JULIANA BRUM MORAES

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Tese apresentada ao Programa de Pós-Graduação em Ciências da Saúde da Universidade Estadual de Londrina - UEL, como requisito parcial para a obtenção do título de Doutora em Ciências da Saúde.

Orientadora: Profª. Drª. Sandra Odebrecht Vargas Nunes

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“Mas os que esperam no Senhor
renovarão suas forças; subirão com asas como águias;
correrão, e não se cansarão; caminharão, e não se
fatigarão.”

Isaías 40.31

MORAES, Juliana Brum. **Abordagens multidimensionais na Depressão Resistente ao Tratamento: Variantes Genéticas de *MTHFR*, mecanismos epigenéticos, características clínicas e aspectos psicossociais**. 2026. 238p. Tese (Doutorado em Ciências da Saúde) – Centro de Ciências da Saúde, Universidade Estadual de Londrina, Londrina, 2026.

RESUMO

Introdução
A depressão resistente ao tratamento (DRT) constitui um importante desafio clínico e científico, desde a heterogeneidade de seus critérios de definição e dificuldades na comparabilidade dos estudos publicados, até a maior gravidade de sintomas, recorrência, prejuízo funcional e aumento do risco de suicídio. Evidências crescentes indicam que a DRT resulta da interação entre fatores genéticos, epigenéticos, clínicos e psicossociais. Entre eles, variantes genéticas do *MTHFR* têm sido associadas tanto à vulnerabilidade ao Transtorno Depressivo Maior (TDM) quanto à resistência ao tratamento, com potenciais implicações terapêuticas.

Objetivos
Este estudo investigou a associação entre as variantes genéticas do *MTHFR* 677C>T (rs1801133) e 1298A>C (rs1801131) e a DRT, focando em como a redução prevista da atividade enzimática afeta marcadores de gravidade clínica, a funcionalidade e resposta ao tratamento. Além de revisar a literatura e analisar fatores psicossociais como experiências adversas na infância (ACEs) e adesão ao tratamento, a pesquisa realizou a adaptação e validação para o português da escala *Massachusetts General Hospital Antidepressant Treatment Response Questionnaire* (MGH-ATRQ). Por fim, o trabalho avaliou o potencial translacional de um programa educacional baseado no modelo *Training of Trainers* (ToT) para capacitar profissionais de saúde em mecanismos epigenéticos e interações gene-ambiente no TDM.

Métodos
O primeiro estudo consistiu em uma revisão sistemática conduzida de acordo com as diretrizes do PRISMA, com o objetivo de investigar a associação entre variantes do *MTHFR* (677C>T e 1298A>C) e DRT. O segundo estudo teve delineamento metodológico e realizou a validação do MGH-ATRQ para o português em uma amostra de 156 pacientes com TDM. As propriedades psicométricas do instrumento foram avaliadas por meio de análises de concordância, sensibilidade, especificidade e acurácia. O terceiro estudo adotou um delineamento observacional transversal, com 78 pacientes adultos com TDM, a fim de investigar a associação entre atividade enzimática predita da MTHFR, gravidade clínica, resistência ao tratamento, funcionalidade e ACEs. As análises estatísticas incluíram testes comparativos e modelos de regressão. O quarto estudo apresentou o desenvolvimento e a avaliação de um módulo educacional baseado no modelo ToT, com metodologias ativas e aprendizagem baseada em casos (CBL), para capacitar 47 profissionais de saúde a compreender a interação entre fatores genéticos, epigenéticos e ambientais no TDM.

Resultados
Os resultados foram apresentados e discutidos em um artigo de revisão sistemática e três artigos originais. No primeiro artigo, sete estudos atenderam aos critérios de inclusão, e os resultados indicam uma possível ligação entre as variantes do *MTHFR* 677C>T e 1298A>C e um risco aumentado de DRT. A variabilidade nos desenhos dos estudos, nas definições de DRT e em fatores de confusão contribuem para as inconsistências nos resultados. No segundo artigo, o MGH-ATRQ classificou com precisão os indivíduos como portadores de DRT em comparação com os critérios clínicos padrão, demonstrando sensibilidade de 88,89% e especificidade de 97,56%. Os casos de DRT apresentaram maior gravidade depressiva, maior comprometimento funcional, menor adesão à medicação e maiores taxas de experiências adversas na infância. No terceiro artigo, 78 pacientes com atividade enzimática prevista de MTHFR reduzida (≤50%) apresentaram maior gravidade dos

sintomas depressivos (HDRS-17: 12,1 ± 6,8 vs 9,1 ± 5,0; p = 0,04), maior frequência de episódios depressivos (≥3 episódios: 86,2% vs 63,3%; p = 0,04), mais tentativas de suicídio (24,1% vs 6,1%; p = 0,03) e maior uso de antipsicóticos como adjuvantes (27,6% vs 8,2%; p = 0,04). O comprometimento funcional nos domínios de trabalho/escola, social e familiar foi significativamente pior no grupo com baixa atividade (p ≤ 0,05). Pontuações mais altas de ACEs foram associadas a maior gravidade do TDM em todos os subgrupos, particularmente entre pacientes com atividade reduzida de MTHFR e DRT. No quarto artigo, resultados qualitativos indicaram que os participantes desenvolveram uma compreensão mais ampla do TDM. Os relatos sugeriram maior sensibilidade a apresentações clínicas não específicas, e maior consciência de como a história de vida e os fatores contextuais podem contribuir para a vulnerabilidade ao TDM.

Conclusões

Embora as evidências sugiram um papel para as variantes do *MTHFR* na DRT, a heterogeneidade entre os estudos limita conclusões definitivas. Pesquisas futuras devem padronizar as definições de DRT, controlar os fatores de confusão e explorar a integração de testes genéticos na prática clínica. A versão brasileira do MGH-ATRQ é um instrumento válido para detectar pacientes com DRT e pode ser uma ferramenta útil tanto no contexto clínico quanto em protocolos de pesquisa. Amostras maiores e mais diversas serão importantes em estudos futuros para confirmar ainda mais a robustez psicométrica e a validade externa da versão brasileira do MGH-ATRQ. A estratificação funcional baseada na atividade prevista da MTHFR pode ajudar a identificar subgrupos clinicamente vulneráveis e refinar a avaliação prognóstica no TDM. Estratégias educacionais baseadas em ToT e CBL podem apoiar a disseminação do conhecimento epigenético entre profissionais de saúde e promover sua aplicação na prática.

Limitações

Uma limitação significativa da revisão sistemática é a ausência de uma meta-análise, devido à heterogeneidade entre os estudos. Em nosso estudo, a definição de DRT baseou-se apenas em resposta farmacológica, excluindo estratégias de psicoterapia ou neuromodulação. Os participantes foram recrutados em clínicas psiquiátricas privadas, o que pode limitar a generalização dos resultados para outras populações. No relato de experiência educacional, a ausência de uma avaliação do conhecimento prévio dos participantes limitou a capacidade de quantificar os ganhos de aprendizagem. Além disso, os resultados educacionais podem estar sujeitos a viés de relato. Por fim, a sustentabilidade e o impacto a longo prazo da disseminação do conhecimento não foram avaliados sistematicamente, com tal recomendação para estudos futuros.

Palavras-chave: depressão resistente ao tratamento; MTHFR; epigenética; experiências adversas na infância; funcionalidade.

MORAES, Juliana Brum. **Multidimensional Approaches to Treatment-Resistant Depression: *MTHFR* Genetic Variants, Epigenetic Mechanisms, Clinical Characteristics, and Psychosocial Aspects.** 2026. 238p. Thesis (Doctorate in Health Sciences). Londrina State University; 2026.

ABSTRACT

Introduction

Treatment-resistant depression (TRD) represents a major clinical and scientific challenge, ranging from the heterogeneity of its definitional criteria and difficulties in comparing published studies to increased symptom severity, recurrence, functional impairment, and elevated suicide risk. Growing evidence indicates that TRD results from the interaction of genetic, epigenetic, clinical, and psychosocial factors. Among these, genetic variants of the MTHFR gene have been associated with both vulnerability to major depressive disorder (MDD) and treatment resistance, with potential therapeutic implications.

Objectives

This study investigated the association between MTHFR genetic variants 677C>T (rs1801133) and 1298A>C (rs1801131) and TRD, focusing on how predicted reductions in enzymatic activity affect markers of clinical severity, functioning, and treatment response. In addition to reviewing the literature and analyzing psychosocial factors such as adverse childhood experiences (ACEs) and treatment adherence, this research included the cross-cultural adaptation and validation of the Massachusetts General Hospital Antidepressant Treatment Response Questionnaire (MGH-ATRQ) for Brazilian Portuguese. Finally, the study evaluated the translational potential of an educational program based on the Training of Trainers (ToT) model to capacitate healthcare professionals in epigenetic mechanisms and gene–environment interactions in MDD.

Methods

The first study consisted of a systematic review conducted according to PRISMA guidelines, aiming to investigate the association between *MTHFR* variants (677C>T and 1298A>C) and TRD. The second study employed a methodological design to validate the MGH-ATRQ in Portuguese in a sample of 156 patients with MDD. Psychometric properties were assessed through agreement analyses, sensitivity, specificity, and accuracy. The third study adopted a cross-sectional observational design involving 78 adult patients with MDD to examine associations between predicted MTHFR enzymatic activity, clinical severity, treatment resistance, functioning, and ACEs. Statistical analyses included comparative tests and regression models. The fourth study described the development and evaluation of an educational module based on the ToT model, using active methodologies and case-based learning (CBL), to train 47 healthcare professionals to understand the interaction between genetic, epigenetic, and environmental factors in MDD.

Results

The results were presented and discussed in one systematic review and three original articles. In the first article, seven studies met the inclusion criteria, and findings suggested a possible association between MTHFR 677C>T and 1298A>C variants and increased risk of TRD. Variability in study designs, TRD definitions, and confounding factors contributed to inconsistent findings. In the second article, the MGH-ATRQ accurately classified individuals with TRD compared to standard clinical criteria, demonstrating sensitivity of 88.89% and specificity of 97.56%. TRD cases showed greater depressive severity, worse functional impairment, lower medication adherence, and higher rates of ACEs. In the third article, patients with reduced predicted MTHFR enzymatic activity (≤50%) exhibited greater depressive symptom severity (HDRS-17: 12.1 ± 6.8 vs. 9.1 ± 5.0; $p = 0.04$), higher frequency of depressive episodes (≥3 episodes: 86.2% vs. 63.3%; $p = 0.04$), more suicide attempts

(24.1% vs. 6.1%; p = 0.03), and greater use of antipsychotics as adjunctive treatment (27.6% vs. 8.2%; p = 0.04). Functional impairment across work/school, social, and family domains was significantly worse in the low-activity group ($p \leq 0.05$). Higher ACE scores were associated with greater MDD severity across all subgroups, particularly among patients with reduced MTHFR activity and TRD. In the fourth article, qualitative findings indicated that participants developed a broader understanding of MDD, with reports suggesting increased sensitivity to non-specific clinical presentations and greater awareness of how life history and contextual factors contribute to vulnerability to MDD.

Conclusions

Although evidence suggests a role for *MTHFR* variants in TRD, heterogeneity across studies limits definitive conclusions. Future research should standardize TRD definitions, control for confounding factors, and explore the integration of genetic testing into clinical practice. The Brazilian version of the MGH-ATRQ is a valid instrument for identifying patients with TRD and may be useful in both clinical and research settings. Larger and more diverse samples are needed to further confirm the psychometric robustness and external validity of the Brazilian version of the MGH-ATRQ. Functional stratification based on predicted MTHFR enzymatic activity may help identify clinically vulnerable subgroups and refine prognostic assessment in MDD. Educational strategies based on ToT and CBL may support the dissemination of epigenetic knowledge among healthcare professionals and promote its application in clinical practice.

Limitations

A major limitation of the systematic review was the absence of a meta-analysis due to study heterogeneity. In our study, TRD was defined solely based on pharmacological response, excluding psychotherapy or neuromodulation strategies. Participants were recruited from private psychiatric clinics, which may limit generalizability. In the educational intervention, the absence of baseline knowledge assessment limited the ability to quantify learning gains, and outcomes may be subject to self-report bias. Long-term sustainability and impact of knowledge dissemination were not systematically evaluated and should be addressed in future studies.

Keywords: treatment-resistant depression; MTHFR; epigenetics; adverse childhood experiences; functionality.

