ANALYSIS OF THE CONSUMPTION OF SELECTIVE SEROTONIN REUPTAKE INHIBITORS (SSRIS) AND TRICYCLIC ANTIDEPRESSANTS (TCA), BEFORE AND DURING THE COVID-19 PANDEMIC, IN COMMUNITY PHARMACIES IN BRAZIL

Abstract: **Introduction**: The COVID-19 pandemic has changed the way we live. It brought several effects to the lives of society as a whole and showed us an increase in the use of antidepressant medications. **Objective:** To evaluate the consumption of antidepressants in the period from 2015 to 2020 and the estimate for 2021 to 2025; as well as possible animated between consumption and the socioeconomic and demographic conditions of the different Brazilian regions. **Methodology:** The research was developed in three stages. 1st stage: search for data in the National Controlled Products Management System (SNGPC). 2nd stage: research on the platform of the Brazilian Institute of Geography and Statistics, IBGE for the collection of sociodemographic data and variables of interest. 3rd stage: descriptive statistical analysis, comparison of consumption rates and correlations to verify the association between numerical variables. Medians and interquartile ranges were left (median [Q1; Q3]) and the Kruskal-Wallis and Spearman non-parametric test was performed (ρ using the R 4.0.2 software (R Core Team, 2020). **Results:** if the increase in the consumption of antidepressant medications in the period from 2015 to 2021, and it is controlled that, in the year 2020, at the beginning of the pandemic by Covid-19, this increase of 15%, compared to the year 2019. However, the estimate from 2021 to 2022 is that there will be an increase of only 3% pre and pandemic caused by COVID-19 in Brazil Sociodemographic variables have a significant influence on the consumption of antidepressants. **Conclusion:** An observation from the analytical side found that, in this study, the increased consumption of antidepressants in Brazil during the pre- and pandemic period caused by COVID-19. The study shows the relationship between socioeconomic and demographic conditions.

Keywords: *Antidepressants; Mental health; Coronavirus; Pandemic; Social distancing.*

I. Introduction

The COVID-19 pandemic, caused by Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2), first emerged in Wuhan, China, in December 2019. In Brazil, the first case occurred in March 2020 The COVID-19 pandemic has overloaded health systems in most countries, causing huge economic losses (OCHANI et al.; 2021) and changing the way we live. From the routine of remote work to the distance from friends and family, the mental health of people around the world is affected (WHOOLEY, 2000 and BRANDÃO, 2021). From this perspective, it is clear that the COVID-19 pandemic has had numerous impacts on the lives of society as a whole from different angles and, increasing the use of drugs related to mental health disorders (BRANDÃO, 2021).

The Diagnostic and Statistical Manual of Mental Disorders (DSM-5, 2014) says that depressive disorders include disruptive mood dysregulation disorder, major depressive disorder (insert major depressive episode), persistent depressive disorder (dysthymia), pre-existing dysphoric disorder -menstrual disorder, substance/medication-induced depressive disorder, depressive disorder due to another medical condition, other specified depressive disorder, and unspecified depressive disorder (DSM-5, 2014). There are Bipolar Disorders and Related Disorders, the common feature of these disorders is the presence of sad, empty or irritable mood,

accompanied by somatic and cognitive changes that significantly affect the individual's ability to function, what differs between them are the aspects of duration, time or presumed etiology (DSM-5, 2014).

Depression is the second common clinical condition in medical practice, and secondary only to systemic arterial hypertension (WHOOLEY, 2000). Mental disorder is a medical condition and must be treated with medication, however, it does not imply as the only possibility of treatment (ALCÁNTARA, 2018). Psychotropic drugs (psyche=mind, topos=alteration) are selective modifiers of the Central Nervous System and can be classified as: anxiolytics and sedatives; antipsychotics (neuroleptics); antidepressants; psychomotor stimulants; psychomimetics and enhancers of cognition (RANG, DALE, RIITTER, 2001;DE ABREU, 2021).

Among antidepressants, selective serotonin reuptake inhibitors (SSRIs) have been frequently used because they are safe and well tolerated. Currently, fluoxetine is the SSRI prescribed in Brazil and worldwide (RANG, DALE, RITTER, 2001; DE ABREU, 2021). They are relatively selective, about 10 times selective for inhibition of Serotonin Transporters (SERT) over Norepinephrine Transporters (NET) (GOODMAN and GILMAN, 2012). Tricyclic antidepressants, on the other hand, non-selectively inhibit the reuptake of monoamines (serotonin, norepinephrine, dopamine) (ANDRADE, et al., 2004).

In Brazil, the legislation that approves the technical regulation on substances and medicines subject to special control is Ordinance No. 344/98 - SVS/MS, of May 12, 1998 (CFF, 1999/2000), which defines the following list of substances: A1 and A2 (narcotics), A3, B1 and B2 (psychotropics), C1 (other substances subject to special control), C2 (retinoics for systemic use) and C3 (immunosuppressants). The National Health Surveillance Agency (ANVISA) controls this regulation and defines the National Controlled Products Management System, or SNGPC, as a very important tool to control the production, circulation, trade and use of substances or medicines subject to special control in the country. This system replaced traditional bookkeeping (manual or computerized) the information did not leave the company. With the exclusively electronic SNGPC, this data must be sent to ANVISA (ANVISA, 2007). The objective of the study is to investigate the consumption of antidepressant classes, SSRIs and ADT, before and during the COVID-19 pandemic, in community pharmacies in Brazil, and possible correlation with socioeconomic and demographic conditions in Brazilian regions.

