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Article

Analysis of depression in Brazil and the feasibility of incorporating pharmacogenomics as an auxiliary tool in antidepressant treatment

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Depression has substantially increased in the last 10 years in Brazil, and mental health became a concerning issue for the public health globally, especially considering the COVID-19 pandemic. The therapeutic conduct in depression mainly relies on medication and psychotherapy. However, more than one attempt in the treatment can be considered a common procedure before finding out the right medication. This conduct leads many patients to give up following pharmacological treatment. In this scenario, pharmacogenomics emerges as a possible supporting tool of the medical treatment. This paper aims to analyze the scenario of depression in Brazil and the viability of pharmacogenomic tests implementation as a part of the medical procedure. Official data bank from the Brazilian government was used to analyze the prevalence of depressive disorder, as well as Pharmacogenomic data bases and relevant articles around this topic. Additionally, pharmacogenomic tests typically take into consideration the genes *CYP2D6* and *CYP2C19*, which are relevant for antidepressant treatment. Data shows that these tests could help patients achieve remission of symptoms, and they could also be economically advantageous. Thus, pharmacogenomic tests present as an interesting approach for the therapeutic conduct of depression and can significantly improve the health quality of this affected population.

Keywords: Depression. Pharmacogenomics. Pharmacogenomic testing.

INTRODUCTION

There was an increase in the prevalence of mental disorders in the period between 1990 and 2019, according to the Global Burden of Disease (GBD). Among the disorders, depression was an important contributor to the larger number of cases (Ferrari *et al.*, 2022). The COVID-19 pandemic has also negatively influenced mental health. The new reality negatively impacted society in different ways, one of them being the likely increase in the prevalence of depression in 2020 (Santomauro *et al*., 2021).

Treatment of depression consists of the use of antidepressants and psychotherapy. On average, it takes 4 to 8 weeks after starting the medication for the effectiveness of the antidepressant to be evaluated (Tuteja *et al.,* 2022). However, throughout the treatment, it is common for an individual to change the medication and dose, which characterizes treatment as "trial and error" (Tuteja *et al.,* 2022). Prior to the correct therapy, the patient may suffer several adverse effects, in addition to not having their condition treated. These factors can lead to the abandonment of pharmacotherapy. Moreover, statistics show that the more attempts with different antidepressants, the lower the chances of remission (Greden *et al.,* 2019).

The response to a particular antidepressant may vary, which may be partly explained by genetic variability. The P450 cytochrome is formed by enzymes directly involved in the metabolization of antidepressant drugs and, allelic variations in genes encoding some of these enzymes can result in different metabolization phenotypes, which are related to enzyme activity (Bousman *et al.,* 2021). In particular, the enzymes CYP2C19 and CYP2D6 play an important role in the metabolization of antidepressants (Milosavljević *et al.,* 2021).

Phenotypes range from ultra-rapid metabolizer (UM) (enzyme with higher-than-normal activity) to poor

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metabolizer (PM) (enzyme with low activity). These variations in activity affect both the efficacy and adverse effects an individual may experience (Murphy *et al.,* 2021). Because of these variations, PM and intermediate metabolizers (IM) are more susceptible to the adverse effects of medications, while UM metabolizers do not have the desired therapeutic effect according to the dose administered (Milosavljević *et al.,* 2021).

In this context, an opportunity arises for pharmacogenomics. The goal of pharmacogenomics is to find the most appropriate drug and dose according to one's genotype/phenotype (Pirmohamed, 2023). This paper aims to analyze the scenario of depression in Brazil and to evaluate the possibility and feasibility of implementing pharmacogenomic tests as an auxiliary tool in the antidepressant treatment.

MATERIAL AND METHODS

The scenario of depression in Brazil will be analyzed based on public data published in official Brazilian government service platforms. Pharmacogenomics data bases will be consulted, such as Pharmacogenomics Knowledge Base (PharmGKB) and Table of Pharmacogenetic Association from Food and Drug Administration (FDA) in addition to literature research that will be performed, preferably with articles not older than 5 years from now.