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LISTA DE ABREVIATURAS E SIGLAS

ACE: *Adverse Childhood Experiences Questionnaire*

ACEs: Experiências Adversas na Infância (*Adverse Childhood Experiences*)

BMI: *Body mass index*

BT: *Back Translation*

BT1 / BT2 / BT12: Versões retro traduzidas do MGH-ATRQ

BDNF: Fator Neurotrófico Derivado do Cérebro

CAAE: *Ethical Appreciation Presentation Certificate*

CANMAT: *Canadian Network for Mood and Anxiety Treatments*

CBL: *Case-Based Learning*

CID-11: Classificação Internacional das Doenças, 11ª edição

CPIC: *Clinical Pharmacogenetics Implementation Consortium*

COMT: Catecol-O-Metiltransferase

CYP: *cytochrome P450*

CYP2C19: *Cytochrome P450 family 2 subfamily C member 19*

CYP2D6: *Cytochrome P450 family 2 subfamily D member 6*

DTD: Depressão de Difícil Tratamento (*Difficult-to-Treat Depression*)

DMTRD: *Dutch Measure for quantification of Treatment Resistant Depression Model*

DNA: Ácido Desoxirribonucleico

DNMT: DNA Metiltransferase

DRT: Depressão Resistente ao Tratamento

DSM-5-TR: Manual Diagnóstico e Estatístico de Transtornos Mentais, 5ª edição, texto revisado

ECT: Eletroconvulsoterapia

EMA: *European Medicines Agency*

EMBASE: *Excerpta Medica Database*

FDA: *Food and Drug Administration*

$HDRS_{17}$: Escala de Avaliação da Depressão de Hamilton (17 itens)

HHA: Eixo Hipotálamo–Hipófise–Adrenal

HTR2A: *5-hydroxytryptamine receptor 2A gene*

IC: Intervalo de Confiança

IMAO: Inibidor da Monoamina Oxidase

MADRS: *Montgomery–Åsberg Depression Rating Scale*

MARS: *Medication Adherence Rating Scale*

MDD: *Major Depressive Disorder*

MeSH: *Medical Subject Headings*

MGH-ATRQ: *Massachusetts General Hospital Antidepressant Treatment Response Questionnaire*

MGH-s: *Massachusetts General Hospital Staging Model*

MSM: *Maudsley Staging Model*

MTHFR: Metilenotetraidrofolato Redutase

NICE: *National Institute for Health and Care Excellence*

PR: Paraná

PCR: Reação em Cadeia da Polimerase

PECOT: *Population, Exposure, Comparator, Outcome, Time*

PRISMA: *Preferred Reporting Items for Systematic Reviews and Meta-Analyses*

PHQ-9: *Patient Health Questionnaire-9*

PROAP: *Post-Graduation Support Program*

PROSPERO: *International Prospective Register of Ongoing Systematic Reviews*

PubMed: *Public MEDLINE*

ReBEC: Registro Brasileiro de Ensaios Clínicos

RNAs: Ácidos Ribonucleicos

ROC: *Receiver Operating Characteristic*

SAM: S-Adenosilmetionina

SCID: Entrevista Clínica Estruturada para os Transtornos do DSM-5

SLC6A4: *Solute carrier family 6 member 4 (serotonin transporter gene)*

SD: *Standard Deviation* (Desvio Padrão)

SDS: Escala de Incapacidade de Sheehan

T1 / T2 / T12: Versões traduzidas do MGH ATRQ

TDM: Transtorno Depressivo Maior

ToT: *Training of Trainers*

TRD: *Treatment-Resistant Depression*

UEL: Universidade Estadual de Londrina/ *State University of Londrina*

WFSBP: *World Federation of Societies of Biological Psychiatry*

WHO: *World Health Organization*

SUMÁRIO

1. INTRODUÇÃO

O Transtorno Depressivo Maior (TDM) representa uma das principais causas de incapacidade em todo o mundo, associado a elevada carga individual, social e econômica[1,2]. Apesar dos avanços terapêuticos nas últimas décadas, uma parcela expressiva de pacientes não apresenta resposta adequada aos tratamentos disponíveis, evoluindo para quadros de depressão resistente ao tratamento (DRT)[3]. Estima-se que em torno de 30% dos indivíduos com TDM desenvolvam resistência terapêutica[4], mais comumente definida como a falha em responder a 2 ou mais tentativas com antidepressivos em dose terapêutica e duração adequada em um mesmo episódio depressivo[5,6], quadro associado a maior gravidade sintomática, maior recorrência de episódios ao longo da vida, prejuízo funcional, risco de suicídio, utilização intensiva de serviços de saúde e mortalidade geral[7-9].

Embora a hipótese monoaminérgica do TDM tenha contribuído de forma decisiva para o desenvolvimento dos antidepressivos atuais[10], tal modelo é insuficiente para explicar a heterogeneidade clínica deste transtorno, bem como a variabilidade na resposta terapêutica e a complexidade dos quadros resistentes[11-13]. Diante disto, a psiquiatria de precisão emerge como um campo promissor, propondo a identificação de subgrupos clínicos mais homogêneos e que considera o TDM um conjunto de fenótipos clínicos resultantes da interação dinâmica entre vulnerabilidades genéticas, exposições ambientais e processos neurobiológicos moduladores ao longo do desenvolvimento e da vida adulta[14-16].

É importante destacar que o TDM não está associado à disfunção de um único gene[17]. Ao contrário, evidências provenientes de estudos genômicos de larga escala, incluindo estudos de associação genômica ampla (GWAS), indicam que a vulnerabilidade ao TDM envolve a contribuição cumulativa de centenas de variantes distribuídas em diferentes sistemas biológicos, como aqueles relacionados à neurotransmissão monoaminérgica, à resposta ao estresse, à neuroplasticidade, à inflamação e ao metabolismo energético[18]. Assim, o risco para TDM emerge de uma arquitetura genética poligênica, na qual fatores biológicos diversos se somam e interagem com experiências ambientais.

Entre os sistemas biológicos implicados na fisiopatologia do TDM e da DRT, o metabolismo de um carbono tem recebido atenção crescente[19]. Esse sistema engloba vias bioquímicas fundamentais para a síntese de nucleotídeos, regulação da metilação do Ácido Desoxirribonucleico (DNA), produção de neurotransmissores e manutenção do equilíbrio redox. A enzima metilenotetrahidrofolato redutase (MTHFR) desempenha papel central nesse processo, catalisando

a conversão do 5,10-metilenotetrahidrofolato em 5-metiltetrahidrofolato, forma biologicamente ativa do folato necessária para a remetilação da homocisteína em metionina e subsequente produção de S-adenosilmetionina (SAM), principal doadora de grupos metil no organismo[20].

O gene *MTHFR* está localizado no braço curto do cromossomo 1 (chr1p36.3) e possui diversas variantes genéticas que causam alterações de aminoácidos na MTHFR[21]. Dentre elas, as mais amplamente investigadas são a variante 677C>T (rs1801133) - que consiste em uma transição de citosina para timina na posição 677, levando a uma substituição de alanina por valina no aminoácido 222 da proteína - e a variante 1298A>C (rs1801131), que envolve uma transição de adenina para citosina na posição nucleotídica 1298, resultando em uma mudança do aminoácido glutamato para alanina.

As variantes do *MTHFR* 677C>T e 1298A>C estão associadas à redução variável da atividade enzimática, com repercussões metabólicas relevantes[22]. A variante 677C>T, particularmente, leva a uma alteração estrutural na enzima que confere à mesma um fenótipo termolábil, com redução significativa de sua atividade catalítica.

A diminuição da atividade da MTHFR pode resultar em alterações nos níveis de folato ativo, aumento da homocisteína plasmática, redução da capacidade de metilação e maior vulnerabilidade ao estresse oxidativo e à neuroinflamação[23]. Evidências acumuladas sugerem que essas alterações podem influenciar tanto a suscetibilidade ao TDM quanto a gravidade dos sintomas, a recorrência dos episódios depressivos e a resposta aos tratamentos antidepressivos[24-26].

Além dos fatores genéticos, mecanismos epigenéticos têm sido amplamente implicados no TDM e em sua resistência terapêutica[27]. Esses mecanismos atuam como uma interface entre o genoma e o ambiente, permitindo que experiências ao longo da vida, especialmente durante períodos críticos do desenvolvimento, exerçam efeitos duradouros sobre a função cerebral e o comportamento[28]. Alterações epigenéticas associadas ao estresse precoce, à inflamação e a disfunções metabólicas têm sido descritas em pacientes com TDM, particularmente naqueles com curso mais grave e resistente[29].

As experiências adversas na infância (*adverse childhood experiences* – ACEs) constituem um dos fatores psicossociais mais robustamente associados ao risco de TDM, maior gravidade clínica, recorrência e pior resposta ao tratamento[30-32]. Exposições como abuso físico, emocional ou sexual, negligência e disfunção familiar estão relacionadas a alterações duradouras nos sistemas de resposta ao estresse, incluindo o eixo hipotálamo-hipófise-adrenal (HHA), bem como a mudanças epigenéticas em genes envolvidos na regulação emocional e na inflamação[33-35]. No entanto, nem todos os indivíduos expostos a ACEs desenvolvem TDM ou DRT, sugerindo que fatores genéticos e biológicos modulam essa vulnerabilidade[36]. Nesse sentido, modelos integrativos

de gene-ambiente têm sido propostos para explicar a heterogeneidade dos desfechos clínicos no TDM[18]. A interação entre variantes genéticas que afetam o metabolismo de um carbono, como aquelas do *MTHFR*, e exposições ambientais adversas pode contribuir para trajetórias clínicas mais graves e complexas[37]. Achados descritos na literatura ainda são heterogêneos, e poucos estudos exploraram de forma sistemática como a atividade enzimática prevista da MTHFR se relaciona simultaneamente a características clínicas, funcionais e psicossociais em pacientes com DRT[38].

Além da gravidade sintomática, a DRT está associada a importante comprometimento funcional, incluindo prejuízos no desempenho ocupacional, acadêmico, social e familiar[39,41]. A avaliação funcional, frequentemente negligenciada em estudos clínicos e nos próprios critérios de definição de DRT, representa um desfecho relevante, pois reflete de forma mais direta o impacto da doença na vida dos pacientes.

Diante desse cenário, torna-se fundamental investigar de forma integrada como variantes genéticas de *MTHFR*, mecanismos epigenéticos, características clínicas e fatores psicossociais se articulam na DRT. Uma compreensão mais abrangente desses múltiplos níveis de vulnerabilidade pode fornecer subsídios para a identificação de subfenótipos clínicos, aprimorar estratégias de estratificação de risco e orientar intervenções mais personalizadas, incluindo abordagens farmacológicas e psicossociais.

Diante do exposto, esta tese parte da hipótese de que a DRT decorre da interação entre fatores biológicos e ambientais ao longo da vida, modulados por mecanismos epigenéticos, resultando em maior gravidade clínica, prejuízo funcional e complexidade terapêutica. Postula-se que variantes genéticas funcionalmente relevantes do *MTHFR*, associadas à redução da atividade enzimática, estejam relacionadas a perfis clínicos mais graves e a menor resposta ao tratamento antidepressivo. Adicionalmente, levanta-se a hipótese de que mecanismos epigenéticos atuem como mediadores entre predisposição genética e exposições ambientais, especialmente ACEs, influenciando a expressão gênica e a trajetória clínica do TDM. Por fim, pressupõe-se que a convergência desses fatores biológicos e psicossociais se manifeste em desfechos clínicos relevantes, como maior recorrência de episódios depressivos, maior risco de comportamento suicida, maior comprometimento funcional e maior complexidade no manejo terapêutico.

1.1 JUSTIFICATIVA

A DRT representa um desafio clínico significativo, associado a elevada morbidade, sofrimento persistente e limitações substanciais na qualidade de vida dos pacientes. Apesar de sua relevância clínica, os mecanismos subjacentes à resistência terapêutica permanecem incompletamente compreendidos, e a maioria das abordagens terapêuticas ainda se baseia em

estratégias empíricas, com resultados insatisfatórios em aproximadamente um terço dos pacientes que buscam tratamento. A identificação de fatores biológicos e psicossociais que contribuam para a gravidade e a complexidade clínica da DRT é essencial para o avanço da psiquiatria de precisão.

Nesse contexto, o presente estudo se justifica pela proposta de integrar diferentes dimensões — genéticas, epigenéticas, clínicas, funcionais e psicossociais — na investigação da DRT, com foco nas variantes funcionais do *MTHFR* e sua atividade enzimática prevista. Ao explorar a interação entre metabolismo de um carbono, mecanismos epigenéticos ACEs, esta tese busca contribuir para uma compreensão mais abrangente da DRT, oferecendo subsídios para estratégias diagnósticas e terapêuticas mais individualizadas e fundamentadas biologicamente.

2. REFERENCIAL TEÓRICO

2.1 DEPRESSÃO RESISTENTE AO TRATAMENTO (DRT)

O TDM é um transtorno mental altamente prevalente e incapacitante em todo o mundo[1]. Apesar de múltiplas possibilidades terapêuticas disponíveis para o seu tratamento, aproximadamente 30% dos indivíduos diagnosticados e acompanhados por TDM não respondem satisfatoriamente às intervenções terapêuticas estabelecidas[4], com sérias consequências clínicas e funcionais[2,3], tais como maior risco de suicídio, maior risco de recorrência da depressão ao longo da vida, desemprego e absenteísmo e piores marcadores de saúde física[39-41].