II. Material and methods

This is a quantitative, retrospective and bibliographical review study to support the theoretical framework. The research developed in 3 stages (DE OLIVEIRA et al., 2018). The first stage collects data on the ANVISA platform on the consumption of SSRI and ADT medication, from 2015 to 2020, and estimated consumption for the period from 2021 to 2025. The second stage is research, on the IBGE-Instituto Brasileiro de Geografia platform and Statistics, for the collection of sociodemographic data and variables of interest for the Brazilian states. In the third stage, descriptive statistical analyzes were performed, comparison of annual consumption rates and correlations to verify the association between numeric variables.

For the first stage, information was collected on the ANVISA platform, with regard to the dispensation of industrialized medicines subject to bookkeeping in the SNGPC (National Controlled Products Management System). Data on the dispensation of medicines subject to bookkeeping at the SNGPC are separated into Industrialized and Manipulated.

The collected data referred to the dispensations of all psychotropic drugs, SSRIs and ADT, in the period from 2015 to 2020. The theme “sales of industrialized medicines” was selected and the year of sale of the medicine, State, cities, State of the professional council , active principles, year and months of sales, prescribing advice and presentation description, respectively. Units are counted in boxes.

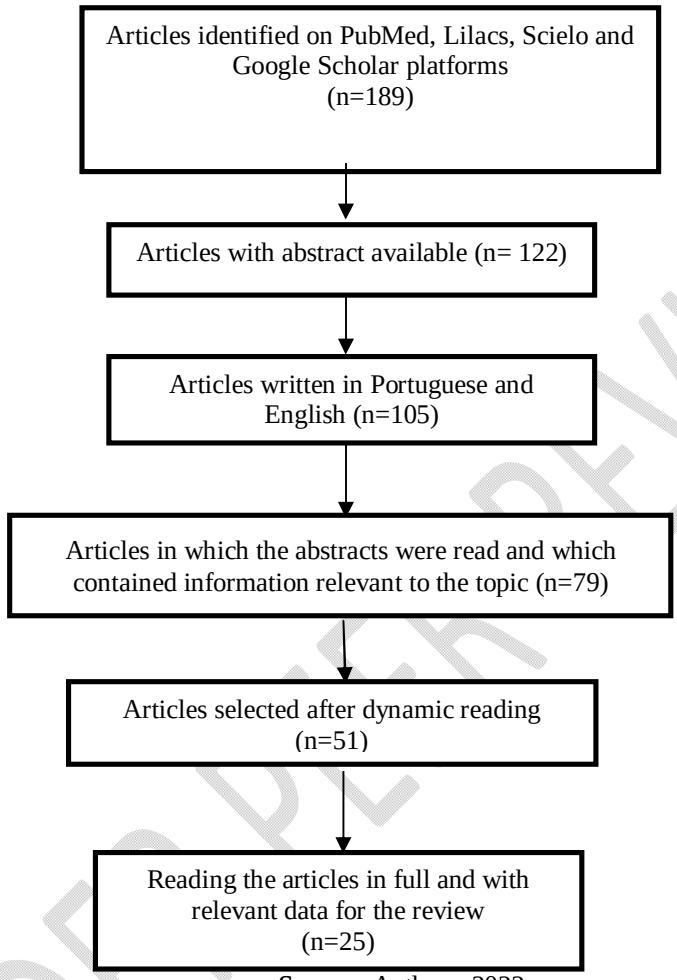
In the second stage, research was carried out on the IBGE platform to collect sociodemographic data and other variables of interest: Human Development Index (HDI), demographic density, monthly household income per capita of the Brazilian states and estimated population of people (2020).

In the third stage, statistical calculations were performed using the R 4.0.2 software (R Core Team, 2020). Descriptive statistics for quantitative variables are presented as medians and interquartile intervals (median [Q1; Q3]), the distribution of consumption rate data in the states does not follow the normal distribution by the Kolmogorov-Smirnov test. For qualitative variables, absolute and relative frequencies, n (%) were considered.

For the comparison of the annual consumption rates, the Kruskal-Wallis non-parametric test was used, the distribution of the variable is not normal and there are two periods compared. The correlations calculated to verify

the association between numerical variables are the Spearman (ρ), (Conover, 1999). For all statistical tests, a significance level of 5% was adopted and considered two-tailed.

Flowchart 1- Screening of articles used in the literature review.



Source: Authors, 2022.

III. Results and discussion

The abusive use of psychotropic drugs in Brazil has grown exorbitantly. Currently, the exacerbated use of these drugs has generated concern among health authorities, the prolonged use of psychotropic drugs can cause serious damage to the health of the population and side effects. Among these, the main ones are the decrease in psychomotor activity, memory impairment, paradoxical disinhibition, tolerance and dependence and the potentiation of the depressant effect by interaction with other depressant drugs, mainly alcohol (Longo & Jhonson, 2000). The use of these medications needs to be carefully monitored, because the knowledge of their effects on the Central Nervous System is still a major challenge for professionals in this area, not fully known (MOURA et al., 2016).

