The information source for this study is the ANVISA Controlled Products Management System (*Sistema de Gerenciamento de Produtos Controlados*, SNGPC/ANVISA), provided for in Ministerial Order SVS/MS No. 344/1998. At intervals of up to seven days, private drugstores and pharmacies submit an XML (eXtensible Markup Language) file to ANVISA containing informa-

tion on purchases, prescriptions dispensed, losses and transfers of medicines subject to special control in Brazil[24]. The spreadsheets provided by the SNGPC/ANVISA record the physical units of pharmaceutical specialities (industrialised products) and formulas (compounded products) with clonazepam purchased, as well as conversion rates to milligrams per year.

Consumption was calculated as the total amount of clonazepam purchased per year, in milligrams. Using the Daily Defined Dose (DDD) specified by the World Health Organisation (WHO), per day, per 1000 population, two indicators were developed, one for the total population and the other for the population 18 or more years old. The formula for the calculation is:

$$\textit{Defined Daily Doses} = \frac{mg \times 1000}{DDD \times pop \times 365}$$

mg = total milligrams of clonazepam purchased per year

DDD = the WHO-standardised Daily Defined Dose of 8mg[25]

pop = total population or population 18 or more years old

For some analyses, a DDD of 1 mg was used in the formula, instead of 8 mg, the latter being the indicated anticonvulsant treatment dose, while 1 mg is the approximate dose for use as a sedative-hypnotic.

Data analysis

The descriptions of consumption in Rio de Janeiro from 2009 to 2013 are presented in milligrams of clonazepam and in DDD, per day, per 1000 population, for total population or population 18 or more years old.

The data by municipality of the Metropolitan Region were subjected to cluster analysis, which enables objects to be assembled, by characteristics, to form groups or clusters. It is an exploratory statistical technique by which a group of observations is reduced in order to allow more substantial data analysis. Ward's hierarchical clustering method was used, which minimises the square of the Euclidean distance to the group means: one group will be merged with another if that merger yields the smallest increase in intragroup variance[26]. The clusters so formed are presented by mean and median consumption of clonazepam.

The municipalities were grouped by: a) Human Development Index (HDI); and b) Gini index. Calculation of HDI involves converting three dimensions – longevity, education and income – into indices that vary from 0 (worst) to 1 (best) and combining them into a summary index. The Gini index measures the degree to which income is concentrated in a given group. It indicates the difference between the income of the poorest and wealthiest and varies from zero to one, with zero representing equality, i.e., all with the same income[27].

The Gini index data were sourced from the 1991, 2000 and 2010 demographic censuses, which were processed by the Economic and Applied Research Institute (*Instituto de Pesquisas Econômicas e Aplicadas*, IPEA) according to the criteria of the Gini index for per capita household income, item B.9 of the basic data and indicators of the Interagency Health Information Network (*Rede Interagencial de Informações para a Saúde*, Ripsa). The DATASUS provides Gini index information for per capita household income at http://tabnet.datasus.gov.br/cgi/ibge/censo/cnv/ginibr.def[28].

In 2012, the UNDP Brazil, Ipea and Fundação João Pinheiro took up the challenge of adapting the Global HDI methodology to calculating the Municipal HDI of Brazil's 5,565 municipalities. This calculation was performed using information from the three last IBGE censuses – i.e., 1991, 2000 and 2010 – and the municipal arrangement in place in 2010.[29]

The study was approved by the research ethics committee of the Universidade do Estado do Rio de Janeiro.

Results

Table 1 shows that clonazepam consumption in Rio de Janeiro State increased by a factor of nearly six between 2009 and 2013, when it reached around 100 kilos. The number of Defined Daily Doses (DDDs) per year per 1000 population increased from 0.35 to 1.97. when only individuals over 18 years of age are considered, the values are higher (2.64 in 2013). When a DDD of 1 mg is used in the formula, instead of 8mg, the values increase considerably and, in 2013, reached 21.09 DDD per year per 1000 population over 18 years old.