A DRT - mais frequentemente definida como a falha em responder a 2 ou mais tentativas com antidepressivos em dose terapêutica e duração adequada em um mesmo episódio depressivo[5,6] - possui muitos fatores de risco como condições médicas e psiquiátricas concomitantes, não adesão ao tratamento, interações medicamentosas, diagnóstico incorreto, efeitos ambientais e genes[7,9].

Apesar de amplamente reconhecida como um subtipo mais grave e complexo do TDM, a DRT ainda não possui uma definição única aceita pela comunidade científica, o que dificulta a pesquisa nesta área, prejudicando a comparabilidade de achados científicos por falta de consenso[42]. As diretrizes da *World Federation of Societies of Biological Psychiatry* (WFSBP), em consonância com a *European Medicines Agency* (EMA), definem TRD como a ausência de resposta terapêutica, documentada por uma redução inferior a 50% dos sintomas avaliados por escalas padronizadas (como a *Hamilton Depression Rating Scale* – $HDRS_{17}$ ou a *Montgomery–Åsberg Depression Rating Scale* – MADRS), após pelo menos dois ensaios farmacológicos realizados em dose adequada, duração apropriada (tipicamente 6–8 semanas) e com adesão confirmada ao tratamento[5]. De forma semelhante, na Inglaterra, o *National Institute for Health and Care Excellence* (NICE) define TRD como um episódio depressivo maior que não responde a pelo menos dois antidepressivos diferentes, administrados em dose e duração adequadas durante o episódio atual[6]. A *Food and Drug Administration* (FDA) dos Estados Unidos adota critérios praticamente equivalentes no contexto de ensaios clínicos[43].

Apesar dessas definições convergentes, elas permanecem essencialmente focadas na resposta sintomática, sem necessariamente capturar dimensões críticas da doença, como funcionalidade, qualidade de vida e persistência longitudinal do quadro. Além disso, não levam em conta intervenções psicoterapêuticas, que são medidas de primeira linha para quadros depressivos leves e moderados[44].

Nesse contexto, as diretrizes do *Canadian Network for Mood and Anxiety Treatments* (CANMAT) propuseram o conceito de Depressão de Difícil Tratamento (*Difficult-to-Treat*

Depression, DTD)[45], que amplia o escopo da TRD. Nesse modelo, o foco terapêutico desloca-se da remissão completa dos sintomas para o manejo sustentado da doença, priorizando desfechos como funcionamento social, ocupacional e qualidade de vida. A DTD é, portanto, caracterizada por uma depressão persistente que falhou a múltiplas estratégias terapêuticas ao longo do tempo, em contraste com o critério mínimo de duas tentativas antidepressivas utilizado na definição clássica de TRD.

Além das definições categóricas, diversos modelos de estadiamento foram desenvolvidos com o objetivo de quantificar a gravidade e a complexidade da resistência ao tratamento. O modelo de Thase e Rush[46] propõe um contínuo de cinco estágios de falha terapêutica, incluindo diferentes classes de antidepressivos e a Eletroconvulsoterapia (ECT). O *Maudsley Staging Model*[47] (MSM), por sua vez, integra três dimensões fundamentais: (1) número de tratamentos antidepressivos previamente fracassados, incluindo estratégias de potencialização e ECT; (2) duração do episódio depressivo atual; e (3) gravidade basal dos sintomas. Já o *Massachusetts General Hospital Staging Model*[48] (MGH-s) conceitua a resistência ao tratamento como uma variável contínua, na qual cada falha terapêutica contribui para um escore acumulativo, sendo a falha da ECT ponderada de forma mais intensa. O *Dutch Measure for quantification of Treatment Resistant Depression Model* (DMTRD)[49] também leva em consideração a presença de 2 comorbidades psiquiátricas (sintomas ansiosos e transtornos de personalidade), funcionalidade e estresse psicossocial, além de considerar a falha em psicoterapia como um fator de resistência. As principais definições clínicas de DRT se encontram sumarizadas no Quadro 1.

Quadro 1. Principais definições clínicas de Depressão Resistente ao Tratamento (DRT).

Autor/Diretriz	**Ano**	**Critério principal de DRT**	**Número de falhas antidepressivas**	**Dose da medicação e duração do tratamento**	**Observações**
Fava[46]	2003	Falha em alcançar resposta clínica significativa	≥ 2	Dose terapêutica mínima conforme bula e duração ≥ 6 semanas	Definição clássica, mais comumente utilizada em pesquisas clínicas
FDA[41]	2018	Falha em obter resposta terapêutica	≥ 2	Doses e duração recomendadas, com adesão confirmada	Classificação desenvolvida para critérios de ensaios clínicos
NICE[6]	2022	Falha em obter resposta terapêutica	≥ 2	Depressão que não responde adequadamente a tratamentos sucessivos, após revisão diagnóstica, adesão e fatores psicossociais.	Destaca a importância de fatores ambientais e clínicos.

WFSBP[5]	2017	Falha em obter resposta terapêutica documentada por uma redução inferior a 50% dos sintomas avaliados por escalas padronizadas	≥ 2	Dose adequada, duração apropriada (tipicamente 6–8 semanas) e com adesão confirmada ao tratamento.	Busca confirmar a noção de DRT mais comumente aceita, destaca critério padronizado de não-resposta.
Thase and Rush Staging Model[44]	1997	Falha em obter resposta terapêutica	1	Estágio I: falha em responder a pelo menos uma tentativa adequada de antidepressivo; Estágio II: falha em responder a pelo menos 2 tentativas adequadas de antidepressivos de 2 classes diferentes; Estágio III: Estágio II + falha em responder a uma tentativa adequada com antidepressivo tricíclico; Estágio IV: Estágio III + falha em responder a uma tentativa adequada com inibidor da monoamina oxidase (IMAO); Estágio V: Estágio IV + falha em responder a um curso de Eletroconvulsoterapia bilateral (ECT).	Classificação progressiva da resistência É uma classificação simples, pragmática e que tenta refletir tomadas de decisão do dia a dia clínico.
Maudsley Staging Model[45] (MSM)	2009	Falha em obter resposta terapêutica	1	Resistência ao tratamento é definida como falha em obter um nível de melhora significativa em um determinado episódio depressivo após tratamento com um antidepressivo em dose adequada por período mínimo de 6 semanas. Inclui 3 dimensões de resistência: falha no tratamento, duração do episódio depressivo e gravidade.	Classificação progressiva da resistência. Foi desenvolvido para superar algumas limitações do modelo de Thase e Rush. Não considera tentativa de psicoterapia.

Dutch Measure for quantification of Treatment Resistant Depression Model (DMTRD)[47]	2016	Falha em obter resposta terapêutica	1	Além das variáveis consideradas em MSM, a DMTRD adiciona prejuízo funcional, ansiedade comórbida, transtorno de personalidade comórbido, estressores psicossociais, categorias de combinação de fármacos, psicoterapia e terapias intensivas.	Tenta melhorar a pontuação do MSM. Modelo mais extenso, apesar de não incluir estresse de vida precoce nem comorbidades não-psiquiátricas.
Massachusetts General Hospital Staging Model (MGH-s)[46]	2003	Falha em obter resposta terapêutica	1	Um ponto para cada tentativa de tratamento antidepressivo sem resposta, com duração mínima de 6 semanas e dose adequada. Meio ponto para cada tentativa de otimização de dose ou estratégia de combinação de fármacos. Três pontos para falta de resposta à ECT.	Pontuação um tanto arbitrária para tentativas de tratamento, mesmo peso para estratégias de aumento de dose e combinação de agentes.

Abreviações: FDA: U. S. Food and Drug Administration, NICE: National Institute for Health and Care Excellence; WFSBP: World Federation of Societies of Biological Psychiatry; CANMAT: Canadian Network for Mood and Anxiety Treatments; IMAO: inibidor da monoamina oxidase; ECT: Eletroconvulsoterapia; Maudsley Staging Model: MSM; DMTRD: Dutch Measure for quantification of Treatment Resistant Depression Model; MHG-s: Massachusetts General Hospital Staging Model.

Apesar desses avanços conceituais, a ausência de uma definição padronizada de TRD ainda compromete a comparabilidade entre estudos, dificulta a realização de meta-análises robustas e limita a generalização dos achados[3]. Além disso, o uso exclusivo de critérios de resposta sintomática ignora o fato de que melhora parcial não equivale à restauração do funcionamento pré-mórbido, aspecto particularmente relevante em pacientes com TDM crônico, recorrente ou biologicamente vulnerável[44].

A adoção de modelos de estadiamento e de definições que integrem tanto a resistência farmacológica quanto o impacto funcional do TDM torna-se essencial para pesquisas que buscam compreender os determinantes biológicos, genéticos e clínicos da resistência ao tratamento, incluindo a contribuição de variantes do gene *MTHFR* e seus efeitos sobre vias metabólicas, epigenéticas e neurobiológicas relevantes.

2.2 FATORES GENÉTICOS EM DRT

A DRT apresenta elevada heterogeneidade clínica e biológica, o que sugere que fatores genéticos desempenham papel relevante tanto na vulnerabilidade ao transtorno quanto na resposta insuficiente às intervenções terapêuticas[27,28]. Evidências provenientes de estudos familiares, de gêmeos e de associação genética indicam que a herdabilidade do TDM é moderada[50,51], enquanto a resistência ao tratamento parece refletir um fenótipo ainda mais complexo, influenciado pela interação entre múltiplos genes e fatores ambientais ao longo do desenvolvimento[28,52].

Dentre os genes mais investigados nos estudos de associação genética e análises de larga escala, destacam-se aqueles relacionados ao sistema serotoninérgico, como o transportador de serotonina (*SLC6A4*)[53] e receptores de serotonina, especialmente (*HTR2A*), cujas variantes têm sido associadas à modulação do humor, reatividade emocional e resposta ao estresse[54]. Além disso, genes envolvidos na regulação do eixo HHA, como o receptor de glicocorticoide (*NR3C1*) e o gene *FKBP5*[55], têm sido consistentemente implicados na interação entre estressores ambientais e risco depressivo. Evidências sugerem que variantes nesses genes podem influenciar a sensibilidade aos glicocorticoides e a regulação do feedback do eixo HHA, contribuindo para alterações duradouras na resposta ao estresse, especialmente quando combinadas a ACEs. Outro gene amplamente estudado é o *BDNF*, fundamental para processos de neuroplasticidade, neurogênese e adaptação sináptica, sendo sua variante funcional mais conhecida Val66Met (rs6265) associada a maior vulnerabilidade ao TDM, pior recuperação funcional e maior impacto de eventos estressores ao longo da vida[56].

Mais especificamente no contexto da DRT, a genética relacionada à farmacocinética e à farmacodinâmica dos antidepressivos assume especial relevância[57]. Variantes em genes do sistema do citocromo P450, como *CYP2D6*, *CYP2C19* e *CYP2C9*, influenciam significativamente a metabolização de antidepressivos e outros psicofármacos, podendo resultar em concentrações plasmáticas subterapêuticas, maior ocorrência de efeitos adversos ou falha terapêutica[58]. Esses fatores podem contribuir para quadros de pseudorresistência, frequentemente confundidos com resistência verdadeira ao tratamento.

Adicionalmente, genes envolvidos em vias metabólicas essenciais para a neurotransmissão e a regulação epigenética, como o *MTHFR*[59], podem influenciar a disponibilidade de cofatores necessários à síntese de neurotransmissores e aos processos de metilação do DNA. Nesta linha, variantes genéticas relacionadas ao metabolismo do carbono único (*one-carbon metabolism*), sistema bioquímico essencial para a síntese de neurotransmissores, regulação do estresse oxidativo e manutenção de padrões adequados de metilação do DNA[18,20,21], têm sido alvo de pesquisas. Alterações nesse sistema podem impactar processos neurobiológicos centrais associados à fisiopatologia do TDM e à resposta ao tratamento[22], como por exemplo a redução de

atividade da enzima MTHFR.

O gene *MTHFR* ocupa posição central nesse metabolismo, uma vez que esta enzima catalisa a conversão do 5,10-metilenotetrahidrofolato em 5-metiltetrahidrofolato, forma biologicamente ativa do folato necessária para a remetilação da homocisteína em metionina e, consequentemente, para a produção de SAM, principal doador de grupos metil no organismo[60]. A disponibilidade adequada de SAM é crucial para reações de metilação que regulam a expressão gênica, a síntese de monoaminas e a plasticidade neuronal[61].

Variantes genéticas do *MTHFR*, especialmente 677C>T (rs1801133) e 1298A>C (rs1801131), estão associadas à redução da atividade enzimática, com impacto variável conforme o genótipo[19]. A variante 677C>T, em particular, resulta em uma enzima termolábil, com diminuição significativa da atividade catalítica, enquanto a variante 1298A>C apresenta efeitos mais modestos, mas potencialmente relevantes quando combinada com outras alterações genéticas. A presença dessas variantes tem sido associada a níveis elevados de homocisteína, menor disponibilidade de folato ativo e comprometimento da capacidade de metilação[62].