In order to understand the consumption of antidepressant drugs in Brazil and the influence of the variables of interest, we evaluated the correlations between consumption and the Human Development Index —2010, estimated demographic densities (hab/km^2) — 2020, monthly household income per capita — 2020 and estimated population of people (2020) (Table 1).

Table 1: Correlations between the total number of antidepressant drugs consumed in 2020 and other variables of interest.

Variables	Correlation. From Spearman with consumption of antidepressants (2020) (n = 27)	p-valor
Human Development Index – 2010	0.55	**0.003**
Estimated population density (inhabitant/km²) – 2020	0.59	**0.001**
Household monthly income per capita – 2020	0.64	**< 0.001**
Estimated population of people (2020)	0.86	**< 0.001**

Source: Authors, (2022).

All correlations were significant. Consumption is proportional to the size of the population. For this reason, correlations of consumption rates (total of drugs divided by population) were calculated in order to remove the influence of population size (Table 2). Thus, there was a greater correlation between the consumption of antidepressant drugs and monthly household income per capita (0.81 p-value < 0.001).

Table 2: Correlations between the rate of antidepressant medication consumed by inhabitants in 2020 and variables of interest.

Variables	Correlation. From Spearman with consumption of antidepressants(2020) (n = 27)	p-valor
Human Development Index - 2010	0.70	< 0.001
Estimated demographic density (inhabitant/km²) – 2020	0.55	0.003
Household monthly income per capita - 2020	0.81	< 0.001
Estimated population of people (2020)	0.45	0.019

Source: Authors, (2022).

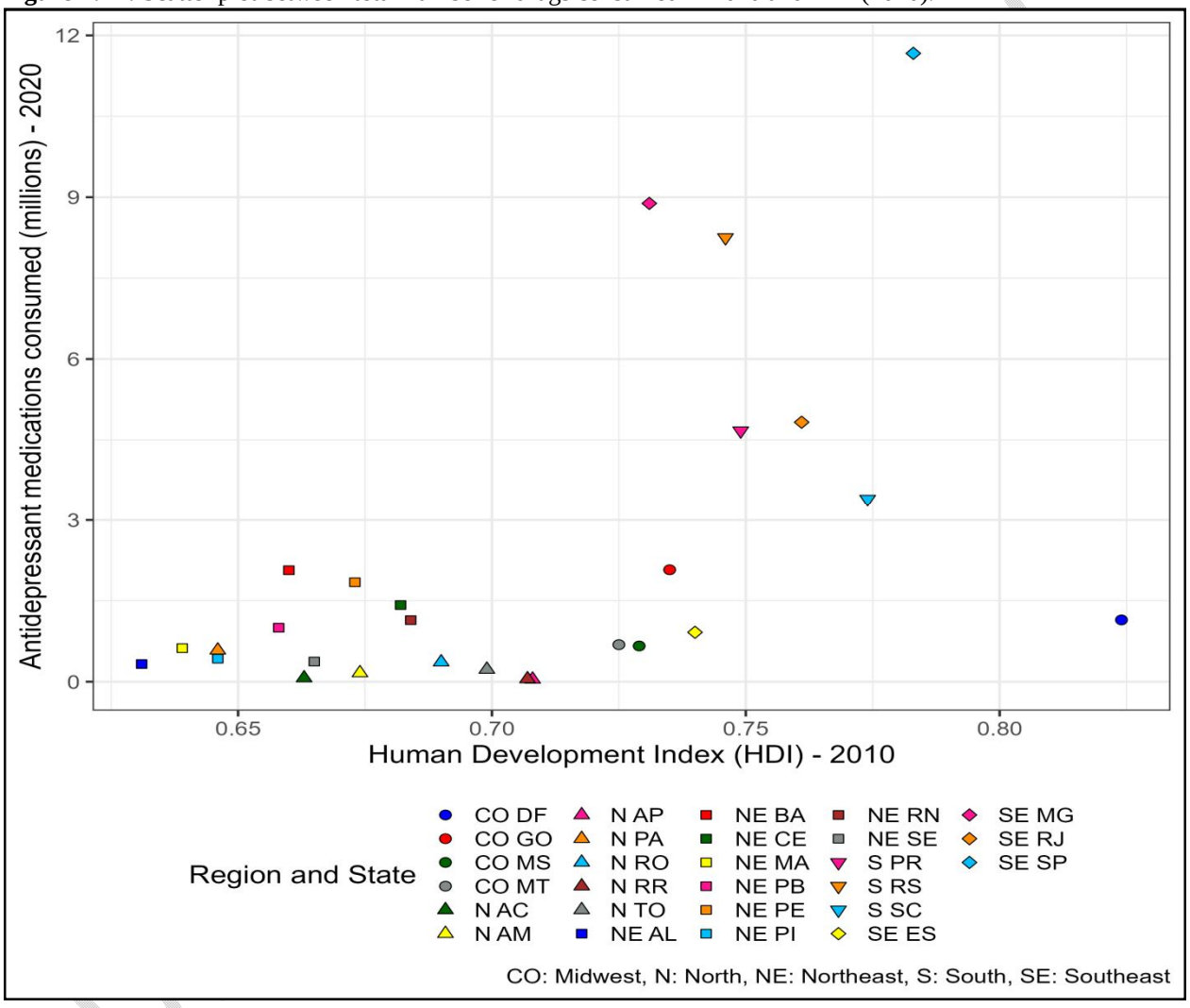
EThis result corroborates the findings by Garcias et al. (2008). The authors conducted a study with 1327 adults in the city of Pelotas, Brazil, in 2006, to assess the prevalence and factors associated with the consumption of antidepressants in residents of the urban area of the municipality. It was found that 9.3% of respondents consumed antidepressants in the last fifteen days. The consumption of these drugs was significantly associated with being female and with high socioeconomic status classes A and B (income). The fact that access to medication is conditioned to per capita household income demonstrates that access to medication must be guaranteed by the public authorities, as determined by the Federal Constitution.

