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Análise farmacogenética das variantes do gene *CYP2C19* no tratamento antidepressivo de pacientes com Transtorno Depressivo Maior

Porto Alegre
2023

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Trabalho de Conclusão de Curso apresentado como requisito parcial para obtenção do título de Bacharel em Biotecnologia com ênfase em Biotecnologia Molecular na Universidade Federal do Rio Grande do Sul.

Orientadora: Prof. Dra. Ursula da Silveira Matte
Coorientadora: Dra. Mariana Rodrigues Botton

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"*Give your dreams all you've got, and you'll be amazed at the energy that comes out of you.*"

- William James

RESUMO

O Transtorno Depressivo Maior (TDM) é uma condição psiquiátrica que afeta profundamente o indivíduo de forma clínica, funcional e social, com significativa prevalência na população mundial. O tratamento eficaz do TDM é complexo, devido à natureza multifatorial da resposta a antidepressivos. A influência genética é um dos principais componentes nesse cenário. Dessa forma, a farmacogenética surge com o objetivo de otimizar a terapia medicamentosa, personalizando-a conforme o perfil genético do paciente. Este estudo investiga o impacto das variantes do gene *CYP2C19* nos antidepressivos da classe dos Inibidores Seletivos de Recaptação de Serotonina e Antidepressivos Tricíclicos. Uma análise retrospectiva foi conduzida com 163 pacientes do ambulatório PROTHUM no Hospital de Clínicas de Porto Alegre. Os grupos de genótipos/fenótipos dos pacientes foram analisados quanto aos escores da escala de avaliação de depressão de Hamilton (HAM-D), visando avaliar a resposta clínica. Os resultados evidenciaram uma prevalência significativa de metabolizadores não-normais, bem como uma associação entre escores da HAM-D e o fenótipo predito do gene *CYP2C19*. Assim, foi identificado em nossa amostra que pacientes metabolizadores rápidos e ultrarrápidos apresentam maiores escores na escala de HAM-D. Além disso, observou-se associação entre os escores da HAM-D e a severidade e cronicidade do TDM. Esses achados destacam a importância da abordagem farmacogenética devido à diversidade de fenótipos e à interferência da genética na resposta medicamentosa. Contudo, futuras pesquisas são necessárias. Aumentar a amostra e considerar a fenoconversão através de medicações concomitantes levará a resultados mais abrangentes. Assim, é fortalecido o papel genético na resposta aos antidepressivos, particularmente em relação ao gene *CYP2C19* na nossa população.

Palavras-chave: Farmacogenética, gene *CYP2C19*; Tratamento Antidepressivo; Transtorno Depressivo Maior; Medicina Personalizada; Resposta a tratamento; Correlação Genótipo-Fenótipo.

ABSTRACT

Major Depressive Disorder (MDD) is a psychiatric condition that profoundly affects the individual clinically, functionally and socially, with a significant prevalence in the world population. Effective treatment of MDD is complex, due to the multifactorial nature of the response to antidepressants. Genetic influence is one of the main components in this scenario. Thus, pharmacogenetics has emerged with the aim of optimizing drug therapy, personalizing it according to the patient's genetic profile. This study investigates the impact of *CYP2C19* gene variants on antidepressants in the class of Selective Serotonin Reuptake Inhibitors and Tricyclic Antidepressants. A retrospective analysis was conducted with 163 patients from the PROTHUM outpatient clinic at the Hospital de Clínicas in Porto Alegre. The patients' genotype/phenotype groups were analyzed in order to assess the clinical response to the Hamilton Depression Rating Scale (HAM-D). The results showed a significant prevalence of non-normal metabolizers, as well as an association between HAM-D scores and the predicted phenotype of the *CYP2C19* gene. Our sample showed that rapid and ultra-rapid metabolizers had higher scores on the HAM-D scale. In addition, there was an association between HAM-D scores and the severity and chronicity of MDD. These findings highlight the importance of the pharmacogenetic approach due to the diversity of phenotypes and the interference of genetics in drug response. However, future research is needed. Expanding the sample and considering phenoconversion due to concomitant medications will lead to more comprehensive results. This confirms the genetic role in the response to antidepressants, particularly in relation to the *CYP2C19* gene in our population.

Keywords: Pharmacogenetics; *CYP2C19* gene; Antidepressant treatment; Major Depressive Disorder; Personalized medicine; Treatment response; Genotype-phenotype correlation.

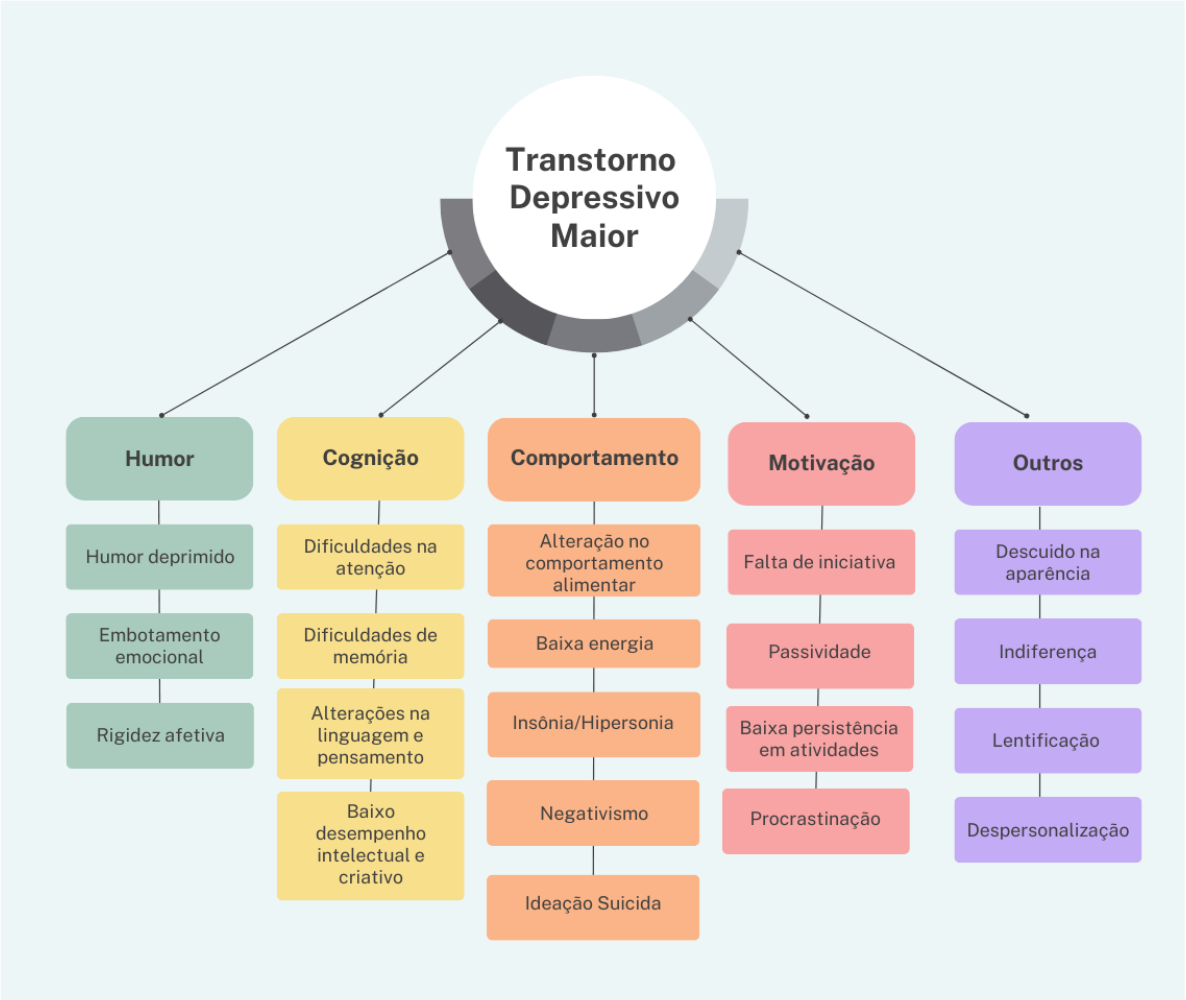
SUMÁRIO

INTRODUÇÃO GERAL

O Transtorno Depressivo Maior (TDM) é uma patologia psiquiátrica de extrema relevância, com características neurobiológicas complexas e heterogêneas, provocando profundo impacto na saúde mental e qualidade de vida dos indivíduos (KAPCZINSKI *et al*., 2011; PITSILLOU *et al.*, 2020). Reconhecido como um distúrbio grave e incapacitante, o TDM manifesta-se em uma variedade de sintomas, sendo os mais proeminentes o humor deprimido e a anedonia, mas também inclui sintomas adicionais, como mudanças na cognição e em funções neurovegetativas, que contribuem para sua complexidade clínica (QUEVEDO *et al.*, 2019; DSM-V, 2014) (A heterogeneidade de sintomas podem ser observados a partir da Figura 1).