Estudos investigaram a relação entre variantes do *MTHFR* e TDM, cujos resultados sugerem associação com maior risco para o aparecimento do transtorno, maior gravidade sintomática e pior resposta ao tratamento antidepressivo[24-26]. Estudos específicos para DRT e variantes do *MTHFR* encontraram associação com um perfil clínico mais complexo, caracterizado por maior recorrência de episódios depressivos, maior gravidade dos sintomas, maior risco de tentativas de suicídio, maior necessidade de estratégias terapêuticas combinadas e maior comprometimento funcional[63,64].

Do ponto de vista bioquímico, a redução da atividade da MTHFR pode contribuir para a DRT por meio de múltiplas vias convergentes, tais como a diminuição da disponibilidade de SAM e redução na síntese de serotonina, dopamina e noradrenalina, comprometendo a resposta aos antidepressivos, bem como alterações nos padrões de metilação do DNA que podem influenciar a expressão de genes envolvidos na regulação do eixo HHA, na inflamação e na neuroplasticidade[65].

A crescente compreensão do papel das variantes do *MTHFR* na DRT tem implicações relevantes para a psiquiatria de precisão. A identificação de indivíduos com redução da atividade enzimática pode auxiliar na estratificação de risco, no reconhecimento de subgrupos com maior probabilidade de resistência terapêutica e na consideração de estratégias adjuvantes, como intervenções nutricionais ou abordagens farmacológicas personalizadas. No entanto, tais aplicações clínicas ainda demandam maior robustez empírica e devem ser integradas de forma cautelosa à avaliação clínica global do paciente[66].

2.3 FATORES EPIGENÉTICOS EM DRT

A epigenética refere-se a modificações herdáveis e potencialmente reversíveis na expressão gênica que não envolvem alterações na sequência do DNA, como a metilação do DNA e modificações das histonas[67].

Embora fatores genéticos contribuam para a vulnerabilidade à DRT, eles não explicam, isoladamente, a expressiva heterogeneidade clínica observada nesse fenótipo. Evidências acumuladas nas últimas décadas indicam que mecanismos epigenéticos tais como a metilação do DNA, modificações pós-traducionais de histonas e a regulação por RNAs (Ácidos Ribonucleicos) não codificantes desempenham papel central na modulação da expressão gênica ao longo da vida, atuando como interface dinâmica entre predisposição genética e exposições ambientais [27,28,68]. Nesse sentido, a epigenética oferece um modelo integrativo particularmente relevante para a compreensão da DRT.

A metilação do DNA tem sido o mecanismo epigenético mais extensivamente investigado nesse contexto. Alterações nos níveis de metilação em regiões promotoras de genes relacionados ao estresse, à neurogênese e à sinalização inflamatória foram associadas à maior gravidade da depressão, maior recorrência e pior resposta ao tratamento antidepressivo[64]. Na DRT, tais alterações parecem ser mais pronunciadas, sugerindo que padrões epigenéticos disfuncionais possam contribuir para a persistência dos sintomas e menor responsividade aos tratamentos convencionais[28].O metabolismo do carbono único, no qual a enzima MTHFR exerce papel central, é diretamente responsável pela disponibilidade de grupos metil necessários para os processos de metilação do DNA. Assim, variantes genéticas que reduzem a atividade da MTHFR podem impactar indiretamente os mecanismos epigenéticos, alterando a capacidade global de metilação. Essa interdependência entre genética e epigenética é particularmente relevante na DRT, na qual múltiplas vias biológicas parecem convergir para um estado de vulnerabilidade persistente.

Além disso, alterações epigenéticas podem influenciar a resposta ao tratamento antidepressivo por modular a expressão de genes-alvo dos fármacos ou de vias envolvidas em sua farmacodinâmica[12]. Alterações na metilação de genes relacionados aos receptores serotoninérgicos, transportadores de monoaminas e fatores neurotróficos, como o BDNF (Fator Neurotrófico Derivado do Cérebro), têm sido associadas à menor eficácia terapêutica e à necessidade de estratégias farmacológicas mais complexas[69].

Do ponto de vista clínico e translacional, o estudo dos fatores epigenéticos na DRT abre perspectivas relevantes para o desenvolvimento de biomarcadores de estratificação clínica e para intervenções mais personalizadas. Estratégias que visem modular vias epigenéticas — direta ou indiretamente —, seja por intervenções farmacológicas ou psicossociais, têm sido propostas como abordagens complementares no manejo da DRT[70-72].

2.4 FATORES AMBIENTAIS EM DRT

A DRT não pode ser compreendida exclusivamente a partir de fatores biológicos ou genéticos, uma vez que aspectos ambientais exercem papel central na modulação da vulnerabilidade individual, na expressão clínica do transtorno e na resposta terapêutica[68]. Evidências consistentes indicam que exposições ambientais adversas, especialmente quando persistentes ou ocorridas precocemente no curso do desenvolvimento, estão associadas a trajetórias mais graves, recorrentes e menos responsivas do TDM[74].

As ACEs englobam diferentes formas de abuso, negligência e disfunção familiar ocorridas durante a infância e adolescência e constituem um dos mais bem estabelecidos fatores de risco ambientais para psicopatologia na vida adulta[75]. Estudos observacionais e meta-análises demonstram que indivíduos expostos a múltiplas adversidades precoces apresentam maior probabilidade de desenvolver depressão crônica ou resistente ao tratamento, além de maior comprometimento funcional[32-34].

Do ponto de vista neurobiológico, a exposição precoce ao estresse tem sido associada a alterações duradouras em sistemas centrais envolvidos na regulação do humor e da resposta ao estresse, incluindo o eixo HHA, neurotransmissão monoaminérgica e vias inflamatórias[35,36]. Tais alterações podem persistir ao longo da vida adulta, criando um estado de vulnerabilidade biológica que favorece maior gravidade depressiva, menor resiliência ao estresse e resposta terapêutica menos favorável[76-79].

Entretanto, a presença de adversidades ambientais não explica, de forma isolada, a heterogeneidade observada nos quadros de DRT. Evidências contemporâneas apontam que o impacto do ambiente é profundamente modulado por fatores genéticos e epigenéticos, configurando um modelo de interação gene–ambiente[80]. Nesse contexto, indivíduos com determinadas vulnerabilidades biológicas podem apresentar maior sensibilidade aos efeitos deletérios do estresse, enquanto outros demonstram maior capacidade adaptativa diante de exposições semelhantes[81].

Além do trauma e do estresse ao longo da vida, a adesão ao tratamento representa um aspecto ambiental frequentemente subestimado na avaliação da DRT[82]. A baixa adesão terapêutica é comum em pacientes com TDM e constitui uma causa relevante de pseudo-resistência, situação em que a ausência de resposta clínica não reflete necessariamente ineficácia farmacológica, mas sim uso irregular, interrupção precoce ou doses inadequadas das medicações prescritas[82]. Fatores como efeitos adversos, crenças negativas em relação ao tratamento, estigma, dificuldades cognitivas, sintomas depressivos persistentes e barreiras psicossociais influenciam significativamente a adesão[83].

Nesse sentido, a avaliação sistemática da adesão ao tratamento é fundamental tanto na prática clínica quanto em estudos sobre DRT, permitindo diferenciar resistência verdadeira de pseudo-resistência. A incorporação da adesão como variável ambiental relevante contribui para uma interpretação mais precisa dos desfechos clínicos e reforça a necessidade de abordagens terapêuticas integradas, que associem intervenções farmacológicas a estratégias psicoeducativas, acompanhamento longitudinal e fortalecimento do vínculo terapêutico[84].

3. OBJETIVOS

3.1 OBJETIVO GERAL

Avaliar, de forma multidimensional, a contribuição de variantes genéticas do *MTHFR*, mecanismos epigenéticos, características clínicas e fatores psicossociais no TDM, investigando suas associações com gravidade clínica, recorrência, risco de suicídio, comprometimento funcional e complexidade terapêutica em pacientes com e sem DRT.

3.2 OBJETIVOS ESPECÍFICOS

1. Revisar sistematicamente a literatura científica acerca da associação entre variantes do gene *MTHFR* 677C>T (rs1801133) e 1298A>C (rs1801131) e DRT, com ênfase em implicações clínicas e potenciais contribuições para a psiquiatria de precisão;

2. Realizar a tradução, adaptação transcultural e validação da escala *Massachusetts General Hospital Antidepressant Treatment Response Questionnaire* (MGH-ATRQ) para o português brasileiro, visando à padronização da avaliação da resposta antidepressiva no contexto clínico nacional;

3. Analisar a influência de ACEs e adesão ao tratamento antidepressivo na expressão clínica e funcional da DRT;

4. Investigar a associação entre a atividade enzimática predita da MTHFR e características clínicas do TDM, incluindo gravidade sintomatológica, número de episódios depressivos ao longo da vida, presença de tratamento resistente, risco de comportamento suicida e uso de estratégias farmacológicas de maior complexidade;

5. Avaliar o impacto funcional associado à redução da atividade enzimática da MTHFR, considerando medidas de funcionalidade e incapacidade no contexto do TDM com e sem DRT;

6. Investigar o potencial translacional de um programa educacional baseado no modelo *Training of Trainers* (ToT) para a disseminação do conhecimento sobre mecanismos epigenéticos e interação gene–ambiente no TDM, visando à capacitação de profissionais de saúde.

4. METODOLOGIA

4.1 ARTIGO 1

Revisão sistemática sobre as variantes genéticas 677C>T e 1298 A>C do *MTHFR* e DRT.

4.1.1 Cadastro

Esta revisão sistemática foi conduzida de acordo com as diretrizes do *Preferred Reporting Items for Systematic Reviews and Meta-Analyses* (PRISMA)[85]. O protocolo do estudo foi previamente registrado no *International Prospective Register of Ongoing Systematic Reviews* (PROSPERO)[86], sob o número de registro CRD42024612628, disponível em: http://www.crd.york.ac.uk/PROSPERO/

A lista de verificação (*checklist*) PRISMA correspondente ao presente estudo foi disponibilizada como material suplementar na plataforma Figshare (http://doi.org/10.6084/m9.figshare.2869087).

4.1.2 Critérios de elegibilidade

O delineamento do estudo foi estruturado com base no modelo PECOT[87] (*Population, Exposure, Comparator, Outcome, Time*) , conforme descrito a seguir:

a) População: adultos diagnosticados com Transtorno Depressivo Maior (TDM);

b) Exposição: variantes genéticas do *MTHFR* 677C>T e 1298A>C;

c) Comparação: adultos com TDM sem DRT portadores das variantes *MTHFR* 677C>T e/ou 1298A>C;

d) Desfecho: associação entre a presença das variantes *MTHFR* 677C>T e 1298A>C e a ocorrência de DRT;

e) Tempo/delineamento: estudos transversais, caso-controle, de coorte e ensaios clínicos.

Foram incluídos artigos completos que atendessem aos seguintes critérios:

a) Estudos originais, independentemente do ano de publicação;

b) Participantes adultos (≥ 18 anos), de ambos os sexos, com diagnóstico de TDM;

c) Análise das variantes genéticas *MTHFR* 677C>T e/ou 1298A>C e sua associação com DRT.

Os critérios de exclusão contemplaram estudos que:

a) Foram conduzidos em modelos animais;

b) Investigaram transtornos depressivos secundários a outras condições médicas ou ao uso de medicamentos;

c) Consistiam em revisões sistemáticas, meta-análises ou relatos de caso;

d) Incluíam exclusivamente adolescentes (menores de 18 anos);

e) Não estavam redigidos nos idiomas inglês, português ou espanhol.

4.1.3 Fontes de dados

As buscas foram realizadas de forma independente em bases de dados eletrônicas internacionais, incluindo PubMed (Public MEDLINE), APA PsycINFO, *Web of Science Core Collection, Excerpta Medica Database* (EMBASE) e a *Cochrane Library*, desde o início das bases até dezembro de 2024.

Os critérios de elegibilidade foram aplicados com o objetivo de identificar todos os estudos potencialmente relevantes.

Os descritores foram definidos com base no vocabulário controlado do *Medical Subject Headings* (MeSH)[88] e incluíram as seguintes combinações: *major depressive disorder* AND methylenetetrahydrofolate reductase (MTHFR) OR variantes 677C>T e 1298A>C (termos de busca adicionais: C677T [rs1801133] OR A1298C [rs1801131]) AND *treatment resistant*, excluindo estudos em animais e revisões sistemáticas.

4.1.4 Extração e síntese dos dados

Duas autoras independentes (LMV e NJE) avaliaram os artigos quanto à elegibilidade. Eventuais discordâncias foram resolvidas por consenso entre as avaliadoras e, quando necessário, discutidas com o grupo de pesquisa, respeitando rigorosamente os critérios de inclusão e exclusão previamente definidos.