Regarding the Human Development Index (HDI), it was observed that the higher the HDI, the greater the consumption of antidepressant drugs. The HDI is a composite statistical index that aims to measure the quality of life by establishing a comparative parameter between different countries, regions or even cities (Júnior, 2010). HDI is formed by the average of three other indices: the life expectancy index, the education index and the income index (SILVA & GUIMARÃES, 2012). The HDI is to emphasize that people and their capabilities should be the best parameter to evaluate the development of a country, state or municipality, and not just economic growth (SOUZA, 2008). Therefore, the HDIs are in an average profile, varying between 0.55 and 0.70, and an index up to 0.50 is considered low and above 0.79 development is considered high.

We observed that the highest consumption of antidepressant drugs occurs in states with an HDI above 0.70; with the exception of the Federative Unit (UF) of the Federal District (DF), which has an HDI of 0.80 and lower

consumption of these medications (Figure 1). This finding may be related to the smaller population size. The results of the antidepressant consumption correlations obtained were: 0.55, 0.59, 0.64, 0.86 p values = 0.003; 0.001; <0.001; <0.001, respectively. Mental disorders are prevalent in low-income populations, where the theory exists that environmental factors predispose to the development of these disorders. Access to treatment has been greater in populations with higher socioeconomic status.

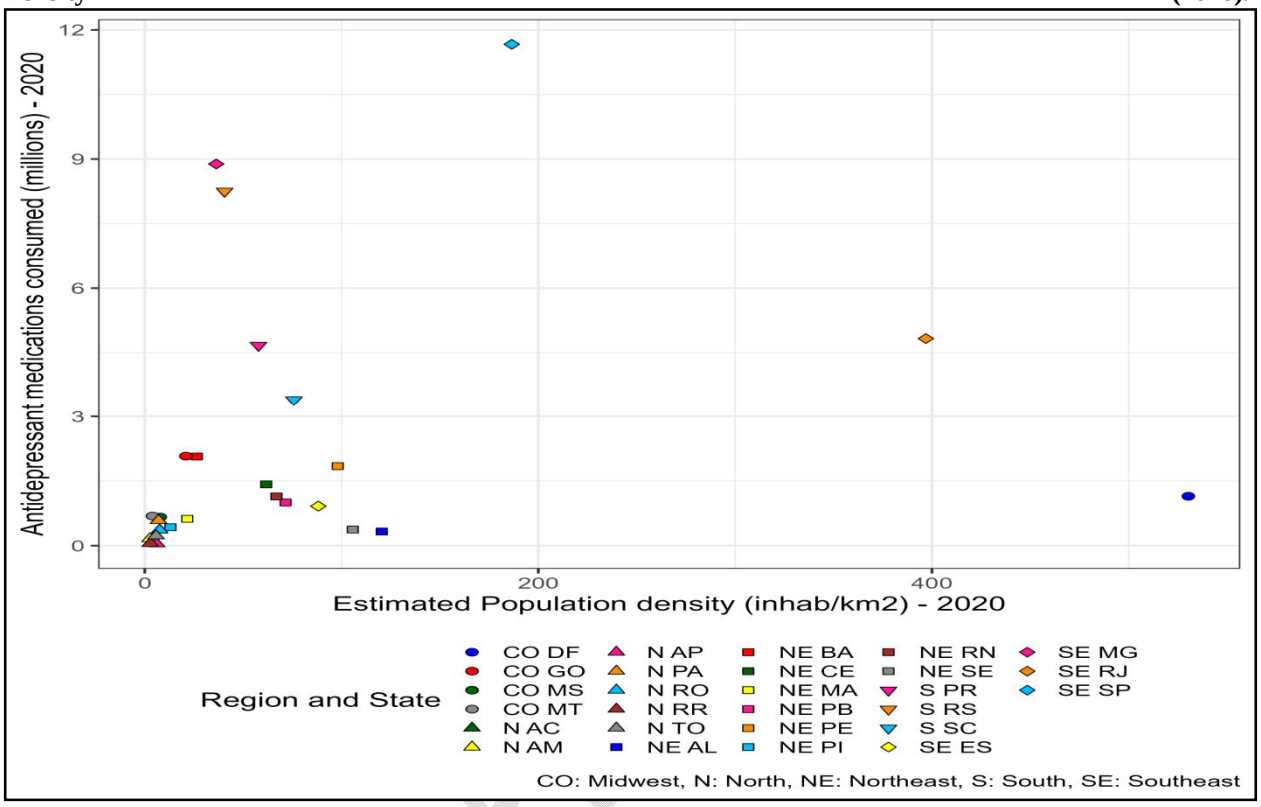
Figure n.º 1: Scatter plot between total number of drugs consumed in 2020 and HDI (2010).