Sua etiologia é multifatorial, envolvendo fatores genéticos, biológicos, ambientais e também psicossociais (LI *et al*., 2021; UHER; ZWICKER, 2017). A identificação criteriosa e o diagnóstico do TDM demanda que os sintomas estejam presentes de maneira intensa e frequente por no mínimo duas semanas, com pelo menos cinco dos sintomas mais representativos, sendo o humor deprimido e/ou falta de motivação necessariamente inclusos (DSM-V, 2014). Há um significativo risco de recorrência após o primeiro episódio do TDM, alcançando 60% ao longo da vida, especialmente dentro de um ano após a interrupção do tratamento, e pode evoluir para um curso crônico (LYE *et al*., 2020). Vale ressaltar que o diagnóstico do TDM baseia-se principalmente em critérios clínicos, uma vez que ainda não há biomarcadores específicos ou exames laboratoriais para sua confirmação (SADOCK *et al*., 2017).

Figura 1. Heterogeneidade de sintomas apresentados no Transtorno Depressivo Maior.



Fonte: Elaborado pela autora (2023).

O impacto social e econômico do TDM não pode ser subestimado, visto que é considerado um dos principais fatores de incapacidade no mundo, afetando aspectos cruciais da vida das pessoas, como educação, emprego e sucesso financeiro (QUEVEDO *et al*., 2019). Além disso, estudos epidemiológicos revelam sua alta prevalência global, afetando aproximadamente 350 milhões de indivíduos (LIU *et al*., 2017). No Brasil, estima-se que cerca de 15,5% da população enfrentará o TDM ao longo da vida, tornando-o uma questão de saúde pública significativa (MINISTÉRIO DA SAÚDE, 2020).

A gravidade do TDM também se reflete em sua associação com o risco de suicídio, o que o coloca em uma posição de destaque entre os transtornos psiquiátricos. Aproximadamente 1 milhão de pessoas no mundo tiram suas próprias

vidas anualmente, e estudos indicam que quase 90% desses indivíduos apresentavam algum transtorno psiquiátrico, sendo o TDM um dos principais contribuintes (ISOMETSA, 2014). Além disso, o TDM está relacionado a outras formas de mortalidade, como homicídios e mortes acidentais (PIATO, 2021), tornando-se uma preocupação crescente de saúde pública.

O tratamento para o TDM é atualmente baseado na hipótese monoaminérgica, que envolve a disfunção nos neurotransmissores serotonina, dopamina e noradrenalina (PIATO, 2021). Assim, os medicamentos mais utilizados têm o propósito de aumentar a disponibilidade desses neurotransmissores no Sistema Nervoso Central (SNC) e pertencem a classes como Antidepressivos Tricíclicos, Inibidores Seletivos de Recaptação de Serotonina e Inibidores de Monoamina Oxidase, sendo os dois primeiros os mais amplamente utilizados (ROSENBLAT; MCINTYRE, 2020).

No entanto, a adesão ao tratamento ainda é um desafio. Sabe-se que apenas metade dos pacientes respondem bem ao tratamento, ao mesmo tempo que apenas 30% conseguem experienciar a remissão dos sintomas (RADOSAVLJEVIC *et al*., 2023). Ainda, dados mostram que quase 50% dos pacientes apresentam reações adversas ao longo do tratamento (KEE *et al*., 2023). Informações como essas elucidam um cenário de má adesão ao tratamento atual, implicando em dificuldades na terapêutica do TDM.

A resposta a medicamentos e a remissão do quadro, por ter caráter multifatorial, está associada a uma ampla gama de fatores. Esses fatores incluem condição socioeconômica, genética, interações medicamentosas, comorbidades, processos fenoconversivos, idade, sexo, funcionamento renal e hepático, estado nutricional, uso de outras substâncias, entre outros (BOUSMAN *et al*., 2019). Aqui, nota-se que a variabilidade genética tem uma contribuição importante, atingindo taxas de 42 a 50% no cenário (BOUSMAN *et al*., 2019). Assim, uma das maneiras de contornar o cenário abordado é investindo em abordagens que destacam a genética como guia para prescrição e dosagem de medicamentos, como é o caso da Farmacogenética.

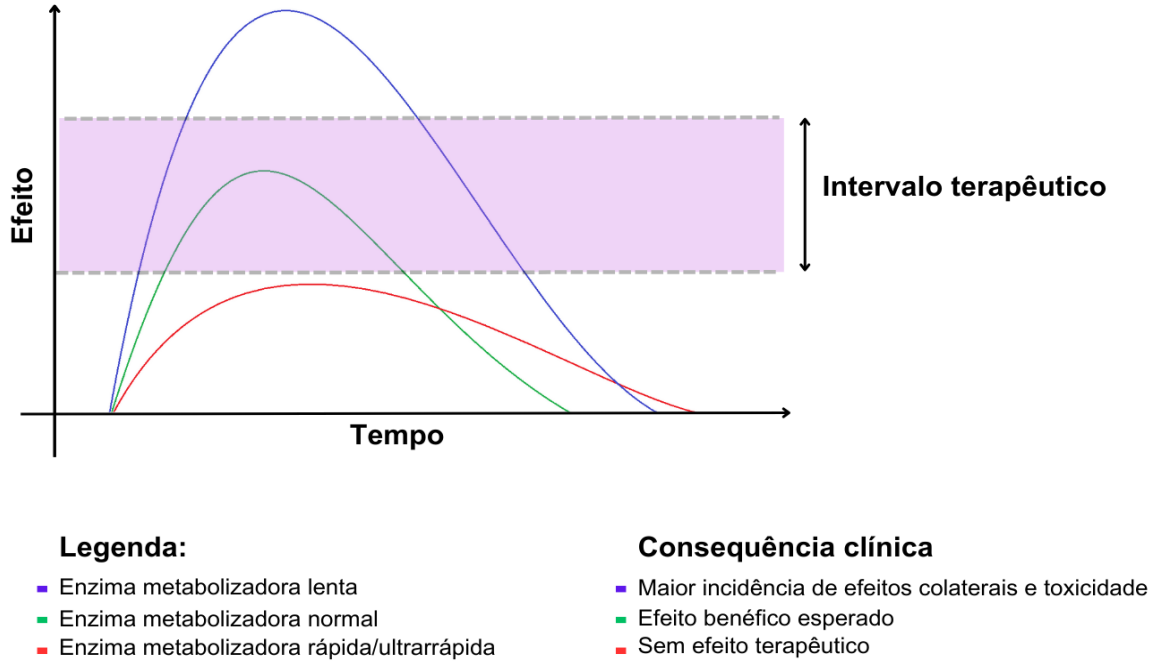
A Farmacogenética é uma ciência que estuda o papel da genética no fenótipo de resposta medicamentosa (BORCZYK *et al*., 2022). Por meio da perspectiva da farmacocinética e farmacodinâmica, ela é capaz de avaliar a influência da

variabilidade genética no metabolismo e nos efeitos de fármacos diversos, o que inclui os antidepressivos (BORCZYK *et al*., 2022).

Um exemplo relevante é o Citocromo P450 2C19 (CYP2C19), uma enzima que atua na farmacocinética de diferentes fármacos, cuja atividade desempenha papel fundamental no metabolismo de medicamentos em geral no organismo (VAN WESTRHENEN *et al*., 2020; BORCZYK *et al*., 2022). Aqui, destacam-se alguns antidepressivos, como é o caso do citalopram, o escitalopram, a sertralina, a amitriptilina, a clomipramina, a imipramina, entre outros (BOUSMAN *et al*., 2023; HICKS *et al*., 2017).