O instrumento de extração de dados incluiu as seguintes informações: título do estudo, autores, objetivo principal, país de coleta dos dados, tamanho da amostra, idade média dos participantes (ou informações correlatas), instrumentos utilizados para avaliação diagnóstica e análise de biomarcadores genéticos, principais desfechos, limitações e pontos fortes de cada estudo incluído (com base na discussão apresentada pelos autores originais e na análise independente dos autores do presente manuscrito), além das conclusões.

4.1.5 Avaliação do risco de viés

A avaliação da qualidade metodológica e do risco de viés foi realizada por meio da ferramenta

Critical Appraisal Tool for Analytical Cross-Sectional Studies, desenvolvida pelo Joanna Briggs Institute[89]. A análise de risco de viés foi conduzida utilizando o software *Review Manager 5*[90], com os resultados apresentados em formato gráfico.

Para cada critério avaliado, foi atribuída uma classificação de risco (baixo, alto ou incerto), acompanhada de uma descrição textual fundamentando o julgamento com base no delineamento, metodologia ou observações específicas de cada estudo. Os itens avaliados incluíram:

a) critérios claramente definidos para inclusão da amostra;

b) descrição detalhada dos participantes e do contexto do estudo;

c) mensuração válida e confiável da exposição;

d) avaliação das condições por meio de critérios objetivos e padronizados;

e) identificação de fatores de confusão;

f) estratégias para controle de fatores de confusão;

g) mensuração válida e confiável dos desfechos;

h) adequação da análise estatística.

4.2 ARTIGO 2

Tradução transcultural, adaptação e validação do *Massachussetts General Hospital Antidepressant Treatment Response Questionnaire* (MGH-ATRQ)[91] para o português brasileiro.

4.2.1 Delineamento do estudo

O presente estudo consistiu em um processo de tradução transcultural, adaptação linguística e validação do MGH-ATRQ para a língua portuguesa do Brasil. Trata-se de um estudo metodológico, observacional e transversal, desenvolvido com o objetivo de disponibilizar uma versão culturalmente adaptada e clinicamente válida do instrumento para avaliação de resposta e resistência ao tratamento antidepressivo no TDM.

O MGH-ATRQ é um questionário de autorrelato que avalia resistência ao tratamento no TDM, definindo como ensaio antidepressivo válido o uso de um antidepressivo por, no mínimo, seis semanas em dose adequada. O instrumento também fornece critérios operacionais específicos para que o entrevistador questione o paciente quanto ao uso de dose adequada para os antidepressivos mais comumente utilizados.

4.2.2 Tradução transcultural e adaptação linguística

O processo de tradução transcultural e adaptação do MGH-ATRQ seguiu as seguintes etapas metodológicas padronizadas para adaptação de instrumentos psicométricos[92]:

1. Tradução inicial: duas traduções independentes do inglês para o português foram realizadas por dois tradutores bilíngues, cuja língua materna era o português (versões T1 e T2);

2. Síntese das traduções: as versões T1 e T2 foram comparadas e sintetizadas em uma única versão consensual em português (T12), com a mediação de um pesquisador médico, permitindo o esclarecimento de divergências semânticas e conceituais;

3. Retrotradução: a versão T12 foi retrotraduzida para o inglês por dois tradutores bilíngues independentes, cuja língua materna era o inglês (versões BT1 e BT2). Em seguida, essas versões foram sintetizadas em uma versão única (BT12) por um especialista com formação tanto na área de saúde bem como linguística;

4. Pré-teste: a versão pré-final do MGH-ATRQ em português brasileiro foi aplicada em uma amostra piloto de 30 indivíduos, com o objetivo de avaliar compreensão, clareza e aceitabilidade dos itens;

5. Avaliação pelo autor original: as seis versões do instrumento (T1, T2, T12, BT1, BT2 e BT12) foram enviadas ao autor do instrumento original, que autorizou formalmente o início do processo de validação da versão brasileira;

6. Validação clínica: a versão final do MGH-ATRQ em português foi aplicada em uma amostra clínica de 156 pacientes com TDM, sendo comparada tanto com os critérios operacionais do próprio instrumento quanto com a definição padrão de DRT baseada em prontuário médico.

4.2.3 Recrutamento dos participantes e critérios de elegibilidade

Os participantes foram recrutados em duas clínicas privadas localizadas na cidade de Londrina, Paraná, no período de julho de 2022 a dezembro de 2024.

Foram incluídos indivíduos ambulatoriais que preenchiam os seguintes critérios:

a) Diagnóstico de TDM, sem sintomas psicóticos, conforme critérios do *Diagnostic and Statistical Manual of Mental Disorders* – 5ª edição (DSM-5-TR)[93], avaliado por meio da *Structured Clinical Interview for DSM-5* (SCID-5)[94], traduzida e adaptada para o português;

b) Diagnóstico compatível com a Classificação Internacional de Doenças – 11ª edição (CID-

11)[95];

c) Idade entre 18 e 65 anos, de ambos os sexos.

Os critérios de exclusão foram:

a) Déficit cognitivo que impedisse a adequada compreensão do termo de consentimento ou dos instrumentos aplicados;

b) Transtorno depressivo secundário a outra condição médica;

c) Transtorno depressivo induzido por substâncias ou medicamentos.

4.2.4 Aspectos éticos

O protocolo do estudo foi registrado no Registro Brasileiro de Ensaios Clínicos (ReBEC)[96], sob o número RBR-3yt263y, e aprovado pelo Comitê de Ética em Pesquisa da Universidade Estadual de Londrina (CAAE 03628120900005231) – ANEXO 1.

Todos os participantes receberam explicações detalhadas sobre os objetivos e procedimentos do estudo e forneceram consentimento informado eletrônico (APÊNDICE A), em conformidade com os princípios da Declaração de Helsinque. Foi garantido o direito de retirada a qualquer momento, sem prejuízo ao tratamento, bem como o anonimato e a confidencialidade das informações.

4.2.5 Cálculo do tamanho amostral

O tamanho amostral de 156 participantes foi estimado com base na fórmula descrita no *Sample Size Calculation Guide*[97], considerando sensibilidade de 0,90, especificidade de 0,90, prevalência estimada de DRT de 30% entre indivíduos com TDM e largura máxima aceitável de 0,123 para o intervalo de confiança de 95%.

4.2.6 Avaliação sociodemográfica

Todos os participantes foram avaliados por meio de um questionário semiestruturado para coleta de dados sociodemográficos e clínicos, incluindo idade, escolaridade, situação ocupacional, estado civil e presença de comorbidades clínicas.

4.2.7 Avaliação do tratamento psicofarmacológico e definição de DRT

O tratamento psicofarmacológico foi avaliado por meio do MGH-ATRQ, assim como a percepção

subjetiva de melhora dos participantes. Com base no instrumento, os pacientes foram classificados como portadores de DRT quando relataram redução de sintomas igual ou inferior a 49% após dois ensaios antidepressivos adequados para o episódio depressivo atual, ou como não resistentes quando relataram redução de 50% ou mais após um ou dois ensaios adequados.

Para fins comparativos, também foi utilizada a definição padrão de DRT baseada em prontuário médico, considerando falha em alcançar melhora clínica significativa (≥50%) após dois tratamentos antidepressivos em dose e duração adequadas.

4.2.8 Avaliação da gravidade da depressão

A gravidade dos sintomas depressivos foi avaliada por meio da *Hamilton Depression Rating Scale* de 17 itens ($HDRS_{17}$)[98], validada e adaptada para a população brasileira[99].

4.2.9 Avaliação do comprometimento funcional

O comprometimento funcional foi avaliado por meio da *Sheehan Disability Scale* (SDS)[100,], instrumento de autorrelato que avalia prejuízos nos domínios trabalho/escola, vida social e vida familiar/responsabilidades domésticas, em escala analógica de 0 a 10. O instrumento inclui ainda dois itens adicionais que avaliam dias perdidos e dias subprodutivos na semana anterior.

4.2.10 Avaliação da adesão ao tratamento

A adesão ao tratamento farmacológico foi avaliada por meio da *Medication Adherence Rating Scale* (MARS)[101], composta por dez itens de autorrelato que investigam comportamentos e atitudes em relação ao uso de medicação.

4.2.11 Avaliação de experiências adversas na infância

A exposição a estressores e traumas na infância foi avaliada por meio do *Adverse Childhood Experiences Questionnaire* (ACE)[102,103], instrumento padronizado composto por dez itens que investigam experiências de abuso, negligência e disfunção familiar ocorridas antes dos 18 anos. Cada resposta afirmativa recebe um ponto, resultando em escore total de 0 a 10, sendo que escores mais elevados indicam maior carga de adversidade precoce.

O instrumento de coleta se encontra no Apêndice C.

4.2.12 Análise estatística

As variáveis quantitativas foram descritas por meio de médias e desvios-padrão, enquanto as variáveis qualitativas foram apresentadas em frequências absolutas e relativas.

Para a comparação de variáveis quantitativas entre os grupos (DRT definida pelos critérios padrão e DRT definida pelo MGH-ATRQ), foram utilizados o teste t de Student ou o teste de Wilcoxon, conforme a distribuição dos dados. As variáveis qualitativas foram comparadas por meio do teste do qui-quadrado ou do teste exato de Fisher.

O nível de significância adotado foi de 5% ($p < 0,05$). Para a validação do MGH ATRQ em relação aos critérios padrão, foram calculados acurácia, coeficiente kappa, sensibilidade, especificidade, valor preditivo positivo e valor preditivo negativo.

Todas as análises estatísticas foram realizadas utilizando o software R[104].

4.3 ARTIGO 3

Variantes genéticas e expressão do gene *MTHFR* associadas à gravidade de sintomas, experiências adversas na infância e DRT em TDM.

4.3.1 Delineamento do estudo e cenário

Trata-se de um estudo observacional transversal, conduzido com uma amostra de conveniência composta por 78 pacientes adultos em acompanhamento psiquiátrico ambulatorial de rotina em duas clínicas privadas localizadas no município de Londrina, Paraná, no período de 2023 a 2025. O objetivo do estudo foi investigar se a atividade enzimática predita da MTHFR está associada à gravidade clínica, à DRT e a desfechos funcionais em indivíduos com TDM.

4.3.2 Participantes e procedimentos

Foram elegíveis para participação no estudo indivíduos que atendessem aos seguintes critérios:

a) Idade igual ou superior a 18 anos;

b) Diagnóstico de TDM conforme os critérios do DSM-5[93], confirmado por psiquiatra por meio da SCID-5[94], versão traduzida e adaptada para o português;

c) Disponibilidade de testes genéticos para as variantes do gene *MTHFR* em prontuário médico.

Foram excluídos pacientes com diagnóstico de transtorno bipolar, transtornos psicóticos ou transtornos neurocognitivos. As informações sociodemográficas e clínicas foram obtidas por meio

de entrevistas estruturadas e revisão de prontuários médicos.

4.3.3 Considerações éticas

O protocolo do estudo foi registrado no ReBec[96], sob o número RBR-3yt263y, e aprovado pelo Comitê de Ética em Pesquisa da Universidade Estadual de Londrina (CAAE 03628120900005231) – ANEXO 1. Todos os participantes elegíveis receberam informações detalhadas sobre o estudo e forneceram consentimento eletrônico (APÊNDICE A), de acordo com os princípios da Declaração de Helsinque. Foi garantido o direito de desistência a qualquer momento, sem prejuízo do tratamento, bem como a confidencialidade e o anonimato dos dados.

4.3.4 Genotipagem e predição da atividade enzimática da MTHFR

A extração de DNA genômico foi realizada a partir de amostras de sangue periférico ou saliva, conforme registros médicos. A genotipagem concentrou-se em duas variantes funcionais do gene *MTHFR*: 677C>T e 1298A>C. Os genótipos foram determinados por métodos baseados na reação em cadeia da polimerase (PCR), utilizando sondas específicas para alelos.

A atividade enzimática predita da MTHFR foi estimada com base no impacto funcional combinado das variantes 677C>T e 1298A>C, de acordo com modelos previamente validados na literatura. A partir dessa estimativa, os participantes foram classificados em dois grupos: atividade enzimática preservada (>50%) ou atividade enzimática reduzida (≤50%), refletindo a atividade residual estimada da enzima em relação ao genótipo selvagem [50,104].

4.3.5 Avaliações clínicas

O diagnóstico de TDM foi estabelecido por meio da SCID-5, eixo I, versão clínica, traduzida e validada para o português[94].

A gravidade dos sintomas depressivos foi avaliada por meio da $HDRS_{17}$, validada para a população brasileira[98,99].

A adesão ao tratamento medicamentoso foi avaliada por meio da MARS[101,102], instrumento de autorrelato validado para o português. Informações adicionais referentes ao histórico de tratamento, número de episódios depressivos prévios, tentativas de suicídio, comorbidades psiquiátricas e farmacoterapia atual foram obtidas a partir de entrevista clínica e revisão de prontuários médicos.

4.3.6 Avaliação funcional

O comprometimento funcional foi avaliado por meio da SDS[100], que mensura prejuízos nos domínios trabalho/escola, vida social e vida familiar/responsabilidades domésticas. Cada domínio é pontuado em uma escala analógica de 0 a 10, em que 0 representa ausência de prejuízo funcional e 10 o maior grau de comprometimento. A escala inclui ainda dois itens adicionais que avaliam dias perdidos de produtividade e dias com produtividade reduzida na semana anterior à avaliação.