Fonte: Autores, (2022).

In relation to demographic density, a positive association was observed with a correlation of 0.59, demonstrating that there is a trend towards higher consumption in states with higher demographic density (Figure 2). Again, the Federal District stands out for, even with a high population density, it is not among the states with the highest consumption. This differed from some studies, which showed that cities with higher demographic density had higher drug consumption (AZEVEDO, 2016). The size of the DF population could justify the lower consumption of medicines.

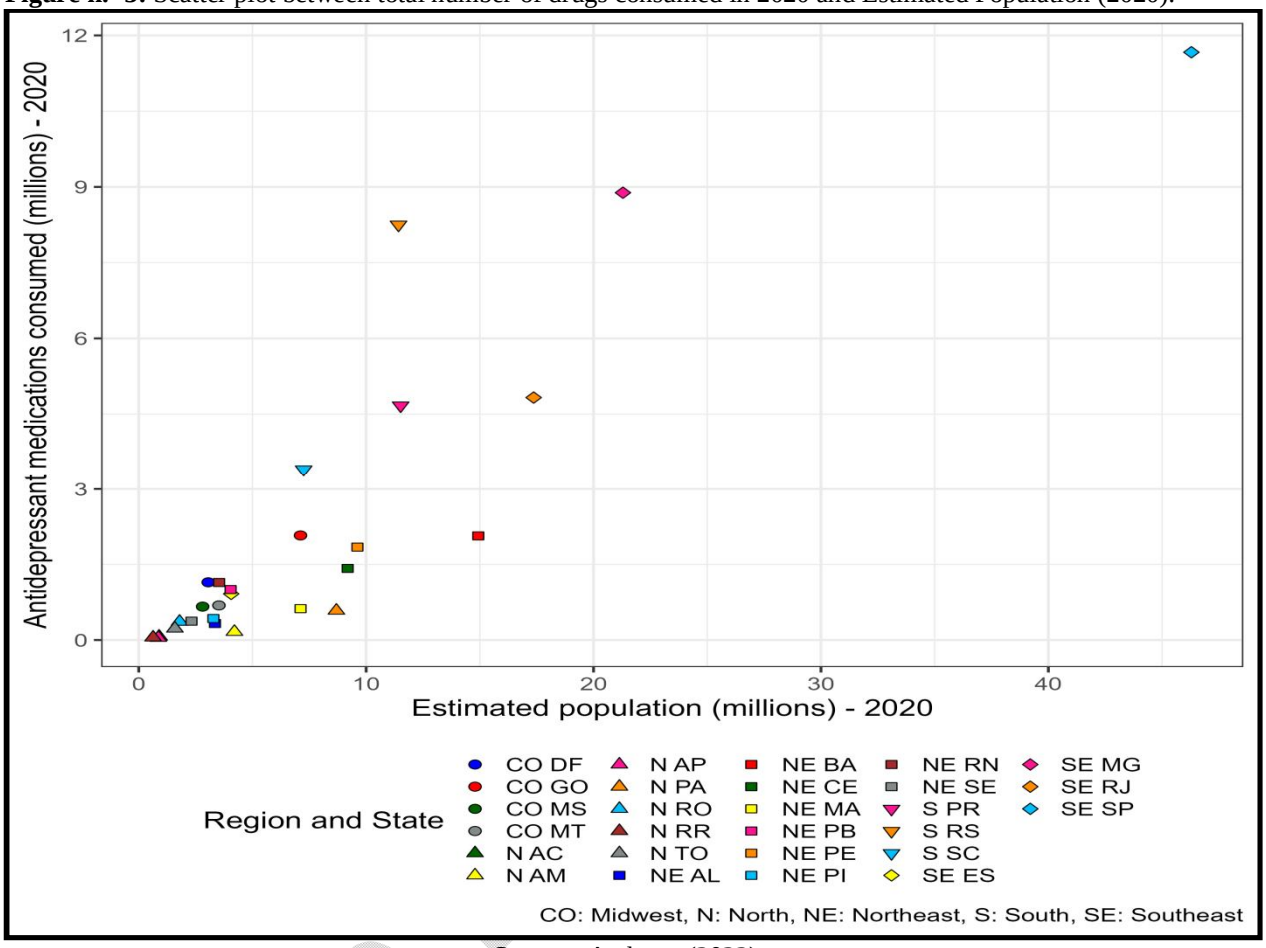
Figure n.º 2: Scatter plot between total number of drugs consumed in 2020 and Estimated Demographic Density (2020).



Source: Authors, (2022).

Considering that, in general, the larger the population, the greater the consumption of antidepressant drugs, it was observed that the state of São Paulo is both the state with the largest population and the highest consumption of antidepressant drugs, followed by Rio de Janeiro (Figure 3). The variables presented in this study constitute essential information in understanding the social panorama and in understanding the evolution of indicators of the consumption of antidepressant drugs.

Figure n.º 3: Scatter plot between total number of drugs consumed in 2020 and Estimated Population (2020).