In Rio de Janeiro State, in parallel with the increase in consumption in milligrams, there was also an increase in the number of pharmacies – and, to a much lesser degree, drugstores – incorporated into the SNGPC (Figure 1). This

differential growth affects the interpretation of consumption estimates, as will be seen below.

The characteristics contemplated for each municipality of the Metropolitan Region (Table 2) are population (total and over 18 years old), sex ratio, HDI and GINI index. Note that Niterói and Rio de Janeiro return the highest HDI values (0.837 and 0.799, respectively), denoting better situations. Rio de Janeiro displays the highest Gini index (0.639) suggesting greatest inequality.

Clonazepam consumption varied widely among municipalities in the Rio de Janeiro Metropolitan Region, although overall it has increased with time. The calculation using population 18 or more years old returned higher values. Thus, the estimates for 2013 varied from 0.28 to 4.52 among municipalities, meaning that there are municipalities where, for every 1000 adults, more than 4 treatment doses were dispensed every day. The values for the Rio de Janeiro and Niterói municipal areas are particularly striking: at 3.38 and 4.52, respectively, they are the highest in the region (Table 3).

Figure 2 shows mean and median consumption for the whole period, expressed in Defined Daily Doses, per day, per 1000 population, and

Table 1. Description of Clonazepam consumption in milligrams, in Defined Daily Dose per day, per 1000 population. Rio de Janeiro State, 2009 to 2013.

Year	Consumption in mg	Year Δ mg (base 2009)	DDD per day, per 1000 population			
			DDD total population		DDD Population > 18 years	
			8mg	1mg	8mg	1mg
2009	16,152,265	1	0.35	2.77	0.48	3.81
2010	27,042,552	1.67	0.58	4.64	0.78	6.27
2011	38,185,220	2.36	0.81	6.50	1.10	8.77
2012	57,294,098	3.55	1.21	9.68	1.63	13.07
2013	93,923,124	5.81	1.97	15.73	2.64	21.09

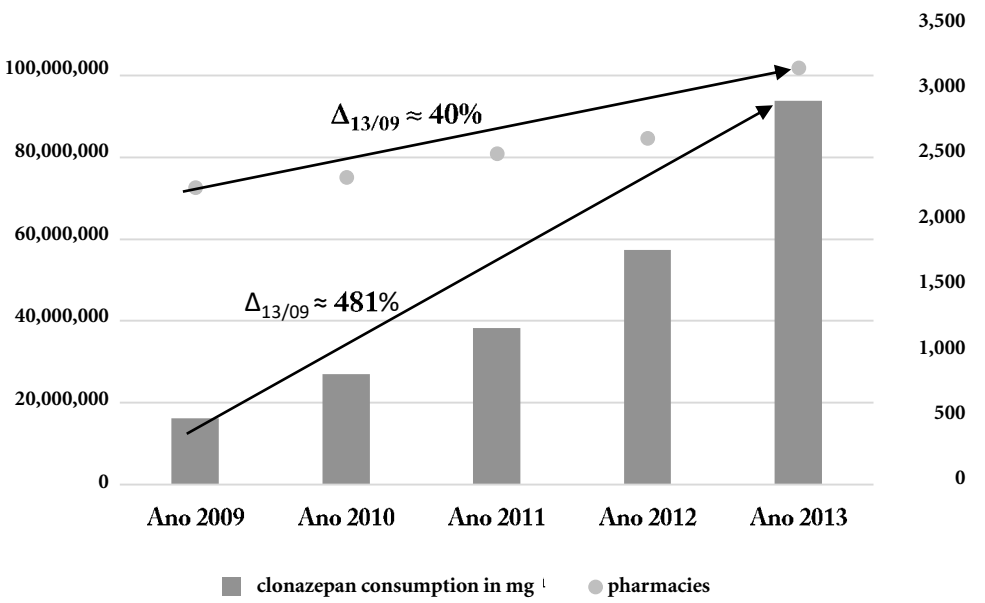

Figure 1. Clonazepam consumption in milligrams and number of pharmacies and drugstores included in the National Controlled Products Management System (Sistema Nacional de Gerenciamento de Produtos Controlados, SNGPC/Anvisa). Rio de Janeiro State, 2009 to 2013.