4.3.7 Histórico de Experiências Adversas na Infância

As ACEs foram avaliadas por meio do Questionário ACE, traduzido e validado para o português[103]. O instrumento avalia a exposição, antes dos 18 anos, a dez tipos de adversidades, incluindo abuso físico, sexual e emocional, negligência física e emocional, tentativa de suicídio no domicílio, conflito parental, separação ou divórcio dos pais, uso problemático de álcool por cuidadores, presença de transtornos mentais em familiares e encarceramento de membro do domicílio. Cada resposta afirmativa corresponde a um ponto, resultando em escore total que varia de 0 a 10, sendo escores mais elevados indicativos de maior exposição a adversidades precoces.

4.3.8 Definição de DRT

A DRT foi definida de acordo com critérios clínicos padronizados[6,43], caracterizados pela resposta inadequada a pelo menos dois ensaios antidepressivos prévios, em doses e duração adequadas, conforme documentação em prontuário médico.

O instrumento de coleta pode ser acessado no Apêndice C.

4.3.9 Análise estatística

As variáveis contínuas foram descritas por meio de médias e desvios-padrão, enquanto as variáveis categóricas foram apresentadas como frequências absolutas e relativas. As comparações entre os grupos com atividade enzimática preservada e reduzida da MTHFR foram realizadas utilizando o teste t de Student ou o teste de Mann–Whitney para variáveis contínuas, e o teste do qui-quadrado ou o teste exato de Fisher para variáveis categóricas, conforme apropriado.

Considerando a correlação observada entre os escores da $HDRS_{17}$ e os escores de ACEs, foi ajustado um modelo de regressão linear incluindo essas variáveis, bem como o status de DRT e a atividade enzimática predita da MTHFR. Quando aplicável, foram calculadas razões de chances (odds ratios) com intervalos de confiança de 95%. O nível de significância adotado foi de 5% ($p <$

0,05). As análises estatísticas foram realizadas utilizando o software R[104].

4.4 ARTIGO 4

Treinamento de profissionais de saúde em epigenética do TDM.

4.4.1 Delineamento do estudo e modelo ToT (*Training of Trainers*)

O presente estudo adotou um delineamento educacional-intervencional baseado no modelo Training of Trainers (ToT)[105], com o objetivo de avaliar a efetividade de um programa de capacitação em epigenética do TDM voltado a profissionais de saúde.

O módulo Epigenética do Transtorno Depressivo Maior integrou um programa educacional mais amplo, denominado EduPrev – Educar para Prevenir em Saúde Mental, desenvolvido com o objetivo de capacitar profissionais da saúde para a promoção da saúde mental, prevenção de transtornos psiquiátricos e redução de fatores de risco ao longo do ciclo de vida. O EduPrev foi estruturado como um programa multiprofissional, com abordagem psicoeducacional baseada em evidências, contemplando diferentes eixos temáticos relacionados à saúde mental, incluindo fatores biológicos, psicossociais, ambientais e de estilo de vida. Dentro desse contexto, o módulo de epigenética foi concebido como um componente formativo específico, voltado à compreensão dos mecanismos epigenéticos envolvidos no TDM e à aplicação desse conhecimento na prática clínica e comunitária, alinhando-se aos princípios do modelo ToT e à proposta translacional do programa.

O modelo ToT é uma estratégia de formação que visa à multiplicação do conhecimento por meio do desenvolvimento de competências pedagógicas e técnicas em participantes previamente capacitados, que passam a atuar como agentes disseminadores em suas comunidades de atuação profissional[106].

O programa fundamentou-se em uma abordagem de educação ativa - *learning by doing*[107]- na qual os participantes desenvolveram competências práticas e teóricas para compreender e transmitir conceitos relacionados à interação entre fatores genéticos, epigenéticos e ambientais na vulnerabilidade aos transtornos depressivos. A capacitação incluiu acesso a materiais educacionais digitais (*eBook*), aulas online síncronas ministradas por docentes e tutores especializados, além de atividades práticas orientadas.

O módulo foi ministrado por uma equipe docente multidisciplinar, composta por profissionais com *expertises* complementares em psiquiatria clínica, epigenética e farmacogenética, desenvolvimento humano e experiências adversas na infância. Essa composição interdisciplinar foi

intencionalmente estruturada para integrar fundamentos teóricos e aplicação prática, alinhando-se ao objetivo do modelo Training of Trainers de transferência de competências e disseminação do conhecimento em contextos reais de cuidado em saúde mental. A iniciativa educacional seguiu princípios éticos aplicáveis à pesquisa educacional, com participação voluntária e sem coleta de dados pessoais identificáveis.

O modelo ToT foi implementado com um grupo de 47 profissionais de saúde da comunidade local de Londrina, Paraná, incluindo médicos de família, enfermeiros, psicólogos, assistentes sociais e nutricionistas. Ao final do programa, foi aplicada uma avaliação com a elaboração de relatórios descritivos sobre o desenvolvimento e a disseminação das competências relacionadas à epigenética da depressão pelos alunos bem como relatos de experiências trazidos nas aulas subsequentes do curso.

4.4.2 Aprendizagem baseada em casos (*Case-Based Learning* – CBL)

O programa educacional incorporou a metodologia de aprendizagem baseada em casos (*Case-Based Learning* – CBL), amplamente utilizada na formação em saúde por favorecer o desenvolvimento do raciocínio clínico, da tomada de decisão e da integração entre teoria e prática[108,109]. Essa abordagem utiliza cenários clínicos reais ou simulados para estimular o pensamento crítico e a aplicação ativa do conhecimento em situações complexas.

Essa estrutura permitiu aos participantes analisar, de forma integrada, como fatores ambientais — em especial as ACEs — podem modificar a expressão gênica por meio de mecanismos epigenéticos, como metilação do DNA, modificações de histonas e regulação por RNAs não codificantes, contribuindo para maior vulnerabilidade a episódios depressivos.

4.4.3 Descrição do caso clínico utilizado no CBL

O caso clínico apresentado envolveu uma mulher de 42 anos, fisioterapeuta, desempregada, casada e mãe de uma criança de três anos, com histórico de cinco anos de sintomas ansiosos e depressivos. O quadro teve início após o falecimento do avô paterno, com surgimento de crises de pânico. Houve resposta parcial inicial ao uso de duloxetina, interrompida por efeitos adversos, incluindo redução da libido e ganho ponderal. Posteriormente, apresentou episódio de depressão pós-parto, com nova tentativa de tratamento farmacológico associada à psicoterapia, novamente com resposta incompleta e intolerância medicamentosa.

A paciente relatou agravamento progressivo dos sintomas nos seis meses anteriores à avaliação, incluindo fadiga, humor deprimido persistente, irritabilidade, isolamento social e sintomas

somáticos de ansiedade, sem ideação suicida ou tentativas prévias. Entre os antecedentes clínicos, destacaram-se diabetes mellitus tipo I e hipotireoidismo secundário à tireoidite de Hashimoto.

A história pessoal revelou exposição precoce a adversidades, incluindo negligência emocional, disfunção familiar e abuso emocional, avaliadas por meio do Questionário ACE, instrumento previamente desenvolvido e validado para a população brasileira. Pontuações elevadas nesse instrumento são associadas a maior risco de transtornos mentais ao longo da vida, com padrão dose–resposta bem estabelecido.

4.4.4 Avaliação genética, epigenética e implicações terapêuticas

No contexto do caso clínico, foi realizado teste farmacogenético, que identificou variantes do gene *MTHFR* 677C>T e 1298A>C, associadas à redução da atividade enzimática da MTHFR. A paciente apresentou atividade enzimática estimada em 60% abaixo do esperado, condição previamente associada a maior risco de transtornos psiquiátricos, recorrência depressiva e gravidade sintomatológica.

Evidências indicam que a redução da atividade da enzima MTHFR pode comprometer o metabolismo do folato, aumentar níveis de homocisteína e interferir em processos de metilação, especialmente quando combinada à exposição a traumas precoces. A interação entre variantes genéticas do *MTHFR* e ACEs tem sido associada a maior recorrência de episódios depressivos, maior gravidade clínica e menor resposta terapêutica.

Com base nos achados farmacogenéticos, foi instituída estratégia terapêutica personalizada, com a associação de L-metilfolato (15 mg/dia) ao escitalopram (15 mg/dia), resultando em melhora funcional significativa, retomada de atividades sociais, prática de exercícios físicos e melhora das relações familiares.

4.4.5 Objetivos educacionais e implicações translacionais

O caso clínico foi utilizado como ferramenta pedagógica para que os participantes do programa ToT compreendessem, de forma integrada, os efeitos do estresse precoce e crônico sobre a expressão gênica e a vulnerabilidade à depressão, mediada por mecanismos epigenéticos. A discussão estimulou a formulação de estratégias de intervenção e o desenvolvimento de ações de psicoeducação voltadas à comunidade.

Ao final do módulo Epigenética da Depressão, os participantes receberam questões estruturadas para discussão, centradas em fatores de risco, adesão ao tratamento, variantes

genéticas e cuidado integrativo em depressão. Essas atividades tiveram como objetivo estimular a reflexão crítica, o raciocínio clínico e a tradução de conceitos epigenéticos para a prática clínica e comunitária. Os materiais educacionais desenvolvidos no âmbito do programa foram disponibilizados publicamente na plataforma Figshare (DOI: https://doi.org/10.6084/m9.figshare.30068353), assegurando transparência e reprodutibilidade do conteúdo formativo.

O processo formativo foi delineado para que, ao término do módulo, os participantes fossem capazes de: (i) identificar fatores clínicos e psicossociais centrais envolvidos no transtorno depressivo maior, incluindo comorbidades médicas e psicossociais; (ii) avaliar estratégias para aprimorar a adesão ao tratamento farmacológico; (iii) compreender o impacto de variantes genéticas — particularmente aquelas relacionadas ao metabolismo do folato — na resposta antidepressiva; e (iv) aplicar um modelo de cuidado integrativo, incorporando dimensões biológicas, psicológicas e sociais no manejo da depressão. A consolidação do conhecimento ocorreu por meio de um processo de aprendizagem reflexiva, no qual os participantes foram incentivados a aplicar os conteúdos discutidos em seus próprios contextos clínicos ou comunitários.

A avaliação pós-treinamento foi realizada de forma qualitativa e processual, ao longo das sessões subsequentes do programa de capacitação, nas quais os participantes compartilharam casos reais, experiências profissionais e desafios encontrados na prática, promovendo troca de saberes e aprofundamento translacional.

5. RESULTADOS E DISCUSSÃO

Os resultados e discussão serão apresentados no formato de quatro artigos científicos sendo um de revisão sistemática e três originais, que foram submetidos a periódicos científicos.

Artigo 1 – "*Systematic Review of Methylenetetrahydrofolate reductase (MTHFR) 677 C>T and 1298 A>C Variants and Treatment-Resistant Depression: Insights for Precision Psychiatry*", submetido e aceito para publicação no Jornal *Complex Psychiatry* - publicação especializada, revisada por pares, com foco nos fundamentos biológicos e genéticos dos transtornos psiquiátricos, apresentando comunicação rápida de pesquisas científicas. No período de 2024–2025, apresentou um fator de impacto reconhecido (por exemplo, na faixa de aproximadamente 1,5 a 2,6, variando conforme o ano específico de referência). A revista abrange temas como neurogenômica, biologia de sistemas e neuropsicofarmacologia molecular, sendo publicada pela Karger Publishers. Referência: Complex Psychiatry 2026;12:9–26 (DOI:10.1159/000548757).

Artigo 2 – "*Validation and adaptation of the Brazilian version of the Massachusetts General Hospital Treatment Response Questionnaire*", submetido no Jornal *Archives of Health Sciences*, Qualis CAPES B1.

Artigo 3 – "*MTHFR Genetic Variants and Expression Linked to Depression Severity, Adverse Childhood Experiences, and Treatment-Resistant Depression in Major Depressive Disorder*", submetido no Jornal *Acta Psychiatrica Scandinavica*, com fator de impacto 4.9 (2 anos)/ 5.6 (5 anos), Qualis CAPES A1.

Artigo 4 – " "*Training Healthcare Professionals in the Epigenetics of Depression: A Training of Trainers and Case-Based Learning Experience*", submetido e sob revisão no Jornal *Epigenetics Reports*,(Taylor & Francis) - periódico mais recente, de acesso aberto, com foco na publicação rápida de comunicações científicas em formato curto. Por se tratar de uma publicação recentemente estabelecida, seu fator de impacto de dois anos ainda não consta nos relatórios de classificação, embora o periódico tenha sido concebido para a rápida disseminação de pesquisas de alta qualidade.