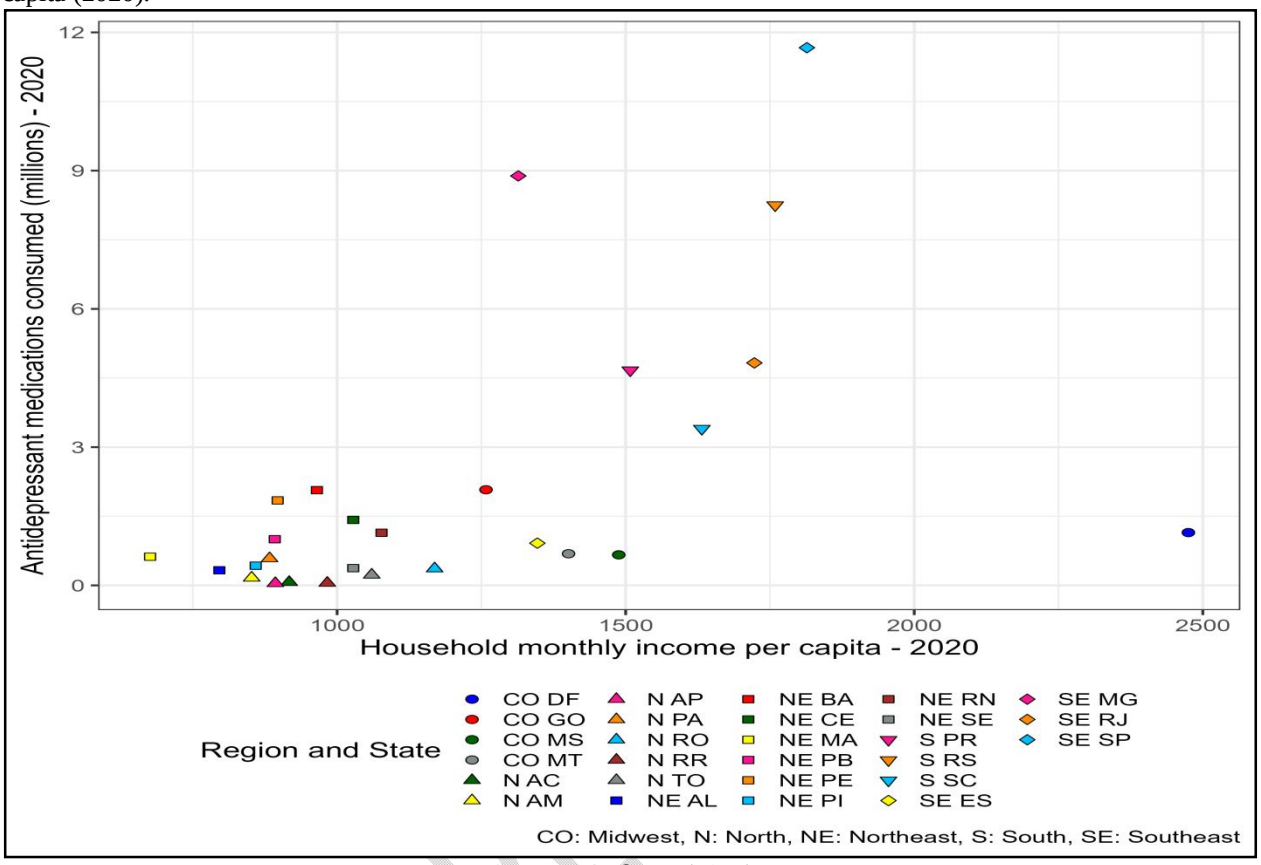


Source: Authors, (2022).

When evaluating the behavior of the consumption of antidepressant drugs with monthly household income per capita (Figure 4) a positive association was observed (correlation of 0.64), with a non-linear relationship occurring, approaching an exponential curve. It was found that for high values of per capita monthly household income (values between 1500 and 2000) there is a higher consumption of antidepressants. The states with the highest consumption have monthly income above R$1250. However, it is not a rule, a large portion of the states with monthly income below R$1250.00 was identified, which consume antidepressants. In the study by Gomes et al., (2017), cities with a large concentration of physicians showed high consumption of these drugs, which may be related to the better purchasing power of the population of these cities, since the data used for this research came from commercial.

Another study carried out in Canada identified that people who were quarantined and who had an annual family income of less than USD$40,000 Canadian dollars, compared to those who earned between USD$40,000 and USD$75,000, presented post-traumatic stress and depressive symptoms. It was observed that, as income was reduced, depressive symptoms and post-traumatic stress increased (HAWRYLUCK et al., 2004). The symptoms probably happen because those people with low income are prone to the effects of loss of income or job, worrying when they are in a situation of quarantine and social distancing (SILVA et al., 2021).

Figure n.º 4: Scatter chart between total number of drugs consumed in 2020 and monthly household income per capita (2020).



Source: Authors, (2022).

According to Noronha (2006), in Brazil, rich families spent an average of 3.10 times on medicines than poor families. In a country with evident social inequalities, such as Brazil, it is expected that there are differences in medication consumption between families with higher and lower incomes. It is understood that the financial difficulty caused by the decrease or cancellation of people's income is an important risk factor for mental health, given that financial losses generate great concern about the probable lack of supplies for family survival in times of a pandemic. (SILVA et al., 2021). Spending on medication accounts for the majority of private health spending. In the Boing study (2011), it was shown that spending on medicines is higher among the rich in community pharmacies. This does not mean that the poor class does not consume antidepressant medication. They are probably users of the Unified Health System (SUS). Consumption among the low-income population can be explained by the expansion of health programs in the SUS, such as Basic Pharmacy, Family Health Strategy and Popular Pharmacy.