Δ= Variação no período

Table 2. Demographic characteristics and Clonazepam consumption – municipalities of the Rio de Janeiro Metropolitan Region, 2010.

Municipality	Population		Sex ratio M:F (%)	HDI*	GINI**
	Total	≥ 18 years old			
Belford Roxo	469,332	325,829	93.5	0.684	0.461
Duque de Caxias	855,048	603,037	92.6	0.711	0.488
Guapimirim	51,483	35,847	96.5	0.698	0.523
Itaboraí	218,008	155,281	95.0	0.693	0.497
Itaguaí	109,091	76,747	99.5	0.715	0.500
Japeri	95,492	64,931	101.4	0.659	0.458
Magé	227,322	158,201	94.7	0.709	0.508
Maricá	127,461	95,421	96.7	0.765	0.510
Mesquita	168,376	121,424	90.1	0.737	0.492
Nilópolis	157,425	117,669	88.0	0.753	0.481
Niterói	487,562	387,133	86.3	0.837	0.598
Nova Iguaçu	796,257	561,073	92.1	0.713	0.514
Paracambi	47,124	35,845	102.0	0.720	0.472
Queimados	137,962	94,809	93.3	0.680	0.458
Rio de Janeiro	6,320,446	4,815,996	88.1	0.799	0.639
São Gonçalo	999,728	745,418	90.6	0.739	0.461
São João de Meriti	458,673	330,201	90.7	0.719	0.462
Seropédica	78,186	55,329	96.7	0.713	0.484
Tanguá	30,732	21,785	99.0	0.654	0.462

**HDI - Human Development. Index. **GINI - Gini Index.*

also per 1000 individuals 18 or more years old, by municipality in the Rio de Janeiro Metropolitan Region. The differences become more salient when municipalities are grouped by HDI and when total population is used as reference (Figure 2c). Then, the medians for groups 1, 2 and 3 of municipalities are, respectively, 1.14, 0.67 and 0.36 DDD, per day, per 1000 population, while the means are 1.46, 0.70 and 0.47 DDD per day, per 1000 population. Under other conditions – using the GINI index and population 18 or more years old, the pattern is similar.

Discussion

Access to standardised, validated information on medicine use can be useful for audits, problem identification, educational purposes and for monitoring intervention outcomes. This is why the SNGPC/ANVISA, set up in 2009, is so important as recognition of the significance of rational use of medicines in the health care context. That system made it possible to identify misuse of fluoxetine hydrochloride, other than for its therapeutic indications as an antidepressant[30]; to ascertain sales volumes and consumption distribution of appetite suppressants[24]; and to estimate benzodiazepine consumption and its relation to social indicators[31]. The SNGPC is comprehensive in coverage; in 2010, it comprised at least one pharmacy or drugstore on record in 69% of Brazil's municipalities, that is, a total of 41 032 units registered, corresponding to 58% of the total[20]. This study underlines the importance of deploying large administrative data bases in epidemiological investigations, particularly in the field of pharmacovigilance and in medicine use studies.

The data analysed here indicated increasing consumption of clonazepam in Rio de Janeiro State between 2009 and 2013, both as measured in milligrams (which has implications for family spending and medicine policies) and in Defined Daily Doses (DDDs), a WHO indicator weighted for population size (which makes it possible to make comparisons and assess how rationally clonazepam is being used). The growth in consumption is real and has occurred independently of the entry of new pharmacies and drugstores

Table 3. Clonazepam consumption in DDD* per day, per 1000 population – municipalities of the Rio de Janeiro Metropolitan Region, 2009 to 2013.