O gene responsável por sua codificação apresenta uma diversidade de variantes. De acordo com o PharmVar (2021), existem 35 alelos estrelas conhecidos para o gene *CYP2C19*. Considerando a população brasileira, é possível identificar a prevalência de algumas variantes, como, por exemplo, os alelos variantes *17, *2 e *3 (SUAREZ-KURTZ, 2010), que alteram significativamente a função da enzima, provocando influência no fenótipo predito. Assim, considerando as diferentes possibilidades de genótipos do gene *CYP2C19*, verifica-se uma alta diversidade de fenótipos para a enzima. Esta pode se apresentar através de diferentes padrões de metabolização, como o lento, intermediário, normal, rápido e ultrarrápido (THIELE et al., 2022). Cada um deles proporciona um grau de metabolização do medicamento, o que por sua vez está inversamente associado à efetividade, adesão ao tratamento e à ocorrência de efeitos adversos (como demonstrado na Figura 2) (CARTA *et al*., 2022). Alterações envolvendo o fenótipo predito podem acontecer diante a processos fenoconversivos. Este é um fator decorrente de interações medicamentosas e/ou comorbidades associadas, em que determinado padrão de metabolismo sofre alteração, podendo ser inibido ou induzido (HAHN; ROLL, 2021). No entanto, esse é um cenário que requer uma investigação mais detalhada, abrangendo ambos os fatores mencionados (DE JONG *et al*., 2023).

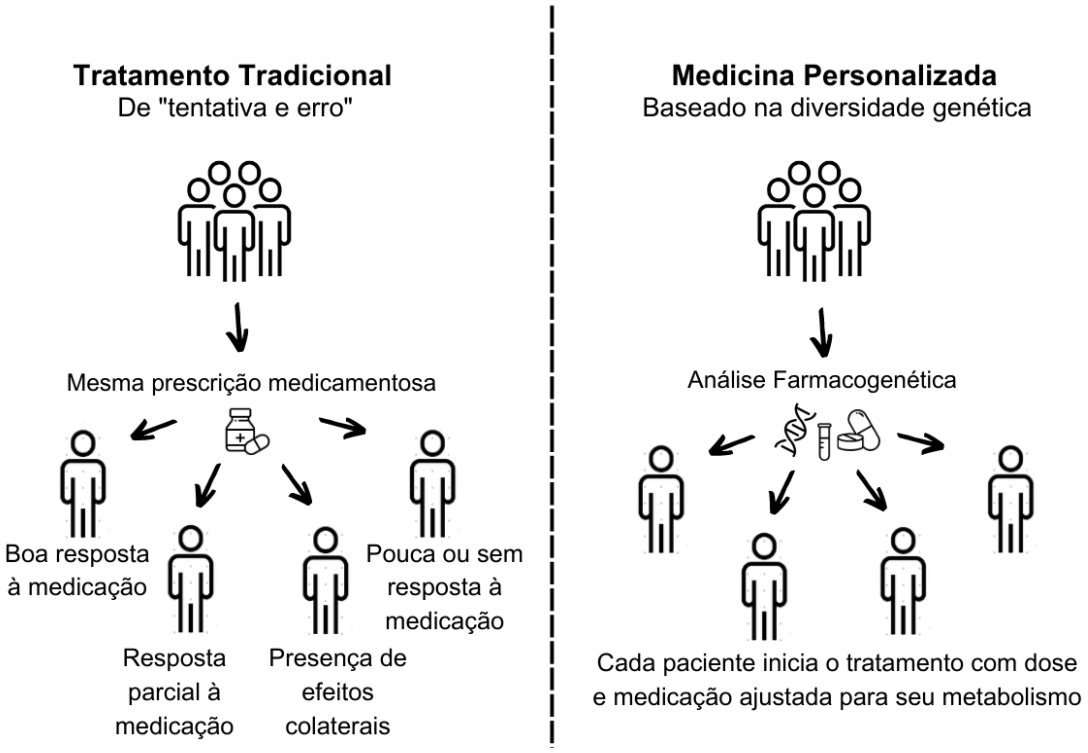
Figura 2. Comparação dos diferentes padrões de metabolização e suas consequências clínicas.



Fonte: Elaborado pela autora (2023).

Dessa forma, a alta frequência do TDM, o alto risco de recorrência e cronicidade, a redução na qualidade de vida e a contribuição para mortes prematuras, quando relacionadas a uma resposta não satisfatória ao tratamento, nos leva a uma situação de urgente resolução (ARNONE *et al*., 2023). Assim, a Farmacogenética emerge como uma aliada na melhoria do tratamento antidepressivo de pacientes com TDM, proporcionando uma abordagem mais precisa e efetiva para essa complexa condição de saúde mental. Diferentemente da abordagem clínica tradicional de "tentativa e erro", a Farmacogenética oferece a perspectiva de uma terapia personalizada e direcionada, potencialmente aumentando a eficácia do tratamento e melhorando a qualidade de vida dos pacientes (como é possível entender a partir da Figura 3) (BORCZYK *et al*, 2022).

Figura 3. Diferenças clínicas entre o Tratamento Tradicional com prescrição padronizada de dose e fármaco e a Medicina Personalizada.



Fonte: Modificado de ISLAM; GORBOVSKAYA; MÜLLER (2021, p. 233).

OBJETIVOS

Geral

Verificar a influência de variantes genéticas no gene *CYP2C19* (**2, *3* e **17*) no efeito dos medicamentos Antidepressivos Tricíclicos (TCA) e Inibidores Seletivos da Recaptação da Serotonina (ISRS).

Específicos

1. Através de inferência pelos diplótipos, verificar a frequência de metabolizadores lentos, metabolizadores intermediários, metabolizadores normais, metabolizadores rápidos e metabolizadores ultrarrápidos para a enzima CYP2C19 na população de pacientes com TDM atendidos no ambulatório do Programa de Transtornos de Humor do Hospital de Clínicas de Porto Alegre (PROTHUM-HCPA);
2. Verificar a influência que fatores clínicos e demográficos apresentam no efeito dos medicamentos antidepressivos;
3. Verificar a influência dos diferentes tipos de metabolizadores para a enzima CYP2C19 no efeito dos medicamentos antidepressivos.

Os resultados desse trabalho serão contemplados sob forma de artigo científico a ser submetido para a revista Pharmacogenomics (Fator de Impacto: 2.638).

Pharmacogenetic analysis of *CYP2C19* gene variants in antidepressant treatment of patients with Major Depressive Disorder

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Journal: Pharmacogenomics

ABSTRACT

Background: Major Depressive Disorder (MDD) profoundly impacts lives worldwide, and successful treatment is not always achieved. To improve outcomes, personalized antidepressant selection using genetic-guided pharmacotherapy can be employed. **Methods:** We examined the influence of *CYP2C19* variants on MDD treatment response using phenotype inference in a study involving 163 patients. Treatment efficacy was evaluated using the Hamilton Depressive Rating Scale (HAM-D). **Results:** Our findings displayed 25.2% IM, 30.1% RM/UM, and no PM individuals in total. We found an association between Rapid/Ultrarapid Metabolizers and decreased drug response measured by HAM-D. The HAM-D scores in IM, NM and RM/UM individuals were 15.5, 15.0, and 18.8, respectively. **Conclusion:** Our findings reveal prevalent altered CYP2C19 phenotype metabolism and highlight the severity's impact on treatment efficacy. This research reinforces the genetic impact on drug metabolism, significantly influencing MDD treatment outcomes.

Keywords: Pharmacogenetics; *CYP2C19* gene; Antidepressant treatment; Major Depressive Disorder; Treatment response.

1. INTRODUCTION

Major Depressive Disorder (MDD) is a complex psychiatric condition that significantly impacts individuals' lives [13,17]. With approximately 350 million people affected worldwide, MDD is recognized as a major global health problem [11]. The primary symptoms of MDD include persistent sadness, lack of motivation, and impairments in behavior, cognition, and neurovegetative functions [12,20]. Additionally, MDD is associated with various physical consequences such as Diabetes mellitus, cardiovascular illness, obesity, Alzheimer's disease, and premature death through suicide, homicide, or accidents [1,20,27,30]. Due to these detrimental health effects, MDD is a serious public health problem that requires effective treatment.

Pharmacological treatment, often combined with psychotherapy and, in some cases, neurostimulation, is the primary approach to alleviate depression symptoms [29]. Supported by strong evidence, antidepressants are effective in reducing major depressive episodes [25]. However, the response rate of these medications is around 60%, resulting in a population of patients resistant to treatment [2]. Furthermore, antidepressants can cause various side effects that impact the prognosis of MDD and contribute to treatment non-adherence [18]. Clinical experience alone may not be sufficient to determine the most suitable medication for an individual, leading to a high prevalence of reduced adherence [22]. Thus, there is a critical need to improve treatment strategies to target resistant patients and minimize the occurrence and severity of side effects.