5.1 ARTIGO 1

Systematic Review of Methylenetetrahydrofolate reductase (MTHFR) 677C>T and 1298A>C *Variants and Treatment-Resistant Depression: Insights for Precision Psychiatry*

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Short Title: Systematic Review: *MTHFR* Variants and Treatment-Resistant Depression

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Keywords: Methylenetetrahydrofolate Reductase; Treatment-resistant depression; Major depressive disorders; Genetic Polymorphism; Genomics

Abstract

Introduction: Treatment-resistant depression (TRD) is a major clinical challenge, affecting approximately one-third of patients with major depressive disorder (MDD). Genetic factors, particularly genetic variants in the *MTHFR* gene, have been implicated in antidepressant response variability. The *MTHFR* 677C>T (rs1801133) and 1298A>C (rs1801131) variants are associated with altered folate metabolism, increased homocysteine levels, and potential disruptions in neurotransmitter synthesis, which may contribute to TRD. This systematic review aims to evaluate the association between *MTHFR* variants and TRD, exploring their potential role in predicting antidepressant response and guiding personalized treatment strategies.

Methods: A systematic literature search was conducted following PRISMA guidelines (PROSPERO registration: CRD42024612628). Studies were included if they investigated *MTHFR* 677C>T and/or 1298 A>C variants in adults with MDD and assessed their association with TRD.

Results: Seven studies met the inclusion criteria, and the findings indicate a potential link between *MTHFR* 677TT and 1298CC genotypes and an increased risk of TRD. However, conflicting evidence exists, as other studies found no significant effect of the *MTHFR* variants on treatment outcomes. Variability in study designs, definitions of TRD, and confounding factors such as dietary folate intake and comorbidities contribute to inconsistencies in findings.

Conclusion: While evidence suggests a role for *MTHFR* variants in TRD, heterogeneity among studies limits definitive conclusions. Future research should standardize TRD definitions, control for confounding factors, and explore the integration of genetic testing into clinical practice. L-methyl folate supplementation may represent a promising adjunctive strategy for MDD patients carrying *MTHFR* risk variants.

Introduction

Major depressive disorder (MDD) is a recurrent mental disorder with genetic and environmental interactions [1]. MDD is considered a multifactorial condition involving a complex interplay between genetic variants, environment, and disrupting epigenetic modifiers, which could affect clinical symptoms, such as age at illness onset, comorbidities, responsiveness to treatment, and other clinical variables [2].

The Sequenced Treatment Alternatives to Relieve Depression (STAR*D) clinical trial found that an estimated rate of 33.0% of depressed patients did not respond to four consecutive antidepressant treatments, considering adequate medication dosage and treatment duration, switching antidepressants, and the addition of adjunctive treatment [3]. Treatment-resistant depression (TRD) can be defined as a failure to respond to 2 or more antidepressant trials at a therapeutic dose and adequate duration [4]. There are many risk factors for TRD such as co-occurring medical and psychiatric conditions, non-adherence to treatment, unpleasant side effects, drug interactions, wrong diagnosis, environmental effects, and genes [5,6]. The *MTHFR* gene is located on the short arm of chromosome 1 (chr1p36.3) in humans and contains several missense genetic variants that cause altered amino acid in the 5,10-methylenetetrahydrofolate reductase (MTHFR), an enzyme responsible for the catalyzing the conversion of folic acid to L-methylfolate. Among them, rs1801133 (677 C>T) and rs1801131 (1298 A>C) are the most widely studied [7]. The rs1801133 (677C>T) is located in the exon 4 and consists of a transition of cytosine to thymine in the position 677, leading to an alanine to valine substitution in the 222 amino acid of the protein [8,9]. The rs1801131 (1298A>C) variant involves a transition of adenine by cytosine at nucleotide position 1298, resulting in a glutamate-to-alanine amino acid change. These variants have been associated with decreased MTHFR enzymatic activity and elevated homocysteine levels [7]. The result is a less efficient production of L-methylfolate, which is crucial for various biochemical processes, including the synthesis of neurotransmitters. Furthermore, they have been associated with reduced antidepressant response in patients with MDD [10].

Individuals who carry an MTHFR enzymatic activity reduction through *MTHFR* genetic variants are associated with an increased risk of MDD [11] through folate deficit and increased homocysteine levels that could affect the synthesis of neurotransmitters and dysfunction of the limbic–cortical–striatal–pallidal–thalamic circuits [12,13]. Also, research findings suggested the possibility of folate use in MDD treatment and prevention [14].

Thus, deepening the understanding of the relationship between carrying the *MTHFR* 677C>T and 1298A>C variants and TRD is crucial for identifying personalized therapeutic approaches and improving clinical outcomes. This systematic review aimed to examine whether patients with MDD carrying *MTHFR* 677C>T and 1298A>C variants are associated with TRD.

Methods

Literature search

This systematic review was carried out following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Statement guidelines [15] and it was registered in the International Prospective Register of Ongoing Systematic Reviews (PROSPERO, registration number: CRD42024612628) available on http://www.crd.york.ac.uk/PROSPERO/. The PRISMA Checklist for this study is provided as supplementary material and is also available on Figshare at http://doi.org/10.6084/m9.figshare.2869087 .

Eligibility Criteria

The PECOT framework was used to structure the study design, as follows: a) Population: adults with MDD, b) Exposure: *MTHFR* 677C>T and 1298A>C variants, c) Comparison: adults without TRD with *MTHFR* 677C>T and 1298A>C variants, d) Outcome: TRD could be associated with the presence of *MTHFR* 677C>T and 1298A>C variants, e) Time: cross-sectional, case-control, cohort, and clinical trial.

We included full articles satisfying the following criteria: 1) original studies, regardless of publication date; 2) MDD research subjects were men and women (based on self-report), with a

minimum age of 18 years old; 3) analysis of *MTHFR* 677C>T and/or 1298A>C variants and their association with TRD.

The exclusion criteria were based on the following Medical Subject Heading (MeSH) categories “not” and: 1) carried out in “animals”; 2) depressive disorder due to other medical conditions or medications; 3) systematic review, meta-analysis or case report; 4) adolescents (under 18 years old), and 5) studies not written in English, Portuguese, or Spanish languages.

Data Sources

Two researchers independently conducted a comprehensive search of primary papers published up to December 2024 through the following online databases: Embase (n= 15), PubMed (n= 9), and Web of Science (n= 8), using eligibility criteria to capture all potential studies.

Keywords were determined through MeSH thesaurus, as follows: major depressive disorder AND Methylenetetrahydrofolate reductase (*MTHFR*) OR 677C>T and 1298A>C variants (search terms Screening for *MTHFR* variants: OR C677T (rs1801133) OR A1298C (rs1801131) variants) AND treatment resistant AND Not animal studies AND Not systematic review.

Data extraction and Synthesis

Two independent authors - LMV and NJE - examined each article for eligibility and results were compared between authors. Any disagreements were resolved in consensus and checked with the research group regarding inclusion and exclusion criteria.

The extraction instrument contained the following information: title, authors, primary aim, country of data collection, sample size, the mean age of participants (or any related information), instruments/tools to access diagnostic criteria and genetic biomarkers, main outcomes, limitations/strengths of each selected included study (based on the discussion presented by the authors of the original study and the independent analysis of first and second authors of this actual manuscript), and conclusions.

Risk of Bias Assessment

The quality and risk assessment were conducted using the Critical Appraisal Tool for Analytical Cross-Sectional Studies developed by the Joanna Briggs Institute [16]. The 'Risk of Bias' analysis was implemented in Review Manager 5 [17], with results displayed in graphical format. For each criterion, the judgment (Low risk, High risk, or Unclear risk of bias) was accompanied by a descriptive text box outlining the underlying design, methodology, or observations that informed the judgment.

The evaluated items included: (a) clearly defined criteria for inclusion in the sample; (b) detailed descriptions of study subjects and settings; (c) valid and reliable measurement of exposure; (d) measurement of conditions using objective and standardized criteria; (e) identification of confounding factors; (f) strategies for addressing confounding factors; (g) valid and reliable measurement of outcomes; and (h) appropriate statistical analysis. Consensus was achieved in all cases, and no studies were excluded from the review based on the assessed risk of bias.

Results

Search results

A description of the study selection is presented in Figure 1. Out of the 23 studies found in the literature search, 12 duplicates were removed. Additional to the 11 studies left screened through databases (Embase, PubMed/Medline and Web of Science), 2 other studies were identified from websites and 2 from citation searching comprising 15 reviewed studies. A total of 8 studies were excluded for failing to fulfill the specified criteria: 2 studies with wrong population (children and adolescents), 1 study with incompatible language, 4 studies with incompatible study type (4 reviews, and 2 case reports), and 1 study with wrong outcome. Thus, 7 studies were eligible to examine the impact of *MTHFR* genetic variants and TRD.

The reviewers achieved a 95.6% agreement, as indicated by Cohen's Kappa Coefficient of 0.849, demonstrating substantial inter-rater reliability. Selected studies were cross-sectional (n=2), case-control (n=3), and clinical trials (n=2), and their main characteristics are described in Table 1.

Variability in TRD definition across studies was substantial and is presented in Table 2. It is worth of note that most of the studies used the Hamilton Depression Rating Scale (HDRS) [18] as the standardized instrument to evaluate depressive state and most studies considered participants to be treatment resistant after one antidepressant trial without sufficient response.

Studies reported associations between *MTHFR* genetic variants and the risk of developing MDD. For example, a study carried out in the United States of America (USA) reported that the *MTHFR* 677C>T variant is associated with TRD in MDD patients [19] and a study in the Netherlands found that the *MTHFR* 677C>T genotype was more prevalent among MDD patients than controls, with higher homocysteine and lower vitamin B6 levels in the group of depressed individuals [20]. Similarly, a study in Italy reported that women carrying the *MTHFR* 1298A>C variant exhibited greater vulnerability to MDD, although no significant effects were observed in terms of treatment response [21]. A British cohort study also identified an association between the 677C>T genotype and increased risk of MDD [22].

In contrast, studies focusing on treatment outcomes yielded mixed findings. A study in the USA found that patients with TRD carrying the *MTHFR* 677C>T genotype had a high prevalence of the variant [19]. Another study identified a borderline association between the 1298A>C variant and remission status in patients receiving selective serotonin reuptake inhibitors (SSRIs) [23]. However, some trials found no significant effect of the 677C>T variant on treatment response [24]. Two studies from China [25,26] also yielded divergent findings regarding *MTHFR* haplotypes and treatment resistance.

Studies that investigated *MTHFR* variants in relation to the development of MDD but did not assess their role in TRD were excluded from the present study, such as Lewis et al. [22]. This

study did not meet our inclusion criteria, which specifically focused on *MTHFR* variants in the context of TRD.

The distribution of allele frequencies of *MTHFR* genetic variants in each study is presented in Table 3. The *MTHFR* 677C>T variant showed notable differences in allele and genotype distributions across studies conducted in the USA, Europe, and Asia. The frequency of the T allele varied between 27.4% and 53.5%, demonstrating substantial genetic variability among populations. Higher T allele frequencies were observed in studies conducted in the USA [19,24] and Italy [21], ranging from 42.0% to 53.5%, which suggests a potentially increased genetic predisposition in these populations. In contrast, the lowest T allele frequency (27.4%) was reported in Chinese control groups [25], while Chinese MDD patients had a slightly higher frequency (40.9%), indicating potential ethnic and regional differences in genetic susceptibility to MDD. The European studies [20,21] reported intermediate frequencies, with T allele frequencies in MDD patients ranging from 32.8% to 44.7%, reinforcing the hypothesis of population-specific genetic predispositions.

Bias Analysis

Figures 2 and 3 summarized the risk of bias across the studies included in this systematic review.

Most studies exhibited a low risk of bias in domains such as "Criteria for inclusion in the sample clearly defined," "Study subjects and setting described in detail," and "Outcomes measured validly and reliably". However, "Confounding factors identified" and "Strategies to deal with confounding factors" showed a significant proportion of studies with high or unclear risks. This suggests that confounding variables were not consistently acknowledged or addressed, potentially affecting the reliability of conclusions.

Moreover, "Appropriate statistical analysis" was predominantly low risk, though a minority of studies presented unclear or high risks, highlighting variability in the application of statistical methods.

Figure 3 presented a study-specific summary of the risk of bias across the same domains, highlighting heterogeneity in methodological quality. Studies by Duprey et al. [19] and Yuan et al. [25] have some unclear risks (yellow) and high risks (red), particularly in addressing confounding factors and applying appropriate statistical methods. In contrast, studies such as Nielsen et al. [21] and Lok et al. [20] exhibited consistently low risks (green) across all domains, reflecting robust methodologies and comprehensive reporting practices. The inconsistent handling of confounding factors, evident in a study [24], raised concerns about the comparability of findings and the potential influence of unmeasured variables.