Municipality	DDD per day, per 1000 population									
	2009		2010		2011		2012		2013	
	Total population	Population > 18 years	Total population	Population > 18 years	Total population	Population > 18 years	Total population	Population > 18 years	Total population	Population > 18 years
Belford Roxo	0.07	0.10	0.14	0.20	0.22	0.32	0.44	0.64	0.56	0.80
Duque de Caxias	0.17	0.24	0.36	0.51	0.71	1.00	1.01	1.43	1.00	1.40
Guapimirim	0.67	0.98	0.92	1.31	0.83	1.19	0.64	0.92	0.89	1.25
Itaboraí	0.77	1.11	0.94	1.32	0.71	1.00	0.80	1.12	1.57	2.18
Itaguaí	0.16	0.24	0.16	0.23	0.17	0.24	0.48	0.68	1.16	1.62
Japeri	0.08	0.12	0.08	0.12	0.14	0.20	0.14	0.21	0.24	0.35
Magé	0.17	0.25	0.24	0.34	0.22	0.31	0.31	0.44	0.61	0.87
Maricá	0.44	0.59	0.62	0.82	0.88	1.18	1.28	1.71	1.13	1.47
Mesquita	0.02	0.03	0.12	0.17	0.11	0.15	0.25	0.34	0.21	0.28
Nilópolis	0.73	0.99	0.71	0.95	0.67	0.89	0.61	0.82	1.68	2.24
Niterói	0.64	0.82	0.98	1.23	1.51	1.90	2.42	3.04	3.60	4.52
Nova Iguaçu	0.15	0.22	0.29	0.41	0.46	0.65	0.75	1.06	1.10	1.55
Paracambi	1.73	2.34	0.74	0.97	0.95	1.26	1.18	1.55	1.80	2.35
Queimados	0.22	0.32	0.44	0.64	0.50	0.73	0.82	1.19	1.79	2.57
Rio de Janeiro	0.32	0.43	0.58	0.76	0.78	1.02	1.21	1.58	2.59	3.38
São Gonçalo	0.23	0.31	0.38	0.52	0.67	0.90	1.22	1.63	2.01	2.67
São João de Meriti	0.12	0.17	0.31	0.44	0.44	0.61	0.64	0.89	0.78	1.08
Seropédica	0.29	0.42	0.91	1.28	0.95	1.34	1.18	1.67	1.00	1.40
Tanguá	0.27	0.39	0.43	0.61	0.64	0.90	1.17	1.65	1.05	1.46
Mean	0.38	0.53	0.49	0.68	0.61	0.83	0.87	1.19	1.30	1.76
Standard deviation	0.40	0.54	0.30	0.41	0.35	0.46	0.52	0.66	0.83	1.04
Median	0.23	0.32	0.43	0.61	0.67	0.90	0.80	1.12	1.10	1.47
Minimum	0.02	0.03	0.08	0.12	0.11	0.15	0.14	0.21	0.21	0.28
Maximum	1.73	2.34	0.98	1.32	1.51	1.90	2.42	3.04	3.60	4.52