The increase in the consumption of SSRI and ADT antidepressants, over the years 2015 to 2020, is shown in Table 3. The values show that there was an increase in the consumption rate over time and, considering the rates of the states (p-value = 0.176), there was no statistical difference.

Table 3: Medians and interquartile ranges of antidepressant consumption rate (per thousand inhabitants) per year and test result.

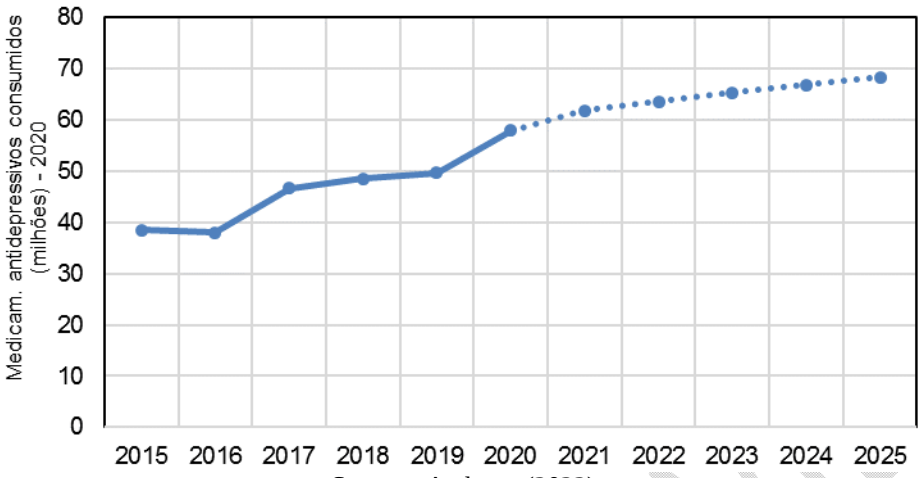
YEAR	Consumption rate per year (thousand inhab.)	p-valor
2015	131.7 [80.1; 180.0]	0.176
2016	145.4 [69.7; 199.1]	
2017	168.3 [91.2; 249.9]	
2018	178.2 [83.7; 279.7]	
2019	207.8 [90.7; 284.6]	
2020	194.8 [113.9; 284.9]	
Total	**159.9 [83.4; 250.7]**	

Source: Authors, (2022).

The behavior and quantity of medicines consumed per year in Brazil, in the period from 2015 to 2020 and estimates from 2021 to 2025, are represented in Figure 5. The results showed that there is a growing scenario and that the year 2020 was the higher consumption of antidepressant medication.

The medians and interquartile ranges of the rate of antidepressant consumption (per thousand inhabitants) per year were evaluated. Based only on the history of annual consumption in Brazil from 2015 to 2020, the consumed amount of antidepressant drugs (SSRIs and ADTs) in the country, estimated until 2025. This estimate obtained with the estimated function: 40.000.000 × y^(0.2228), where y is the point that represents the year, that is: 2015 is point 1, 2016 is point 2, 2021 is point 7 and so on. We obtained the following results: Years 2015, 2016, 2017, 2018, 2019, 2020, presented the following consumption rates per year (thousand hectares): 131.7 [80.1; 180.0], 145.4 [69.7; 199.1], 168.3 [91.2; 249.9], 178.2 [83.7; 279.7], 207.8 [90.7; 284.6], 194.8 [113.9; 284.9], in which the total of 159.9 [83.4; 250.7] and the value of p= 0.176. The results of the analysis of the amount of drugs consumed and estimated per year in Brazil were: 2015, 2016, 2017, 2018, 2019, 2020, 2021*, 2022,* 2023*, 2024*, 2025*, with amounts consumed per year in Brazil, 38,430,629, 37,959,749, 46,612,930, 48,464,185, 49,650,237, 57,919,648, 61,708,904, 63,572,376, 65,262,728, 66,812,849, 68,79,824, 68,79,824, respectively In the estimate analysis, Figure 5, considering a growth scenario, but at a slowing pace when compared to recent years, for example: 2019 and 2020, there was an increase of 15%, while, in the estimate for 2021 and 2022, there was an increase of 3%.

Figure n.º 5: Number of antidepressant drugs consumed from 2015 to 2020 and estimate from 2021 to 2025.



Source: Authors, (2022).

The Pan American Health Organization (PAHO) projected that depression would be the second biggest public health issue in 2020 (PAHO, 2001). It is estimated that depression will be the first disease by 2030, surpassing those of the heart (WHO, 2017). Since 2016, Brazil leads the ranking of prevalence of depression in 36 million affected people, equivalent to 10% of all depressed individuals around the world (GOMES et al., 2022).