RESULTS AND DISCUSSION

In 2013 and 2019, Brazil conducted a National Health Survey (*Pesquisa Nacional de Saúde - PNS*) to monitor chronic diseases in the country. The PNS is a population-based survey of the Ministry of Health with the Brazilian Institute of Geography and Statistics (IBGE) that aims to monitor the health conditions at a national level. One of the topics analyzed was the percentage of people aged 18 years or older who reported a diagnosis of depression by a mental health professional. The data can be found on IBGE (2022) and FIOCRUZ (2021).

In 2021 and 2023, other surveys were carried out with the aim of investigating chronic diseases. The studies were conducted by the surveillance of risk and protective factors for chronic diseases by telephone survey (Vigitel, 2022; Vigitel, 2023), which is an initiative part of the Ministry of Health. There is also an indicator of percentage of adults (≥ 18 years old) who reported a medical diagnosis of depression (Vigilância de Fatores de Risco e Proteção para Doenças Crônicas por Inquérito Telefônico (Vigitel), 2022; Vigilância de Fatores de Risco e Proteção para Doenças Crônicas por Inquérito Telefônico (Vigitel), 2023).

In 2013, the nationwide percentage of people who self-reported a diagnosis of depression by a mental health professional was 7.6%. This number increased in 2019 and 2021, reaching 10.2% and 11.3%, respectively. In 2023, this number reached 12.3% considering the 26 state capitals of Brazil and the country's federal district. The capital with the highest percentage in the last three surveys was Porto Alegre (19.1% in 2019, 17.5% in 2021 and 21.8% in 2023). The prevalence of depression had a percentage change of +10.78% between 2019 and 2021 and +8.85% between 2021 and 2023. The 3 capitals with the highest percentage of depression in 2021 were in ascending order, Florianópolis (SC), Belo Horizonte (MG) and Porto Alegre (RS). In 2023, the ascending order was Rio Branco (AC), Belo Horizonte and Porto Alegre, as shown on figure 1. Rio Branco was the capital with the greatest prevalence variation (+68.31%). Porto Alegre also had a significant positive variation (+24.64%). An overview of the data from 2021 and 2023 shows that 62.96% of the capitals in Brazil had a positive variance in this indicator, which indicates a general growth of depression amongst state capitals and federal district.

Data from Vigitel (2022 and 2023) and PNS indicate an increase in the prevalence of depression nationwide over the years. However, the data collected refers only to those who actually sought help. Thus, it is possible that the number of people with depressive disorders is underrepresented.