* *DDD = 8mg.*

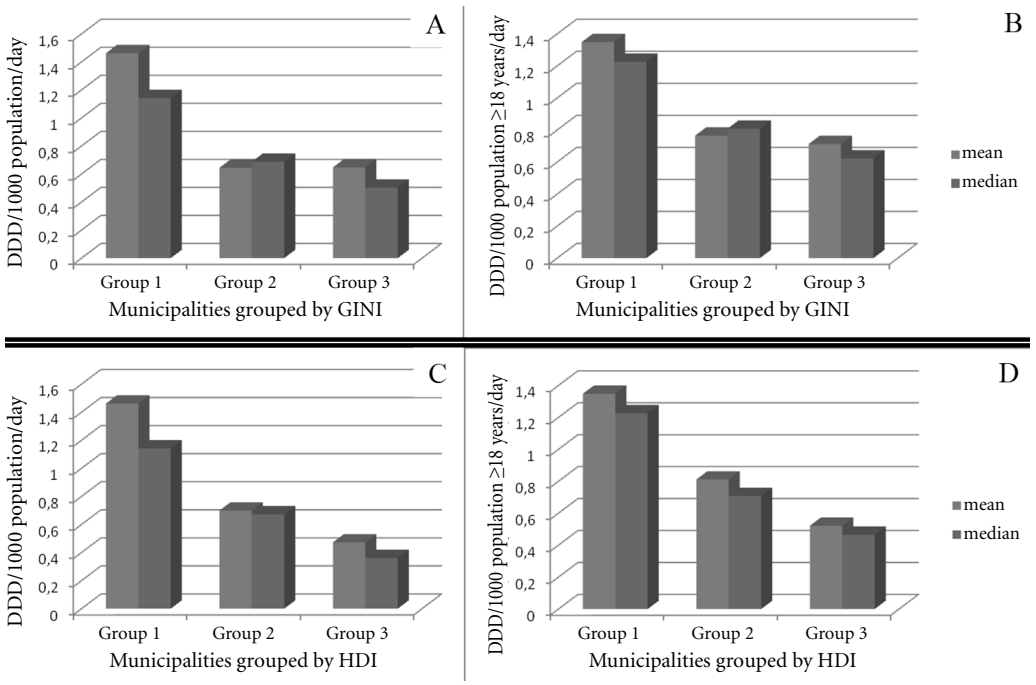

Figure 2. Mean and median consumption of Clonazepam in DDD per day, per 1000 population, by groups of municipalities in the Rio de Janeiro Metropolitan Region, grouped by Human Development Index (HDI) and GINI index, 2009 to 2013 (DDD = 8mg).

A : total population; B: population > 18 years, GINI. Municipalities: Group 1 - Rio de Janeiro, Niterói; Group 2 - Nova Iguaçu, Maricá, Magé, Guapimirim, Itaguaí, Itaboraí, Seropédica, Nilópolis, Mesquita, Duque de Caxias; Group 3 - Paracambi, Queimados, Japeri, Tanguá, São João de Meriti, São Gonçalo, Belford Roxo; C: total population; D: population > 18 years, HDI. Municipalities: Group 1 - Rio de Janeiro, Niterói; Group 2 - Nilópolis, Maricá, São Gonçalo, Mesquita, Itaguaí, Magé, Paracambi, Nova Iguaçu, Itaboraí, Seropédica, São João de Meriti, Guapimirim, Duque de Caxias; Group 3 - Tanguá, Japeri, Queimados, Belfort Roxo.

into the SNGPC, even those added when antimicrobial drugs were included in the SNGPC in mid-2011. This study shows that in Rio de Janeiro State, between 2009 and 2013, the number of establishments added increased by around 40%, while consumption in milligrams grew by about 500% (Figure 1).

The DDD resulted from an endeavour to develop a unit of measurement for comparing medicines consumed over time and among counties or regions. Created in the mid-1970s, it specifies the assumed average maintenance dose per day for a drug used for its main therapeutic indication in adults. Together with the Anatomical Therapeutic Chemical (ATC) classification, it forms the ATC/DDD system coordinated by the Collaborating Centre for Drug Statistics Methodology[25]. The method was developed in order to standardise the information about large sales volumes that is available at pharmacies in units that make sense from the medical standpoint[17]. It is useful for chronic-use drugs where the DDD value coincides with the mean dose[32], when therapeutic indications and dosages vary widely and when the active ingredients are marketed individually and not in association. The DDD is formulated on the basis of commitments resting on review of available information on the doses used in various countries. However, it does not necessarily correspond to recommended or prescribed doses, which are influenced by pharmacokinetic considerations, individual or patient group characteristics[32] and therapeutic indications.