In the United States, anxiety and depression hit people, in which there was an increase in suicidal ideation, as found by the Center for Disease Control and Prevention (CDC) and several mental health institutions (Observador, 2021). According to research by the Kaiser Family Foundation (KFF), the Covid-19 pandemic has shown an increase in worries and stress that has translated into difficulties sleeping (for 36% of individuals) or eating (32%) and increased consumption of alcohol or substances (12%). Mental health symptoms have increased during the COVID-19 pandemic. From September 29 to October 11, 2021, 31.6% of US adults reported symptoms of anxiety and/or depressive disorder, up from 11.0% in 2019 (PANCHAL et al., 2021).

According to the National Health Council (CNS), European countries are in second place in mental disorders. Depression affects 10% of Portuguese people. Portugal is one of the countries with the highest consumption of anxiolytics, hypnotics and sedatives, and of antidepressants, in which these drugs are commonly used in situations of depression or generalized anxiety (Martins, 2021).

The study by Furtado & Fernandes (2020) analyzed data on the dispensing of medicines reimbursed by the National Health Service in community pharmacies in mainland Portugal. In this analysis, utilization is expressed as defined daily doses (DDD or DHD) per 1000 inhabitants/day. There was stabilization with a tendency towards a decrease in the use of anxiolytics, hypnotics and sedatives, and a clear increase in the use of antidepressants. The evolution of antidepressant consumption went from 64.52 DHD in 2010 to 118.66 DHD in 2019, representing a growth rate of 84% compared to 2010.

The Observador newspaper (2021) reported that Argentina the country that had the greatest quarantine in the world, about eight months, a study by the Faculty of Psychology of the University of Buenos Aires concluded that confinement affected the mental health of 80.3 % of Argentines. Among the visible disorders due to the prolonged confinement in Argentina, fear, anxiety and depression appeared.

Italy developed a survey that took place in two moments: two weeks after the beginning of the blockade and one week after the end of the blockade. It was found, through the DASS Scale-21, that 53.3% of respondents had high scores on the depression subscale in the final period of social isolation. With regard to stress, 58.31% had high scores on the score generated by the subscale, while 30.52% had a lower score and 11.16% scored equally (ROMA et al., 2020). This scale is used to investigate the participants' mental health.

In Germany, a study was conducted by the University of Saarland demonstrating that satisfaction with day-to-day life decreased significantly. Researchers analyzed the psychological and social consequences of the year 2020, in 1,500 men and women, it turned out that "worry, stress and depression increased" (OBSERVADOR, 2021).

According to a study, released in January by the Federal Planning Office, a Belgian government body, based on a December 2020 survey, at the peak of the second wave and with new confinement measures in place since October, "the mental health of Belgians has become compromised" (OBSERVER 2021). The cabinet points out that antidepressants and mood regulators are at the root of the growing consumption of psychotropic drugs. As a result, the consumption of antidepressants rises. During the recent pandemic, the rate of mental illness and the use of antidepressants increased considerably, which further aggravated public health problems (FEITOSA, et al., 2021).

This high consumption can be explained due to the increasing number of diagnoses of psychiatric disorders in the population, social distancing, quarantine, loss of work. Grieving in families, health professionals with an exhausting workload, the entry of new psychotropic drugs in the pharmaceutical market and new therapeutic indications for existing psychotropics, enticing the pharmaceutical industries in medical prescriptions, the multispecialty doctors they prescribe (PRADO et. al., 2017). The sudden change in hectic routines, the difficulty of adapting to the restrictions imposed by social isolation are stressors that have contributed to the psychic illness of individuals. The fear of contracting COVID-19 and, when infected or suspected of having Covid-19, people tend to experience sentimental and emotional changes, feeling apprehensive, anguished, frightened, insecure, alone, bored and showing changes in sleep and mood (SHIGEMURA, 2020). These are some of the characteristics that contributed to the increase in the consumption of antidepressants during the pandemic period.

In the study Santos et al. (2018), it was found that most prescriptions were performed by a general practitioner. The studies by Torres et al. (2014) and Facury (2010) found that psychiatrists and neurologists ranked second and third, respectively. The authors emphasize the relevance of these medical specialties in the prescription of antidepressant drugs, since these doctors have greater knowledge of the pharmacological properties and possible risks with the use of these drugs (TORRES et al., 2014; FACURY, 2010).

Medical prescriptions play a key role in preventing medication errors and are directly linked to the Rational Use of Medications (URM). Incomplete, erased or illegible prescriptions directly affect the effectiveness of dispensing, therefore, in the pharmaceutical management of the patient, it happens to lead to a change in pharmacological treatment (SANTOS et al. 2018). In this sense, when used inappropriately, psychotropic drugs can produce important adverse events, causing dependence and generating a series of health problems (SILVA & LIMA, 2017). In this context, the role of the pharmacist is fundamental to improve the quality of life of these patients, they can clarify doubts about the medications, about their disease, providing means for adherence to drug treatment, guiding about the need and benefits of medication, and to promote the rational use of these drugs (SANTOS, 2018).

IV. Conclusions

By observing the analyzed aspects, the present study identified an increase in the consumption of antidepressants in the pre- and pandemic period caused by COVID-19 in Brazil. The study demonstrated positive and significant correlations with socioeconomic and demographic conditions (Human Development Index — 2010; estimated demographic densities (inhabitant/km²) — 2020; monthly household income per capita — 2020 and Estimated population of people (2020). Thus, sociodemographic variables have a significant influence on the consumption of antidepressants.

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