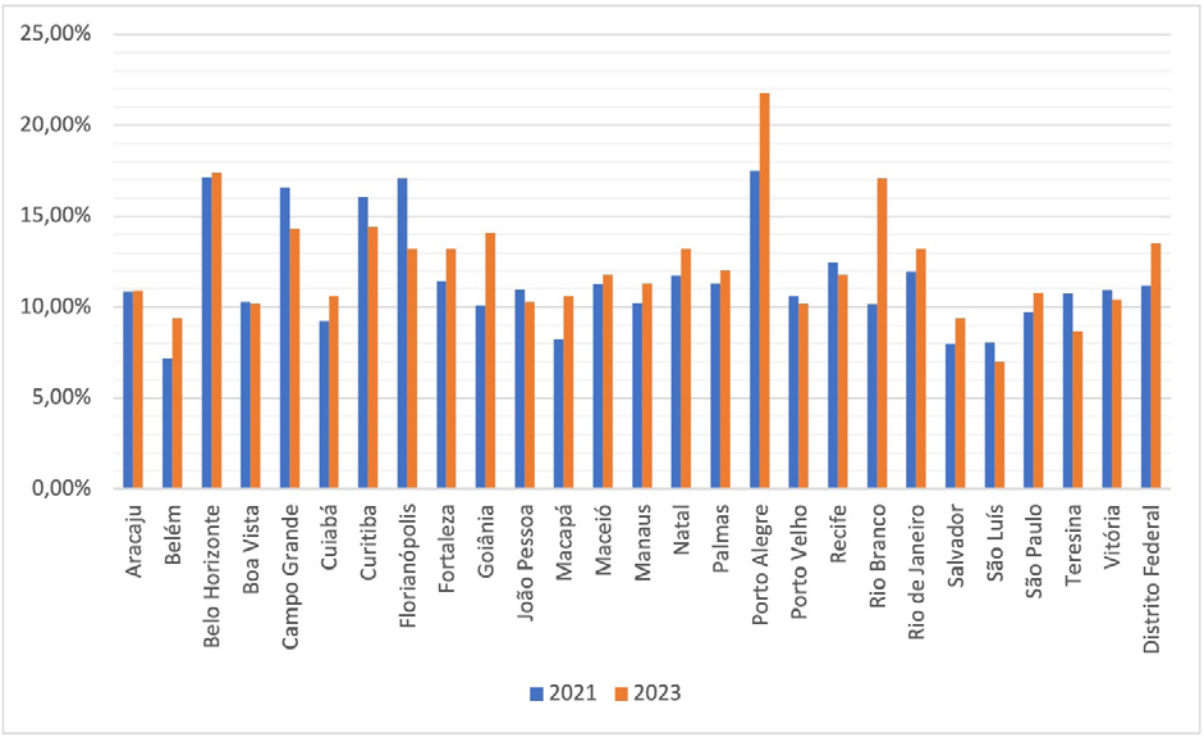

FIGURE 1 – Percentage of adults (≥ 18 years old) who reported a medical diagnosis of depression, according to the capitals of the Brazilian states and the Federal District, in 2021 and 2023.

Prepared by the author. Based on: Vigitel (2022) and Vigitel (2023).

In 2021, antidepressant sales stood out in the public health scenario. The Federal Council of Pharmacy (CFF) pointed to a 13% increase in the sales of antidepressants and mood stabilizers in the period from January to May in comparison to the previous year (Conselho Federal de Farmácia (CFF), 2021). This indicates that the impact from the COVID-19 pandemic, which began in 2020, continues to affect society.

In addition, there was a 55.6% increase in the sales of generic antidepressants during the pandemic (2020 - 2021), according to a survey carried out by the Brazilian Association of Generic and Biosimilar Drug Industries (PróGenéricos) (Fontes, 2022). The best-selling drugs in units were the following: sertraline, fluoxetine, escitalopram, venlafaxine, and amitriptyline (Fontes, 2022).

Data showed an increase in the number of cases of depression in the country, and a growth in sales of antidepressants. This indicates that the mental health of the Brazilian population may have worsened over the years. The higher sales of antidepressants cannot be directly related to the increase in depressive disorder prevalence since antidepressants are used in different psychiatric disorders. But the data indicates that the mental health of the population demands attention from a public health point of view. Pharmacogenomics could potentially be helpful in this scenario, collaborating to find the most adequate drug depending on the individual's characteristics.

The field of pharmacogenomics has made important advances in recent years. The data obtained in several studies and guides were gathered in the Pharmacogenomics

Knowledge Base (PharmGKB, 2023). Moreover, FDA created a Table of Pharmacogenomics Association, where gene-drug interactions are distributed in 3 different categories according to scientific evidence (FDA, 2022).

The main gene-drug interactions mapped in these data repositories are related to pharmacokinetics. There is little evidence on gene-drug interactions in the pharmacodynamics framework (Pirmohamed, 2023). The primary focus of pharmacogenomic testing in psychiatry is on the genes encoding the enzymes CYP2C19 and CYP2D6. From the metabolizing phenotype it is possible to identify the best dosage of a certain drug (Murphy *et al.,* 2021). The choice of drug and dosage is limited to already published guidelines.