In that light, study of the metropolitan region suggests that there are municipalities where more than four clonazepam treatments are dispensed per day for every 1000 adults 18 or more years old. Although this figure is high, it is believed to

be underestimated, because the WHO-standardised DDD is 8 mg, a dose indicated for anticonvulsant treatment, which is its main therapeutic indication in European countries. However, the tablets marketed in Brazil contain between 0.5 mg and 2.5 mg of the active ingredient, a dose indicated for treating anxiety and sleep disorders. As a result, estimates based on the standardised WHO value mask higher levels of use[11]. One Australian study estimated that the number of DDDs rises from 4.46 to 71.42 doses when the DDDs considered are 8 mg and 0.5 mg, respectively[11]. A study in Uruguay using a 1-mg DDD returned a mean of 36.51 doses among hospital pharmacy users[12]. In this present study, when DDDs of 8 mg and 1 mg were considered in the adult population in 2013, the number of DDDs rose from 2.64 to 21.09, respectively.

Explanatory hypotheses for the differences in clonazepam consumption among municipalities may reflect: morbi-mortality factors; inequalities in access to medical care; differences between pharmacies' and drugstores' operational capability to enter the SNGPC; and social and economic inequalities.

Health situation is associated with socioeconomic conditions and, therefore, this study explored relations between HDI, Gini index and unequal clonazepam consumption among municipalities. When cluster analysis was applied, it displayed promising power to distinguish among localities. Rio de Janeiro and Niterói merged into the same cluster (Group 1) in all the analyses, suggesting that the model performed well and consistently. That view is reinforced by the order of magnitude of the consumption means and medians observed for both indices. Consumption displays a downward gradient from Group 1 to Group 3, with the highest levels of consumption in Rio and Niterói. These estimates support the supposition that clonazepam consumption is lower in worse social and economic conditions. There may be a paradox here, involving excess- and access-related deviations, e.g., within the municipality of Rio de Janeiro, where the overall population enjoys better economic and care conditions but, at the same time, there is pronounced inequality, with excessive consumption coexisting alongside other portions of the population in worse conditions and lacking access to necessary medicines.

According to the ANVISA compendium of medicines, clonazepam is recommended, in isolation or with other drugs, for numerous conditions, among them epileptic crises, anxiety disorders, panic disorder, social phobia; mood disorders; bipolar affective disorder, mania; major depression; psychotic syndromes; dizziness and giddiness[22]. Benzodiazepines such as clonazepam are effective in acute treatment of anxiety disorders such as generalised anxiety and panic[1].

Despite the efficacy of benzodiazepines and the epidemiological significance of mental disorder symptoms, it must be noted that the necessity of pharmacological treatment is questionable and even diagnosis is problematical and subject to wide dissent[33]. The abusive and off-label use of benzodiazepines has been highlighted particularly for its role in coping with conditions or difficulties inherent to life, such as anxiety, sadness, attention, memory, childbirth, overweight, male and female sexual performance and aging[33]. The phenomenon known as medicalisation, which rests largely on excessive prescribing, seems to be ubiquitous. In the USA, one in five adults uses at least one drug indicated for a psychiatric problem; some 4% of children use a stimulant; 4% of young people use an antidepressant; and 26% of residents in long-stay institutions use antipsychotics[33].

Adverse reactions, the most frequent of which occur in one third of users, should also be considered; they include somnolence, ataxia, memory loss, reduced attention and transient euphoria. They can cause respiratory depression, falls, impaired motor coordination and convulsions. Among the psychological or psychiatric effects are cognitive deficit, delirium, psychosis and depression. They can trigger aggressive and antisocial behaviour, particularly when combined with alcohol[2]. Dependence can develop in days or weeks and discontinuation can cause effects opposite to those expected or even the intensification of previous symptoms. On the other hand, there are alternative therapies to pharmacological treatment: for social phobia, there are no significant differences between using cognitive-behavioural therapy or clonazepam, both of which treatments produce beneficial effects[34].