Pharmacogenetics, a genetic approach to understanding drug response variability, is a key component of personalized medicine, aiming to benefit both patients and the economy [2,32]. By utilizing genotyping tests, pharmacogenetics enables the assessment of an individual's metabolizing profile, facilitating the selection of the most appropriate antidepressant for personalized treatment [4]. Pharmacogenetics holds the potential to improve treatment outcomes, minimize side effects, and expedite the identification of optimal drugs, thereby enhancing the prognosis for individuals with MDD [22].

Significantly, the effectiveness of antidepressant medications is closely intertwined with the metabolism of some genes, such as *CYP2C19*, which play a vital role in catalyzing the oxidative reactions of substances [14]. The Clinical

Pharmacogenetics Implementation Consortium (CPIC) provides valuable guidelines for genotyping this gene, leading to a better understanding of how certain antidepressants, such as Selective Serotonin Reuptake Inhibitor Antidepressants (SSRIs) and Tricyclic Antidepressants (TCAs), elicit internal reactions [3].

The objectives of this study are to investigate the genetic influence of *CYP2C19* on the antidepressant effects of SSRIs and TCAs. Additionally, we aim to determine the frequency of predicted metabolism phenotypes in a population with Major Depressive Disorder attending a Mood Disorders Program at the Hospital de Clínicas de Porto Alegre (PROTHUM-HCPA). Furthermore, we intend to examine the impact of clinical and demographic factors on the effects of antidepressant drugs and investigate the influence of different types of metabolizers of the CYP2C19 enzyme on the effectiveness of antidepressant drugs.

2. METHODS

2.1. Study Design

This investigation employed a cross-sectional and retrospective design to comprehensively explore the relationship between the phenotype profile across diplotypes inferences and the efficacy of two categories of antidepressants: Selective Serotonin Reuptake Inhibitors (SSRIs) and Tricyclic Antidepressants (TCAs). These associations were evaluated using Hamilton Depression Rating Scale (HAM-D). (The timeline is outlined in Fig. 1).

2.2. Study Participants

For this study, a total of 200 patients were recruited from the Mood Disorders Program at Hospital de Clínicas de Porto Alegre (PROTHUM-HCPA), a university hospital outpatient clinic; however, 163 were included in the analyses. This program focuses on treating individuals who had previously started pharmacological treatment, but without achieving therapeutic success [34]. Recruitment was facilitated through clinical specialists, and the inclusion criteria comprised a confirmed diagnosis of Major Depressive Disorder, use of SSRIs and TCAs as antidepressant treatment, and age over 18 years. On the other hand, individuals diagnosed with Bipolar Disorder, those with unavailable medical records, individuals without data

from psychometric scales, and those for whom DNA samples were not accessible were excluded from the study. The recruitment phase spanned from July 2009 to November 2013 (Fig. 1).

2.3. Ethical Considerations

The study obtained approval from the Research Ethics Committee of Hospital de Clínicas de Porto Alegre (CAAE: 25719119400005327). Participants received comprehensive information regarding the study's objectives, procedures, risks, and benefits before their inclusion. All participants signed the Informed Consent Form. To protect privacy, all data were anonymized using unique codes, and personal identifiers were removed. Participation in the study was completely voluntary.

2.4. Clinical Assessment

Baseline information, including age, gender, and pertinent medical history, was gathered through clinical interviews and a review of medical records. However, ethnicity of individuals was not collected. The diagnosis of Major Depressive Disorder (MDD) was ascertained using the Mini-International Neuropsychiatric Interview (MINI) conducted by psychiatric professionals. Furthermore, the severity of depressive symptoms and their improvement over a 6-month period was evaluated using the 17-item Hamilton Rating Scale for Depression (HAM-D). Assessments conducted at baseline and after 6 months of treatment were compared for outcome measurement.

2.5. Antidepressant Treatment and Clinical Response

Participants in the study were prescribed antidepressant medication(s) following clinical judgment and treatment guidelines. The treating psychiatrists determined the choice of medication(s), dosage, and treatment duration. Although all prescribed drugs were recorded, our analysis focused on Selective Serotonin Reuptake Inhibitors (SSRIs) and Tricyclic Antidepressants (TCAs). Treatment response was assessed using the HAM-D scale at baseline and after 6 months during the treatment period. The final HAM-D score was chosen as the measure of response because the studied population had already initiated treatment before being admitted to the outpatient clinic.

The condition's severity was evaluated using the HAM-D scale, where scores from 1 to 7 were considered normal, 8 to 16 indicated mild symptoms, 17 to 23

represented moderate symptoms, and scores above 24 signified severe symptoms [36]. Treatment response and remission were defined according to Lin and Lin [15]. The former was considered as higher than or equal to a 50% reduction on the HAM-D scale, and the latter was assumed as a HAM-D score lower than or equal to 7 at 6 months of treatment. Moreover, individuals without treatment benefit were defined in case where the initial and final HAM-D scores were equal or when there was an aggravation of the condition (final HAM-D score higher than initial HAM-D score). The analyzed outcomes comprised symptom improvement (differences on initial and final HAM-D scores), medication adjustments, and remission rates. Data for these measures were extracted from the PROTHUM database between March 2023 and August 2023 (Fig. 1).

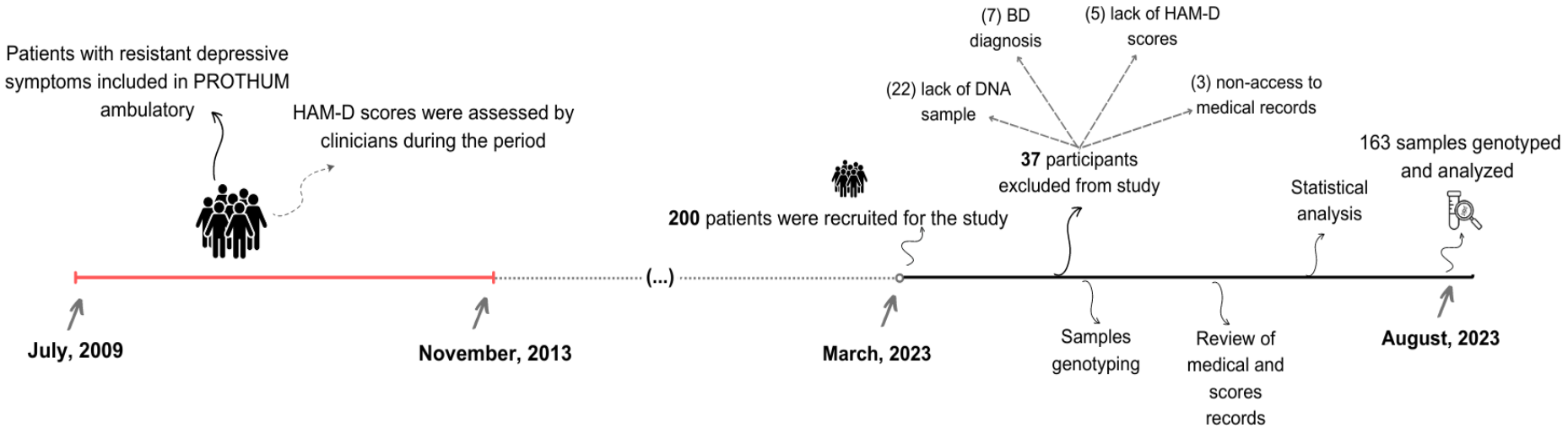
Patients with resistant depressive symptoms included in PROTHUM ambulatory
HAM-D scores were assessed by clinicians during the period
July, 2009
November, 2013
(...)
200 patients were recruited for the study
March, 2023
(7) BD diagnosis
(5) lack of HAM-D scores
(22) lack of DNA sample
(3) non-access to medical records
37 participants excluded from study
Samples genotyping
Review of medical and scores records
Statistical analysis
163 samples genotyped and analyzed
August, 2023

Figure 1. Chronological representation in timeline of the methodology. Its presents the key phases in the study: Recruitment (July 2009 to November 2013) - Participants were enrolled from PROTHUM-HCPA with MDD resistant symptoms. The clinical assessments were made in this period in baseline and after 6 months; Genotyping, Review of Medical Records and Statistical Analysis (March 2023 to August 2023) - Participants' *CYP2C19* Genotype were established from DNA samples and the Medical Records were review from PROTHUM database. Following genotyping and medical records, Statistical Analyses were made. PROTHUM: Mood Disorders Program. HAM-D: Hamilton Depressive Rating Scale. BD: Bipolar Disorder. MDD: Major Depressive Disorder.