It is interesting to compare the gene-drug pair guidelines with a high level of evidence in PharmGKB with the best-selling drugs in Brazil, according to the 2022 news. A summary of the comparison is shown in Table I. PharmGKB gathers clinical annotations from drug dosage pharmacogenomics guidelines, such as Clinical Pharmacogenetics Implementation Consortium (CPIC) and Royal Dutch Association for the Advancement of Pharmacy - Pharmacogenetics Working Group (DPWG).

Guidelines for amitriptyline were heterogeneous in the case of PM and UM. However, for the IM phenotype, there was a consensus for the amitriptyline-CYP2D6 pair. In both the CPIC and DPWG, it is recommended that intermediate metabolizers initiate drug treatment at a dose 25% lower than the reference dose. This pair is also listed in the FDA's Table of Pharmacogenomic Associations and falls into category 3 - Associations in which the evidence indicates only a possible impact on the pharmacokinetics of the drug.

In the case of escitalopram, there is a consensus between CPIC and DPWG that individuals with an UM phenotype for the CYP2C19 enzyme should avoid this drug, (Murphy *et al.,* 2021), since UM would have a lower plasma concentration of escitalopram, which would be insufficient for therapeutic effect. However, in 2023 an update to some CPIC antidepressant guidelines was published. The CPIC recommends that ultra-rapid CYP2C19 metabolizers avoid the use of escitalopram, but if the use of this drug is justified, it may be necessary to increase the dose of the antidepressant (Bousman *et al.,* 2023). In addition, in 2023, the recommendation for PM not to use escitalopram was changed from "moderate" to "strong" (Murphy *et al.,* 2021; Bousman *et al.,* 2023). The escitalopram-CYP2C19 pair falls under category 3 of the FDA's Table of Pharmacogenomic Associations.

Venlafaxine was the only SSRI drug cataloged in these databases (Murphy *et al.,* 2021). The poor metabolizer venalafaxine-CYP2D6 pair falls into the category 1 (gene-drug therapeutic recommendations supported by scientific evidence) of the FDA Table. The FDA recommends that individuals who fall into this category consider decreasing the dose administered. However, the CPIC does not have any treatment guidelines and the DPWG reports that there is little data on this pair (Murphy *et al.,* 2021). There is only an optional recommendation by CPIC that poor metabolizers of CYP2D6 replace venlafaxine for another antidepressant. Although there isn't much data on this, some indicate that there may be an association between this profile and adverse effects (Bousman *et al.,* 2023).

In the case of sertraline, there are no recommendations for variations in the activity of the CYP2D6 enzyme, only CYP2C19. The CPIC and DPWG do not make any specific recommendations for ultra-rapid, normal, and intermediate metabolizers. However, both repositories have a discrete recommendation in the case of PM. The CPIC suggests that sertraline should not be used in these cases or that a 50% lower dose should be administered and the DPWG suggests that the daily dose should not exceed 75mg (Murphy *et al.,* 2021). This recommendation is now considered "moderate", which means it gained more relevance (Bousman *et al.,* 2023). In the FDA table, there is no mention of sertraline. In addition, the FDA does not have any guidelines for fluoxetine. This drug is also not mentioned in the CPIC and DPWG guidelines.

TABLE I – Comparison of guidelines for the best-selling antidepressants in Brazil in 2022

Drug-gene pair	CPIC	DPWG	Classification - FDA
amitriptyline-CYP2D6	IM: dose 25% lower than reference dose		Category 3
escitalopram-CYP2C19	UM: Avoid the drug CPIC: if warranted, increase the dose		Category 3
	PM: substitute the drug or reduce the dose by 50%	PM: reduce the dose by 50%	
venalafaxine-CYP2D6	NA		Category 1
sertraline-CYP2C19	PM: Do not use the drug or get a 50% lower dose	PM: Daily dose should not exceed 75mg	NA

CPIC - Pharmacogenetics Implementation Consortium; DPWG - Royal Dutch Association for the Advancement of Pharmacy - Pharmacogenetics Working Group; Classification FDA – based on Table of Pharmacogenomics Associations; PM – poor metabolizers; IM – intermediate metabolizers; UM – ultra-rapid metabolizers.