In this scenario, analysis of SNGPC data yielded a specific mapping of use of psychoactive substances, especially benzodiazepines such as clonazepam, connecting with the theoretical discussion of the issue of medicalisation and of over-diagnosis that has led to pharmacological treatment for conditions that do not properly form part of clinical syndromes. This discussion is enriched by meanings and the uses they acquire among users, which are revealed by qualitative research, as also conducted by this research

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group. The realities of our milieu are complex, combining current medicalisation processes with situations of flagrant lack of access to essential medicines[35]. For that reason, it is particularly important to study clonazepam use frequency and patterns, because they reveal the local particularities of the study population's relation to use of anxiolytics.

The estimates should be viewed with caution. On the one hand, there are restrictions on extrapolating information about purchases to consumption. Not all products purchased are consumed and not all dosages prescribed are complied with, which would indicate over-estimation. On the other hand, the SNGPC does not comprise doses administered in the hospital system, nor products purchased wholesale and distributed by governmental or other institutions; and the system's coverage of private facilities is still incomplete, which would indicate under-estimation and reduced external validity of the study.

As a data source for epidemiological studies, the SNGPC suffers from the limitations of administrative data bases not designed for input to research. The SNGPC offers no information on user age, sex or diagnosis. Population surveys or hospital patient records are more complete, valid data sources. Nonetheless, the low cost of obtaining SNGPC data and its nationwide scope make the information useful to pharmaco-epidemiology, not only for descriptive studies, but also for raising hypotheses for subsequent testing. One way of circumventing the lack of social, economic and health condition variables was to resort to external data bases, such as the one containing the HDI – which is calculated using longevity, education and income – and the Gini index, which measures the degree of income concentration in a given group.

With the DDD, it is possible to make national and international comparisons, evaluate medicine use trends over time, assess the impact of medicine-related events and to supply useful information for research into safe drug use. However, it only enables the approximate number of treatments to be estimated. Using the formula with an 8-mg dose impairs external validity, underestimates consumption and deserves to be reviewed when used in countries where the main therapeutic indication differs from the WHO standard.

Using a 1-mg standard dose made it possible to obtain a use frequency close to those found in surveys of Brazilian populations (5.4% for benzodiazepines[13] and 1.61% for tranquilizers[16]), underling concerns with the medicalisation of everyday life, chronic use, the risk of dependence, withdrawal syndrome and adverse reactions.

Conclusion and suggestions

The DDD is a useful unit for research purposes, providing it is adjusted to local particularities. Cluster analysis proved promising, in that it was able to discriminate differences in consumption of a medicine by geographical location and population characteristics. Future studies could use this technique to explore other regions. The SNGPC deserves to be used more as a source for studies of controlled medicines.

The high frequency of clonazepam use is an alert to the need for measures to restrict prescribing of products that affect central nervous system functions, targeting particularly health professionals responsible for prescribing. The estimates, which detail and extend the data already indicated by the Anvisa SNGPC system, raise concerns regarding misuse and recommend review of diagnostic and therapeutic criteria in the mental health field. Other studies will be able to consider the impact of the large-scale use of substances for diffuse psychiatric symptoms common in everyday life, such as irritability, depressive mood, excessive shyness, social anxiety, persistent insomnia, fatigue and so on.

Other suggestions are to map in detail the main medical and dental specialities that have prescribed a given substance and to invest in continuing education for prescribers as regards international guidelines restricting the indiscriminate use of benzodiazepines and also in more research into the level of patient knowledge of the possible effects of chronic use.

Social and economic variables play a noteworthy role in consumption of medicines and in health inequality. Possible excessive use may be concealing the fact that more dispossessed sectors with difficulties of access to medical care are being under-diagnosed and -treated.

Collaborations

RT Zorzanelli participated in the conception, planning, analysis and interpretation of the data, the writing of the work and the critical revision. S Rozenfeld, F Giordani and L Guaraldo participated in the planning, analysis and interpretation of data, writing of work and critical review. AG Brito Júnior participated in the statistical analyzes, the writing of the work and the critical review. GC Matos participated in the analysis and interpretation of the data, the writing of the work and the critical review. MG Oliveira, RQM Mota and RM Souza contributed to the critical review of the content.

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