2.6. Pharmacogenetics Analysis

The pharmacogenetic analysis focused on identifying genetic variants within the *CYP2C19* gene that are relevant to antidepressant drugs. The selection of these genetic variants was based on their population frequency, being present in over 1% of Euro or Afro-descendants population, and their known enzyme activity impact. Thus, three specific alleles, *2, *3, and *17, were chosen for inclusion in the study. It's noteworthy to mention that the *CYP2C19* wild-type allele was designated as *1.

Genomic DNA was extracted from peripheral blood samples collected from study participants using the "salting out" procedure [37]. The concentration and quality of the extracted DNA were assessed using spectrophotometry equipment (NanoDrop® 2000). Subsequently, the DNA was appropriately diluted to a concentration of 10 ng/μL for downstream analysis.

To determine the genotypes of the target genetic variants within the *CYP2C19* gene we employed a Real-Time Polymerase Chain Reaction (Real-Time PCR) using TaqMan SNP Genotyping Assays (Applied Biosystems, EUA). The reactions were performed in a Real-Time PCR instrument (QuantStudio3™ Real-Time PCR).

The genotypes of the samples were determined by analyzing the fluorescence signals, following the information provided by the manufacturer. Alleles, on the other hand, were deduced from variant alleles identified in the literature, such as those available on the Pharmacogene Variation Consortium platform (PharmVar) [26,31]. The genotype was determined by considering a combination of *CYP2C19* allele variants. Subsequently, the CYP2C19 phenotype was inferred based on the individual's genotype and categorized into five distinct categories: Poor Metabolizers (PM), Intermediate Metabolizers (IM), Normal Metabolizers (NM), Rapid Metabolizers

(RM), and Ultrarapid Metabolizers (UM), following the guidelines set by CPIC (Clinical Pharmacogenetics Implementation Consortium). Descriptions of each phenotypic category are given in Table 1 [10]. Due to metabolic similarities and in order to increase statistical power, we placed RM and UM as one group denominated RM/UM. We also verified the allele frequencies and checked if the genotypes were in accordance with the Hardy-Weinberg Equilibrium.

Table 1. Detailed information regarding *CYP2C19* genotypes, phenotypes and their impact on enzyme activity and therapeutic effect

Genotype/Haplotype	Phenotype	Enzyme activity	Metabolic effect
*1/*1	NM	Normal function	Therapeutic effect
*1/*2	IM	Decreased function	Surpasses the therapeutic range
*2/*17	IM	Decreased function	Surpasses the therapeutic range
*1/*17	RM	Increased function	Does not reach the therapeutic range
*17/*17	UM	Increased function	Does not reach the therapeutic range
*2/*2	PM	Limited or no function	Surpasses the therapeutic range

*1: wild-type allele. *17: rs12248560. *2: rs4244285 . *3: rs4986893. NM: Normal Metabolizers. IM: Intermediate Metabolizers. RM: Rapid Metabolizers. UM: Ultrarapid Metabolizers. PM: Poor Metabolizers [10].

2.7. Statistical Analysis

Descriptive statistics, such as mean and standard deviation for quantitative parametric variables, and frequency for qualitative variables, were obtained. The chi-square test was used to analyze qualitative variables, while quantitative variables were analyzed using the analysis of variance (ANOVA) test. Finally, DMS post-hoc analysis was used to analyze associations among more than three subgroups. A significance level of $p < 0.05$ was considered statistically significant. All statistical tests were performed using SPSS software version 18.0.

3. RESULTS

3.1. Baseline Population Characteristics

Among 200 patients from PROTHUM, 22 were excluded due to a lack of DNA samples at the time of analysis, 7 were excluded due to a Bipolar Disorder diagnosis, 5 were excluded due to a lack of HAM-D score in the PROTHUM database, and,

finally, 3 were excluded due to non-permission access to online medical records at the time of analysis. Therefore, 163 patients were included in the study.

In our study population there were 139 (85.3%) female and 24 (14.7%) male patients. The mean age of all patients was 52.2 ± 9.8 (19-76) years old, and the mean ages of the female and male patients were 52.2 ± 10.2 (19-76) and 52.0 ± 7.9 (33-72), respectively. The mean duration of follow-up was 205 ± 41.7 (84-455) days, and approximately 39 (23.9%) patients had been hospitalized previously and/or during the treatment.

Regarding the depressive episodes, 47 (28.8%) patients experienced a single episode, while the majority, comprising 116 (71.2%) patients, had recurrent depressive episodes. In terms of the severity of the diagnosis, 3.7% of the individuals were classified as having a mild condition, 30.7% were categorized as moderate, and 46.6% were diagnosed with severe depression. Furthermore, 19.0% of the patients presented with psychotic features in their depressive episodes. The demographic and clinical data are summarized in Table 2.

Table 2. Representation of demographic and clinical characteristics of participants

		Patients
Characteristic		Total (n = 163)
Gender, No. (%)		
	Female	139 (85.3)
	Male	24 (14.7)
Age, mean (SD)		52.22 (9.8)
HAM-D score, mean (SD)		
	Baseline	21.04 (5.4)
	After 6 months	16.33 (7.3)
Depressive episodes, No. (%)		
	Single episode	47 (28.8)
	Recurrent	116 (71.2)
Diagnosis severity, No. (%)		
	Mild	6 (3.7)
	Moderate	50 (30.7)
	Severe	76 (46.6)
	Psychotic	31 (19.0)
Hospitalizations, No. (%)	Yes	39 (23.9)
	No	124 (76.1)

SD: Standard Deviation. HAM-D: Hamilton Depressive Rating Scale.

3.2. Treatment Results

Regarding the use of SSRI and TCA antidepressants at the beginning of the study, 64 (39.26%) patients exclusively used SSRI, 23 (14.11%) exclusively used TCA, and 76 (46.66%) used a combination of both. However, by the end of the study, 53 (32.51%) patients were exclusively using SSRI, 18 (11.04%) were exclusively using TCA, 82 (50.30%) were utilizing both to enhance the antidepressant effect, and 10 (6.13%) stopped using both types of antidepressants. Medication adjustments during the 6 months of treatment were not assessed in the study. The number of patients for each type of SSRIs and TCAs used and evaluated are in the Figures 2 and 3, respectively.

Based only on the antidepressants evaluated, 129 patients maintained the treatment during the analysis period, 33 changed therapeutic strategies during the analysis period, 29 added drugs to reinforce the therapeutic effect, and 25 discontinued medication due to side effects or remission of symptoms. Finally, 126 patients used other psychiatric drug classes during treatment, such as antipsychotics, mood stabilizers, benzodiazepines, and other classes of antidepressants aiming to enhance the antidepressant effect.

The antidepressant effect, as measured by the HAM-D scale, demonstrated that participants initially exhibited a mean HAM-D score of 21.04 ± 5.4 (8-35). By the end of the study, this score had decreased to 16.33 ± 7.3 (0-32), $p < 0.001$ (Fig. 4). Within the sample, 23 (14.1%) patients achieved symptom remission and 11 (6.7%) participants responded to treatment without remitting symptoms. Among the remaining 129 (79.1%) individuals, 45 (27.6%) had no benefit from treatment.