Prepared by the author based on Murphy *et al.*, (2021) and Bousman *et al.*, (2023).

There has been a few meta-analyses reported that analyzed the impact of pharmacogenomics (PGx) testing on depression symptoms remission (Bousman *et al.,* 2019) (Brown *et al.,* 2022) (Rosenblat, Lee, McIntyre, 2018). In all of them, it was concluded that treatment guided by PGx testing improved patient's remission rates when compared to usual treatment. In 2018, it was reported that patients receiving PGx-guided treatment were 71% more likely to achieve depression remission (Rosenblat, Lee, McIntyre, 2018). In 2019 the results indicated a 74% higher chance of remission (Bousman *et al.,* 2019) and in 2022 it was reported that patients had a 41% greater probability of achieving remission (Brown *et al.,* 2022). PGx testing may be a particularly helpful tool for individuals who have already received several types of antidepressant medications and individuals with moderate to severe depression (Brown *et al.,* 2022).

Although the remission rate was different in the studies, it is important to note that in all of them, PGx tests were shown to be indeed beneficial for patients. Thus, it can be expected that more studies should be conducted to evaluate the benefit of the tests in different populations. Moreover, in many commercially available tests, pharmacodynamics related genes are also tested, even though there is little evidence that they interfere with the antidepressant effect (Brown *et al.,* 2022). In addition, the results seem promising for patients who have already undergone successive pharmacological treatments without obtaining the desired therapeutic effect.

In many of the studies conducted on PGx testing, there is little diversity among patients. The vast majority come from European origin (Brown *et al.,* 2022), which does not reflect the global population. The Brazilian population has a great genetic diversity, which would be beneficial for studies of the efficacy of PGx tests. This diversity occurs because the Brazilian population is descendant from European, African, and indigenous people. In addition, the Brazilian Institute of Geography and Statistics (IBGE) also considers the category of Asian descendants when classifying Brazilian population according to their ancestry. This diversity contributes to a variety of response profile to a certain drug, due to

differences in the activity of enzymes responsible for metabolizing drugs (Kim *et al.,* 2020).

Another point of concern is that most pharmacogenomic studies in Brazil are conducted in the Southeast, where most of the population is mainly of European ancestry. However, in Brazil, there was an uneven process of admixture among the country which led to a diverse population from different ethnic backgrounds (Torres-Loureiro *et al.,* 2022). Thus, not only is there an underrepresentation of Latinos in pharmacogenomic studies, but within Brazil there is also a certain lack of diversity in research.

The estimates of Brazilians who are not normal metabolizers of CYP2D6 and CYP2C19 enzymes were, respectively, 32.46% and 49.49%. The estimated frequency of UM for CYP2C19 in Brazil was 27%, and intermediate metabolizers (IM) corresponded to 23% (Koopmans *et al.,* 2021).

This data is important because it shows that there is a relevant portion of Brazilian population that could benefit from antidepressant treatment guided by pharmacogenomic tests. Ultra-rapid and poor metabolizers need dose adjustment in several cases. In addition, the studies themselves would be favored by incorporating a more diverse population, since it would be possible to observe a wide range of responses and different gene-drug relationships according to the genetic variations between individuals.

The potential of pharmacogenomic testing in the clinic has been reinforced by the study PREPARE, since it was demonstrated that through these tests, there was a decrease in adverse reactions to different medications, including antidepressants (Swen *et al.,* 2023). The study was conducted to analyze pre-emptive pharmacogenetic testing and while a group of patients received standard treatment, the other group received PGx-guided treatment according to DPWG guidelines. Among the genes evaluated in the panel, were the *CYP2D6* and *CYPD19* (Swen *et al.,* 2023), and the gene-drug interactions from table 1 were analyzed and taken into consideration in the study.

It is important to note that the genes analyzed interfere with the metabolization of several drugs. Once a patient's allelic variations are known, this data can be used for drugs of different classes throughout their lives. Thus, the result of the PGx test can be used for the therapeutic targeting of multiple medications.

There are a few factors that impact the clinical implementation of PGx testing. Commercially available tests have different gene-drug pairs analyzed, including genes that do not have robust scientific evidence regarding the treatment of depression, and one of the main points, the cost-effectiveness of this tool (Murphy *et al.,* 2021). In a survey involving the cost-effectiveness of PGx tests, more than 90% of Brazilian psychiatrists who had their e-mails made available at the Regional Council of Medicine of the State of São Paulo (CREMESP) expressed concern about access to PGx tests, especially because of the country's economic situation. Their concern was essentially about the cost-benefit of the tests. Moreover, most of them supported the idea that it would be important to include pharmacogenetic testing in the list of procedures of the Brazilian National Agency of Supplementary Health (ANS) (Almeida *et al*., 2021).

Studies focused on depression and PGx testing had promising conclusions about PGx guided treatment from an economics perspective. PGx testing has the potential to be economically advantageous, as they reduce several costs associated with the treatment of individuals with depression. Since the use of these tests can lead to an antidepressant prescription that causes fewer adverse events (AEs) on the patient, there would be a lower cost for the health system to take care of these AEs. The decrease in AEs could also increase patients' adherence to antidepressant drug treatment since the individual could feel less discomfort and feel more motivated to follow it. This could lead to faster remission and fewer hospitalizations in cases of severe depression (Karamperis *et al.,* 2021). Although there are some studies that point to the cost-effectiveness of PGx tests with a focus on psychiatry, more research is still needed on this topic with more standardized forms of economic evaluations

(Karamperis *et al.,* 2021). In fact, most of them are conducted in European or North American countries. There is a lack of studies on this in Latino populations.

Access to PGx testing in Brazil is not widely disseminated. In the country, ANS defines which procedures should be covered by private health insurance through the List of Health Procedures and Events. This document determines the mandatory health care coverage (Agência Nacional De Saúde Suplementar (ANS), 2023). Pharmacogenetic tests are not part of this list (ANS, 2023). Thus, individuals who wish to undergo this type of examination must bear their own costs.

In addition, there is a law that defines the criteria for procedures not included in the List of Health Procedures and Events to be covered by health insurance. Law 14454/2022 (Brasil, 2022) imposes that if a procedure is prescribed by a doctor or dentist, the private health insurance must cover the costs of the procedure, in this case the PGx test, provided that such procedure meets at least one of the following requirements: (i) efficacy scientifically proven, (ii) is recommended by an international health technology assessment body or by the National Committee for Health Technology Incorporation (Conitec). This law allows citizens to contact their health insurance in case their physician concern PGx testing as necessary, as long as the tests fulfill one of the requirements. It is up to them to gather all the information needed before resorting to the health insurance company.

In addition, in Brazil, PGx tests are offered to the public and professionals by clinical laboratories, and laboratories specialized in genetics. The gene panels analyzed are different depending on the laboratory, there is no standardization. Moreover, information displayed, and purchase availability also differ among the laboratories.

CONCLUSION

The analysis of the Brazilian scenario indicates that there was a significant increase in the number of people diagnosed with mental health disorders, especially during and after the COVID-19 pandemic. The increase in the sale of antidepressants in pharmacies corroborates this conclusion. In addition, it is possible to assume that the number of people with depression is even higher than the data collected by the Government, since in the surveys only those who claimed to have received a diagnosis were counted, that is, only those who sought help regarding their mental health. In this sense, it is important to carry out awareness campaigns about mental health and how to seek help throughout the Brazilian territory. The use of PGx as an auxiliary tool for drug treatment contributes to a minimum 40% improvement in the remission of depression symptoms. Individuals who have already undergone several therapeutic approaches would benefit the most from these tests.

In addition, research indicates that PGx tests would be economically beneficial, which justifies its implementation. However, more specific studies in Brazil and Latin America still need to be conducted, since most of them are done in Europe and North America, where the socioeconomic scenario and ethnic backgrounds are different from Latin countries.

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