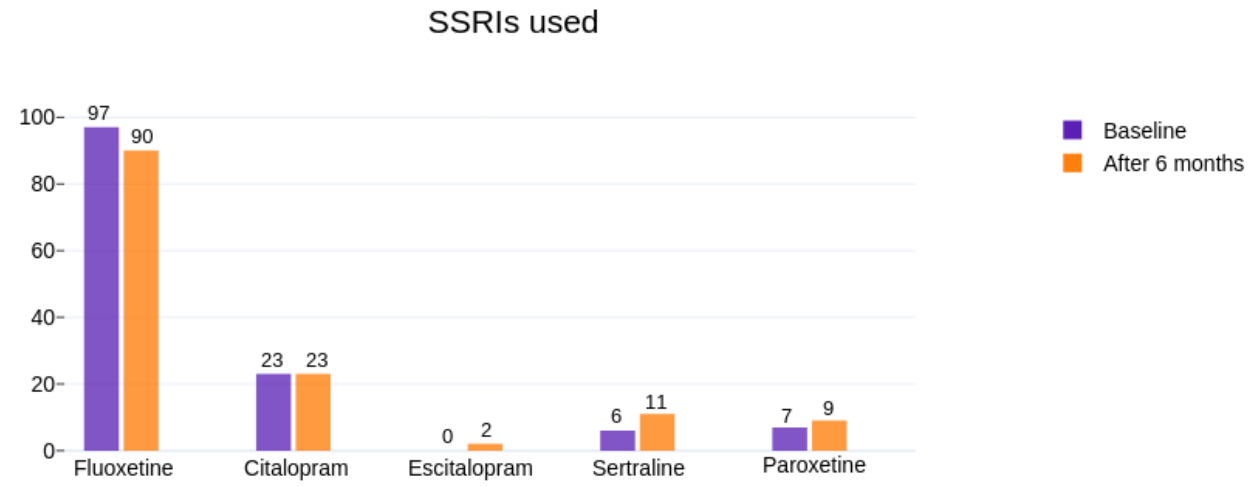

Figure 2. Number of subjects for each type of SSRI antidepressant used at baseline and after 6 months. SSRIs: Selective Serotonin Reuptake Inhibitors.

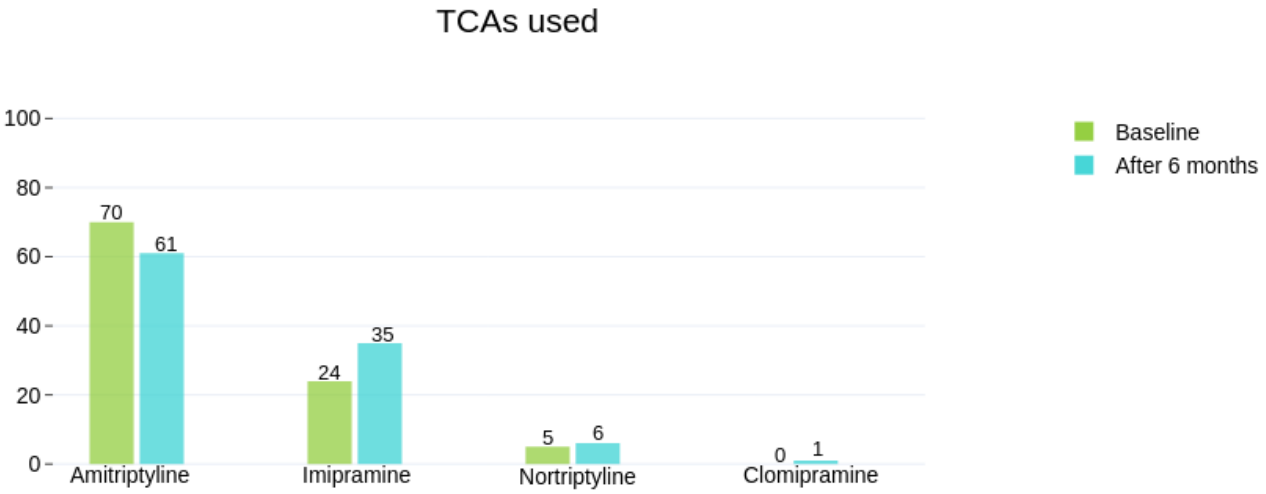

Figure 3. Number of subjects for each type of TCA antidepressant used at baseline and after 6 months. TCAs: Tricyclic Antidepressants.

Figure 4. Mean HAM-D scale scores in all 163 patients at baseline and after 6 months. HAM-D: Hamilton Depressive Rating Scale.

3.3. Genotype and Phenotype

All variants are in Hardy-Weinberg equilibrium. For the rs4244285 (*2) variant, we observed an allele frequency of 12%; however, no homozygous was found in our samples. For the rs12248560 (*17) variant, we identified an allele frequency of 18%. In contrast, variant rs4986893 (*3) was not detected in our sample. The frequencies observed correspond to those provided by the CPIC guidelines [6]. The most prevalent genotype/haplotype was *1/*1, accounting for 44.8% of the individuals, followed by *1/*17 with 27.6%. Notably, the *1/*2 genotype was observed in 20.2% of the participants, while *2/*17 and *17/*17 genotypes were present in 4.9% and 2.5% of the sample, respectively.

Considering the CYP2C19 phenotype distribution, 44.8% of the individuals were classified as normal metabolizers (NM), while 25.2% were intermediate metabolizers (IM). Additionally, 30.1% of the participants were identified as rapid/ultrarapid metabolizers (RM/UM). Intriguingly, no participants exhibited a poor metabolizer (PM) phenotype, indicating the absence of this particular phenotype in our studied population. The information above is summarized in Table 3.

Table 3. Representation of genetic and phenotypic characteristics of participants.

Characteristic		Patients Total (n = 163)
CYP2C19 (MAF)		
*17	(T)	0.18
*2	(A)	0.12
*3	(A)	0
CYP2C19 Genotype, No. (%)		
*17	C/C	106 (65.0)
	C/T	53 (32.5)
	T/T	4 (2.5)
*2	G/G	122 (74.8)
	A/G	41 (25.2)
*3	G/G	163 (100)
CYP2C19 Genotype/Haplotype, No. (%)		
	*1/*1	73 (44.8)
	*1/*2	33 (20.2)
	*1/*17	45 (27.6)
	*2/*17	8 (4.9)
	*17/*17	4 (2.5)
CYP2C19 Phenotype, No. (%)		
	NM	73 (44.8)
	IM	41 (25.2)
	RM/UM	49 (30.1)
	PM	0 (0)

MAF: Minor Allele Frequency. *1: wild-type allele. *17: rs12248560. *2: rs4244285 . *3: rs4986893. NM: Normal Metabolizers. IM: Intermediate Metabolizers. RM/UM: Rapid/Ultrarapid Metabolizers. PM: Poor Metabolizers

3.4. Association of the information obtained with HAM-D final scores

The association between baseline clinical characteristics and the final HAM-D scores of the participants revealed a robust relationship within diagnoses ($p < 0.001$). Regarding participant gender, no significant association was observed with final HAM-D scores ($p = 0.242$). Furthermore, no discernible relationship emerged between previous hospitalizations and/or the analysis period and final HAM-D scores ($p = 0.289$). This data is presented in Table 4.

An association was identified between predicted phenotype and HAM-D scores ($p = 0.014$) after 6 months of follow-up. A post hoc test was performed and showed there is difference between NM vs. RM/UM (p = 0.004) and IM vs. RM/UM (p = 0.036), but not between NM vs. IM (p = 0.665). Specifically, individuals categorized as RM/UM exhibited higher HAM-D scores compared to NM and IM. Moreover, an association emerged between the final HAM-D scores and *CYP2C19*17*

(rs12248560) genotypes (p = 0.023). Notably, individuals carrying one or two variant alleles demonstrated higher final HAM-D scores compared to those without any of these alleles. There was no observed association between *CYP2C19*2* (rs4244285) and the final HAM-D scores (p = 0.486). Additionally, while displaying a certain tendency, no statistically significant relationship emerged between the *CYP2C19* genotypes/haplotypes when considered the three variants together and the final HAM-D scores (p = 0.070). It is important to note that an association could not be established for *CYP2C19*3* (rs4986893) due to the absence of allele variants within our study population. The previous findings are presented in Table 5.

Table 4. Associations between HAM-D score after 6 months and Demographic and Clinical Characteristics.

Characteristic			**HAM-D after 6 months** Mean (SD)
Gender			
	Female		16.6 (7.0)
	Male		14.7 (6.9)
		p-value:	0.242
Diagnosis			
Single episode	Mild		6.0 (4.0)
	Moderate		10.4 (6.8)
	Severe		16.8 (9.1)
	Psychotic		18.0 (4.4)
Recurrent	Mild		2.7 (2.1)
	Moderate		15.5 (6.0)
	Severe		17.9 (6.6)
	Psychotic		19.7 (6.7)
		p-value:	**< 0.001***
Diagnosis			
Episodes	Single episode		14.5 (8.0)
	Recurrent		17.1 (6.9)
		p-value:	**0.043***
Severity	Mild		4.3 (3.3)
	Moderate		14.1 (6.6)
	Severe		17.6 (7.2)
	Psychotic		19.0 (6.0)
		p-value:	**< 0.001***
Hospitalizations			
	Yes		17.4 (7.0)
	No		16.0 (7.4)
		p-value:	0.289

HAM-D: Hamilton Depressive Rating Scale. SD: Standard Deviation. *: *p-value* statistically significant < 0.05.

Table 5. Associations between HAM-D score after 6 months and *CYP2C19* Genotype and Phenotype.

Characteristic			**HAM-D after 6 months** Mean (SD)
CYP2C19 Genotype			
*17	C/C		15.2 (7.1)
	C/T		18.5 (7.6)
	T/T		17.7 (2.6)
		p-value:	**0.023***
*2	G/G		16.5 (7.5)
	A/G		15.6 (6.6)
		p-value:	0.486
*3	G/G		16.3 (7.3)
		p-value:	NA**
CYP2C19 Genotype/Haplotype			
	*1/*1		15.0 (7.3)
	*1/*2		15.5 (6.5)
	*1/*17		18.9 (7.6)
	*2/*17		16.1 (7.1)
	*17/*17		17.7 (2.6)
		p-value:	0.070
CYP2C19 Phenotype			
	NM		15.0 (7.3)
	IM		15.6 (6.6)
	RM/UM		18.8 (7.3)
	PM		NA***
		p-value:	**0.014***

HAM-D: Hamilton Depressive Rating Scale. SD: Standard Deviation. *1: wild-type allele. *17: rs12248560. *2: rs4244285. *3: rs4986893. NM: Normal Metabolizers. IM: Intermediary Metabolizers. RM/UM: Rapid/Ultrarapid Metabolizers. PM: Poor Metabolizers. *: *p-value* statistically significant < 0.05. **: Impossibility to calculate *p-value*. ***: No PM individual was found in our sample..

4. DISCUSSION

Major Depressive Disorder (MDD) is a prevalent global psychiatric illness significantly affecting people's well-being and is closely associated with physical health issues and disabilities, ranked as the fourth highest contributor to global disability [27]. However, treating MDD is challenging, with almost half of patients not responding to initial treatment attempts, remission rates remaining low, as well as adverse drug reactions proving high [21,23]. To address this, genetics play a crucial role, contributing around 50% to how individuals respond to antidepressants, thus influencing the individual pattern of drug metabolism. [21,33]. Accordingly, our longitudinal and retrospective study aimed to demonstrate the genetic influence on treatment response. We enrolled 163 patients displaying resistant depressive symptoms and we evaluated the treatment response through the Hamilton Depression Rating Scale (HAM-D) guided by participants' clinical data and genotype-phenotype correlations.

In summary, the observed *CYP2C19* allele frequencies in this study closely correspond to the population frequencies reported in the CPIC guideline [6]. For instance, concerning allele *2, our study revealed a Minor Allele Frequency (MAF) of 12%, which closely aligns with the biogeographic European and Latino groups at 14% and 10%, respectively. Conversely, for allele *3, our study identified a MAF of 0%, while the compared groups exhibited approximately 0.1%. Lastly, allele *17 in our study exhibited a MAF of 18%, whereas the European group displayed 21% and the Latino group 16%. Moreover, the genotype/haplotype distribution patterns are in harmony with data derived from European and Latino biogeographical groups, paralleling the distribution patterns of phenotypes. These findings collectively underscore the consistency of our results within the context of the Brazilian population.

In our current analysis, we identified only one study conducted within the Brazilian population that aimed to investigate the role of *CYP2C19* variants in antidepressants effect. The observational study by de Brito and Ghedini [35] involved 31 individuals with MDD who were treated with escitalopram and were in symptom remission. Their findings closely resemble our own in terms of the distribution of *CYP2C19* genotypes and phenotypes. Notably, the *17 (17.2%) variant allele

emerged as the most prevalent, followed by *2 (12.7%) and *3 (1.0%) variants. Additionally, they did not observe any CYP2C19 PM individuals in their study population, mirroring our results. In contrast with our results, they did not find association between the phenotypes and the HAM-D scores; however, they analyzed only the patients who had symptoms remission, contrasting our study design, which included both patients who had symptoms remission and those who did not.

Our findings showed significant clinical implications related to HAM-D scores. Specifically, our study reveals that 55.2% of participants exhibited non-normal metabolizer (non-NM) phenotypes of CYP2C19, indicating distinct CYP2C19 metabolism compared to the normal metabolizer (NM) phenotype. Among these, 30.1% displayed rapid/ultrarapid metabolizer (RM/UM) phenotypes, resulting in lower antidepressant serum concentrations compared to NM [24]. This reduction in serum concentrations correlated with decreased therapeutic efficacy [24]. In contrast, 25.2% exhibited intermediate metabolizer (IM) phenotypes, leading to elevated antidepressant serum levels, thereby increasing the probability of adverse drug reactions and toxicity [24]. These observations is corroborated by the final HAM-D scores, which revealed that RM/UM individuals exhibited higher HAM-D scores, indicating over-depressive symptoms compared to NM and IM individual.

Consequently, individuals with non-NM phenotypes may require tailored dosage adjustments or medication changes when using CYP2C19 enzyme substrates (e.g. Citalopram, Escitalopram, Sertraline, Amitriptyline, Clomipramine, Doxepin, Imipramine, and Trimipramine) due to potential drug–gene interactions. The Clinical Pharmacogenetics Implementation Consortium (CPIC) guidelines for SSRIs and TCAs antidepressants [6,7] provide practical recommendations for optimizing treatment strategies.

Parallel studies provide consistent evidence of the prevalence of CYP2C19 non-NM phenotypes across diverse populations. For instance, Ivanov *et al*. [8] conducted a retrospective analysis involving 742 Bulgarian psychiatric patients, identifying altered CYP2C19 metabolizer statuses in approximately 60% of cases. Similarly, Naujokaitis *et al*. [10] reported that only 33.3% of individuals exhibited regular enzyme activity in a Lithuanian cohort of 54 patients. While acknowledging the latter study's limited sample size, it underscores the variability of metabolic patterns across different populations.

Furthermore, our findings align with the outcomes of Jukic et al. [19], who investigated the pharmacokinetic impact of CYP2C19 phenotypes specifically concerning escitalopram. Their investigation revealed significant disparities in serum concentrations across different CYP2C19 phenotypes. Notably, significant increases in serum concentrations were evident in poor metabolizers (PM) and intermediate metabolizers (IM), while rapid metabolizers (RM) and ultrarapid metabolizers (UM) displayed decreased concentrations. Moreover, they noted a higher frequency of switching among non-NM phenotypes, highlighting the substantial influence of CYP2C19 phenotypes on drug metabolism.

Regarding treatment response evaluation using validated depression scales, our study showed a significant association between CYP2C19 phenotypes and the final HAM-D scores. This finding aligns with the clinical implication of RM and UM phenotypes, where the drug's therapeutic range is not achieved. However, our findings diverge from other studies. For instance, Joković *et al*. [9] conducted a retrospective cohort of 102 participants from Serbia, observing reduced symptom reduction rates in PM and IM individuals, while NM, RM, and UM individuals demonstrated similar yet variable improvements. It is important to consider the limited total and subgroup sample size, just like CYP2C19 substrate usage among participants, these factors might influence the strength of the conclusions made. Likewise, Fabbri *et al*. [16] performed a meta-analysis involving 2558 MDD patients, suggesting heightened symptom improvement in CYP2C19 PM and IM phenotypes, with UM individuals closely similar to NMs. It's noteworthy to highlight the study's low sample heterogeneity, characterized by a minimal representation of PM (2.0%) and UM (4.6%) individuals. The divergence in findings could be attributed to two factors. Firstly, our study used a diverse range of medications among our patients, in contrast to Fabbri *et al.* [16] focus on citalopram and escitaopram. Secondly, our study's restricted presence of variant alleles (such as *CYP2C19*2* and **3*) with impaired function, and the absence of homozygous genotypes, contributing to the absence of PM individuals. This is partly due to the rarity of PM phenotype in European-derived populations [28]. The distinct genetic composition in our sample likely contributes to these observed disparities, necessitating further investigation.

In summary, our study reveals notable clinical implications for antidepressant treatment response. We observed a distinct correlation between HAM-D scores, symptom severity and the chronicity of episodes. This finding highlights that

individuals experiencing single and recurrent episodes, as well as different degrees of severity, exhibit different treatment responses. Notably, patients without chronicity exhibited a more favorable treatment response compared to those with recurrent episodes. Furthermore, individuals with mild, moderate, and severe symptoms exhibit distinct HAM-D scores average, with milder symptoms corresponding to lower scores and more severe symptoms resulting in higher scores. Remarkably, the means of HAM-D scores for individuals with severe and severe with psychosis MDD displayed no significant statistical disparities, suggesting a convergence in treatment outcomes. Consequently, our observations suggest that milder depressive features respond more favorably to treatment than severe symptoms, whether accompanied by psychotic features or not.

Given these insights, Kautzky *et al*. [5] present findings that align with our own. Their retrospective cross-sectional study with 1410 patients with MDD-resistant treatment, delved into the influence of clinical data on treatment outcomes. Their results revealed that more severe symptoms are three times more likely to exhibit resistance to treatment in comparison to moderate symptoms, as well as the number of episodes throughout life contribute to MDD-resistant treatment. Furthermore, they identified other influential factors such as comorbidities with anxiety disorders and suicide risk.

While our study's findings offer interesting insights, we have also noticed some limitations in our analysis. Firstly, our sample size, though adequate for initial exploration, might have limited the strength of our results. A larger sample size could reveal trends as strong associations. Secondly, we did not consider participants' ethnicity in our study, which is fundamental in pharmacogenetic research, since we did not have access to this data. Thirdly, we did not evaluate the assessment of adverse reactions in individuals and the differentiation between hospitalizations that happened before the study from those during it. These details could have given us a better understanding of how genetics impact antidepressant treatment outcomes. Fourthly, we did not address a phenoconversion analysis in our results. This phenomenon evaluation could bring us an understanding of how concomitant medications or existing health conditions might have influenced our findings. Finally, the enzyme CYP2C19 does not metabolize all the substrates addressed, which leads us to increase the types of genes studied in future studies, such as *CYP2D6*, *CYP2B6* and *SLC6A4*, for example. Our study's limitations underscore a direction for

future research. Larger, diverse samples, consideration of ethnic backgrounds, concomitant medications, and phenoconversion could deepen insights into genetics and antidepressant response in MDD, leading to more effective personalized treatments, and, as a consequence, benefit the treatment of MDD.

5. CONCLUSION

The study explores gene-drug interactions, specifically *CYP2C19* variants, and their impact on the effectiveness of antidepressant treatment for Major Depressive Disorder. Notably, a significant link emerged between CYP2C19 phenotypes and reduced antidepressant response, particularly in RM and UM individuals. Emphasizing the importance of personalized treatment due to response variability, we also identified a prevalence of non-NM individuals. Furthermore, our findings demonstrated a clinical connection between MDD chronicity, severity and treatment response, influencing therapeutic effectiveness. Through tailored dosages and medication choices based on drug metabolism, treatment outcomes can be optimized. Overall, this research firmly establishes the genetic role in drug metabolism and its considerable influence on treatment efficacy, offering a promising avenue for enhancing MDD treatment outcomes.

SUMMARY POINTS

- MDD is a psychiatric condition marked by substantial impairment, often with limited treatment success and low remission rates.
- The genetic component stands as one of the most predominant factors influencing antidepressant treatment response.
- Utilizing gene-guided therapy could serve as a pivotal tool to enhance response rates.
- We examined HAM-D scores in a cohort of 163 MDD patients and correlated them with *CYP2C19* genotypes and phenotypes.
- We noted a significant prevalence of non-NM phenotypes within the *CYP2C19* gene, signifying a notable proportion of individuals with altered metabolism.

- HAM-D scores in individuals with the CYP2C19 RM/UM phenotype exhibit a significant alteration, resulting in higher scores.
- The severity and chronicity of MDD diagnosis also play a role in influencing treatment response.
- Future studies should be conducted using a larger sample size and evaluation of concomitant medications.

AUTHOR CONTRIBUTIONS

LPLH: genotyped, analyzed and interpreted data, writing the manuscript, investigation, data curation, formal analysis, methodology. **NSS:** genotyped. **ASO:** database organization. **MPAF:** diagnosticated patients and made clinical assessments, PROTHUM coordinator. **MAKC:** diagnosticated patients and made clinical assessments. **UM:** conception and design, drafting the manuscript, or revising it critically for intellectual content. **MRB:** conception and design, drafting the paper or revising it critically for intellectual content, final approval of the version to be published.
All authors agree to be accountable for all aspects of the work.

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DISCLOSURES

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

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DISCUSSÃO GERAL

O estudo apresentado sustenta a hipótese de influência genética das variantes do gene *CYP2C19* no tratamento do Transtorno Depressivo Maior (TDM), respaldando a abordagem farmacogenética. A análise descritiva ainda revelou uma prevalência significativa de indivíduos no nosso estudo que não apresentam o fenótipo de metabolização inferido clássico, o que impõe importância à necessidade de personalizar o tratamento com base no perfil genético do paciente.

Dentre os perfis de metabolização analisados no estudo, o caracterizado como padrão de Metabolismo Rápido/Ultrarrápido (MR/MU) demonstrou significância na análise, ao se associar com respostas terapêuticas menos eficazes, que vai ao encontro da perspectiva farmacocinética. De acordo com Rudberg *et al*. (2006), indivíduos com perfis MR e MU atingem concentrações farmacológicas menores, ficando abaixo do intervalo terapêutico necessário para o sucesso do tratamento. Além disso, o presente estudo reforça outros possíveis fatores de ordem clínica associados à efetividade terapêutica, como é o caso da cronicidade e severidade dos sintomas.

Mediante uma análise comparativa das frequências obtidas em nosso estudo com os dados reportados pela Rede Nacional de Farmacogenética (Refargen) (SUAREZ-KURTZ, 2010), constata-se que os dados obtidos são concordantes com os deste estudo. Conforme apontado pela Refargen, a variante *3 demonstra uma participação restrita na população brasileira. No que se refere às variantes *17 e *2, estas estão presentes, sendo a primeira mais prevalente em relação à segunda. Tais constatações corroboram com a consistência dos nossos resultados.

Considerando as evidências acima mencionadas, o presente estudo, além de enfatizar a abordagem farmacogenética como ferramenta para auxiliar nos desafios associados ao tratamento medicamentoso do TDM, também está alinhado com a literatura atual em relação às frequências alélicas obtidas e aos fatores clínicos correlacionados. Entretanto, deve-se atribuir a devida importância à necessidade de aumentar o tamanho da amostra para obter resultados mais sólidos e representativos, especialmente em relação às variantes genéticas dos alelos *2 e *3. Portanto, estudos futuros, além de abordar as limitações do presente estudo, podem estender a análise farmacológica para considerar o fenômeno da

fenoconversão, especialmente devido à população analisada apresentar polifarmácia decorrente de diversas comorbidades, tanto psiquiátricas quanto físicas, que podem influenciar na resposta ao tratamento. Adicionalmente, seria apropriado incluir fatores sociais e demográficos, como a etnia do grupo analisado, a posição socioeconômica e a influência da faixa etária no cenário investigado.

Além disso, é relevante destacar que futuras pesquisas devem considerar populações com histórico de miscigenação para uma análise mais precisa dos indivíduos. Essa abordagem é necessária, uma vez que estudos farmacogenéticos envolvendo populações latinas apresentam proporções consideravelmente inferiores em comparação com estudos em populações europeias (SCUDELER; RODRIGUES-SOARES, 2020). A consideração desses fatores potencialmente levará a resultados mais detalhados e sensíveis, ao mesmo tempo que fortalecerá a integridade das análises. Consequentemente, os desafios de implementar a abordagem farmacogenética na prática clínica, que atualmente são marcantes, poderão ser atenuados se profissionais de diversas áreas reconhecerem a pertinência dessa abordagem.

Tendo esses pontos em mente, o presente trabalho elucida a abordagem farmacogenética para a otimização do tratamento do Transtorno Depressivo Maior. Tal abordagem tem foco primário na personalização do tratamento medicamentoso consoante ao perfil genético do indivíduo. A abordagem apresentada tem o potencial de aumentar a qualidade de vida, diminuir possíveis efeitos adversos e diminuir taxas de descontinuação do tratamento. Assim, esta se mostra como uma ferramenta aliada para otimizar o efeito antidepressivo dos medicamentos existentes.

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