Discussion

Detecting *MTHFR* variants (677C>T and 1298A>C) reveals metabolic issues, such as high homocysteine and low folate, which may affect depression, supporting the unfavorable effects of some antidepressants. Some mechanisms that may contribute to risk of TRD could be by reduced MTHFR enzyme activity, potentially influenced by gene variants like *MTHFR* 677C>T and 1298A>C, along with elevated homocysteine and decreased folate levels which resulted in decreased levels of S-adenosyl methionine (SAM) in cerebrospinal fluid; meanwhile, SAM as a methyl donor for serotonin (5-HT) and catecholamine pathways exerted significant antidepressant effects, which are crucial for mood regulation [27]. Therefore, *MTHFR* gene variants may affect TRD risk by altering folate and homocysteine metabolism, impacting neurotransmitter pathways and antidepressant efficacy. More research is necessary to clarify these relationships.

Other mechanism that individuals carrying *MTHFR* gene variants can undergo is the risk for folate deficiency, which has correlations with depression, and impacts DNA methylation patterns. Epigenetic mechanisms, such as DNA methylation, non-coding RNA regulation, and histone

modifications, are involved in these processes [28] Additionally, other evidence supports the role of epigenetic modification through DNA methylation by adding a methyl group to cytosine residues in the DNA, which may result in a change in gene expression, underlying the development, presentation, and progression of MDD [29]. Epigenetic alteration mechanisms are mediators of psychiatric disorders; thus, they could influence MDD patients who have TRD. In fact, the *MTHFR* gene variants have also been associated with a diminished level of global DNA methylation [30]. Figure 4 illustrates a proposed biochemical and epigenetic pathway linking *MTHFR* gene variants to TRD.

The findings of this review highlight the potential for integrating genetic testing into clinical practice to tailor TRD strategies. Identifying *MTHFR* gene variants, particularly 677C>T and 1298A>C, can provide valuable insights into a patient's metabolic profile, enabling clinicians to predict treatment responses and optimize therapeutic interventions. Precision psychiatry approaches that incorporate genetic testing could recommend adjunctive therapies, such as L-methyl folate supplementation [31], to address these deficiencies and enhance treatment outcomes.

Furthermore, integrating genetic insights with clinical assessments may help identify patient subgroups at higher risk of TRD. This stratification could guide early intervention strategies, reducing the trial-and-error approach in antidepressant prescriptions. For example, patients with homozygous *MTHFR* variants may benefit from early supplementation with active folate, potentially preventing the escalation to TRD. By addressing the underlying metabolic imbalances associated with these genetic variants, clinicians could achieve more personalized care, improving remission rates and reducing the burden of TRD on patients and healthcare systems.

This review supports associations of reduced folate and elevated homocysteine concentration that could be considered risk factors for TRD. The use of folate treatment for MDD depends on various factors including inflammation, metabolic disorders, and stress. Therefore, we need to establish the profiles of patients with MDD who could benefit from supplemental use of L-

methylfolate [31]. Screening for *MTHFR* variants may help identify MDD patients who would benefit from adjunctive use of active folate, but health professionals should also consider multiple inherited and environmental factors affecting patients' response to L-methylfolate [32]. A study found that added adjunctive treatment with L-methylfolate 15 mg per day may be indicated for patients with MDD who have a partial response or non-response to antidepressants [33].

The use of L-methyl folate as an adjunct to antidepressant therapy for the treatment of MDD is known to be evidence-supported [34], considered second line recommendation for mild-moderate MDD treatment according to CANMAT guidelines [4]. However, to date, it has not been determined whether L-methylfolate supplementation varies according to sociodemographic factors, disease severity, or treatment stage [35]. Adjunctive L-methylfolate prescription appears to be well tolerated, with gastrointestinal and somatic adverse events being the most common [36]. After prescribing L-methylfolate, it is essential to conduct clinical monitoring if this supplement is used in combination with other medications due to the risk of potential drug interactions [37]. A limitation of the studies is that they do not evaluate the long-term efficacy of L-methylfolate.

According to Nielsen *et al.* [21], the low penetrance of *MTHFR* variations is a barrier to the use of L-methylfolate as an augmentation strategy in the treatment of major depressive disorder. Several variables, such as concomitant medication use, dietary habits, smoking, physical conditions, and sociodemographic characteristics, may have a stronger effect on folate variations. Lewis *et al.* [22] hypothesizes that public health L-methylfolate replacement could reduce the prevalence of depression in the population.

The study carried out by Nanri *et al.* [38] demonstrated that only carriers of the CA haplotype of these two *MTHFR* genetic variants (677C>T and 1298A>C) in the male subgroup, but not in the female subgroup, showed a relationship between higher serum folate concentrations and reduced depressive symptoms. This may be due to higher folate concentrations and lower homocysteine levels in women, which compensate for the reduced activity of the *MTHFR* enzyme, making it difficult to detect the relationship between this genetic variant and antidepressant efficacy. Shelton *et al.* [39]

evaluated the use of L-methylfolate in patients with depression who did not respond to SSRIs and found that body mass index (BMI) ≥ 30 kg/m^2 and increased inflammatory markers, such as interleukin (IL)-6, IL-8, C-reactive protein (CRP), tumor necrosis factor (TNF)-α, and leptin, positively influence the response. These data support the idea that the decision to prescribe L-methylfolate should not only consider the issue of *MTHFR* gene variants but also individual issues, as several factors are involved in folate metabolism.

Regarding drug interactions, L-methylfolate may reduce the plasma levels of certain anticonvulsants, including phenytoin, carbamazepine, fosphenytoin, phenobarbital, primidone, or valproate. Likewise, certain medications reduce serum folate levels, such as anticonvulsants, cholestyramine, colestipol, cycloserine, aminopterin, methotrexate, sulfasalazine, pyrimethamine, trianerene, trimethoprim, isotretinoin, fluoxetine, nonsteroidal anti-inflammatory drugs (NSAIDs), methylprednisolone, and pentamine, as well as alcohol and tobacco use. These cases may require higher doses of l-methylfolate [34]. The literature suggests that L-methylfolate replacement should be performed at a dosage of 15 mg / d. According to Kandler [35], in terms of costs, it can reach U$75 for 90 capsules of L-methylfolate 15 mg.

The bias analysis highlighted that while most studies have strengths in defining samples, measuring outcomes, and describing methodologies, significant weaknesses persist in addressing confounding factors. These biases could introduce variability in effect estimates and limit the generalizability of findings. Future research should prioritize rigorous identification and mitigation of confounding to enhance methodological quality. Moreover, it is crucial to consider how specific confounders may mechanistically interact with *MTHFR* variants to influence the pathophysiology of depression and treatment response. For instance, dietary folate intake can modulate the effects of *MTHFR* variants on homocysteine metabolism. Similarly, serum folate, vitamin B12, and inflammatory markers (e.g., IL-6, TNF-α, CRP) have been implicated in both depression severity and antidepressant resistance and may act as mediators or effect modifiers [39,40].

Future studies should implement stratified analyses that account for relevant clinical and biological variables to better delineate the role of *MTHFR* variants in TRD. Stratification involves dividing participants into subgroups based on shared characteristics to examine whether the effect of *MTHFR* variants (e.g., 677C>T or 1298A>C genotypes) varies across specific contexts. For instance, participants may be stratified by serum folate or vitamin B12 levels, as low levels of these nutrients can exacerbate the functional impact of *MTHFR* variants on homocysteine metabolism, thereby enhancing TRD risk [38, 40]. Assessing associations within nutrient-deficient *versus* nutrient-replete subgroups may reveal genotype–nutrient interactions that are masked in unstratified analyses [22].

Similarly, stratification by treatment adherence—measured using standardized tools such as the Medication Adherence Rating Scale (MARS) or pharmacy refill histories—can help separate pharmacogenetic non-response from non-adherence-related pseudo-resistance [41]. Inadequate adherence has been shown to mimic TRD and is a critical confounder if not accounted for [42]. Psychiatric and medical comorbidities, such as anxiety disorders, substance use disorders, obesity, and inflammatory conditions, should also be systematically assessed through structured interviews (e.g., Structured Clinical Interview for DSM Disorders - SCID), and included as covariates or as independent strata, given their known effects on antidepressant response [43].

Moreover, inflammatory markers CRP, IL-6, and TNF-α can serve as mechanistic stratifiers, particularly since *MTHFR*-related metabolic dysregulation may contribute to neuroinflammation, which itself is implicated in antidepressant resistance [33,39]. Integrating these biomarkers into stratified analyses could elucidate shared metabolic–inflammatory pathways underlying poor treatment response.

To operationalize these approaches, future research should adopt multi-modal phenotyping protocols, including blood collection for genotyping *MTHFR* variants, nutrient and cytokine profiling, validated adherence assessments, and comprehensive psychiatric evaluation. Analytically, researchers should conduct interaction tests and multivariable regressions within each stratum to

assess potential effect modification and mediation. Additionally, Mendelian randomization may be employed using *MTHFR* variants as instrumental variables to assess the causal role of homocysteine in TRD pathogenesis, minimizing confounding and reverse causality biases [44,45]. These rigorous methodologies will advance the field toward precision psychiatry by clarifying the contexts in which *MTHFR* genotypes influence treatment outcomes and by identifying high-yield targets for personalized interventions such as L-methylfolate supplementation.

In addition, one significant drawback of the current evidence base—and of this review—is the blurring of conceptual boundaries between studies investigating genetic susceptibility to MDD and those examining pharmacogenetic predictors of treatment resistance. Several studies included in our synthesis report associations between *MTHFR* variants and the incidence or recurrence of MDD (e.g., increased prevalence of the 677C>T genotype in depressed versus non-depressed populations) [20,22], rather than specifically evaluating response to antidepressant treatment or fulfilling a clear definition of TRD. Although these findings provide valuable insights into the pathophysiology of MDD and the neurobiological role of folate metabolism, they do not directly inform clinical decisions regarding pharmacotherapy or the prediction of non-response. Conversely, studies that rigorously define TRD (e.g., failure to achieve remission after two or more adequate antidepressant trials) and assess *MTHFR* genotype in relation to treatment outcomes offer more directly applicable insights for precision psychiatry [19,33].

The studies reviewed defined TRD using different criteria, from nonresponse to one or two antidepressants to broader assessments. Treatment response in MDD patients was typically defined as at least a 50.0% reduction in symptoms recorded by standardized scales - HDRS or the Montgomery-Asberg Depression Rating Scale (MADRS) following antidepressant therapy. Duprey [16] defined TRD as a lack of significant improvement in depressive symptoms despite at least two adequate trials of different antidepressant medications, where an "adequate" trial typically involves appropriate dosing, sufficient duration (usually 6–8 weeks), and proper adherence to the prescribed regimen. Jamerson et al. [23] considered treatment resistance a MADRS end score above 15 after a 12-week acute treatment period. Lok et al. [20] examined recurrence rates in

euthymic individuals with at least two prior MDD episodes within the preceding five years. Mischoulon et al [24] measured treatment response as a reduction of 50.0% or more on the HDRS after antidepressant medication. Nielsen et al [21] defined TRD as the lack of response to a minimum of two adequate trials of different antidepressants. In Shen et al. [25], clinical response was monitored through intra-individual changes in the HDRS score over six weeks. Yuan et al. [25] assessed treatment response after six weeks of antidepressant therapy, also based on alterations in the HDRS.

The World Federation of Societies of Biological Psychiatry (WFSBP) Guidelines for the biological treatment of unipolar depressive disorders references European Medicines Agency to define TRD as a lack of response measured by less than 50.0% symptom reduction documented through standardized scales (e.g. HDRS or MADRS) after two pharmacological trials with proper dosage, and adequate duration (implicitly 6-8 weeks for each trial), and with adequate affirmation of treatment adherence [46]. According to the National Institute for Health and Care Excellence (NICE), TRD is defined as a major depressive episode that has not responded to at least two different antidepressants, prescribed at adequate dose and duration, during the current episode [47]. The US Food and Drug Administration (FDA) proposes a very similar definition of TRD in the context of clinical trials [48], and the CANMAT guidelines [4], despite acknowledging TRD as a failure to respond to 2 or more antidepressant trials at a therapeutic dose and adequate duration, proposes the term Difficult-to-Treat Depression (DTD) to extend the TRD concept and to better characterize this situation. In the DTD model, the therapeutic focus shifts away from symptom remission towards symptom management, prioritizing outcomes such as functioning and quality of life. Therefore, DTD is described as persistent depression that has failed numerous standard treatments - in contrast to the minimum of 2 antidepressants defined by TRD.

Staging models for TRD have also been proposed in an attempt to accurately characterize this group of patients. The Thase and Rush Staging Model proposes that TRD can be classified in a continuum of 5 failed antidepressant trials, considering not only different antidepressant classes but also Electroconvulsive therapy (ECT) [49]. The Maudsley Staging Model (MSM) for TRD

integrates three core dimensions: (1) number of prior failed antidepressant treatments (1–5 points depending on how many trials were unsuccessful, with additional point(s) for failed augmentation strategies or ECT), (2) duration of the current depressive episode (1 point for ≤12 months; 2 for 13–24 months; and 3 for > 24 months), and (3) baseline symptom severity (scored from 1 for subsyndromal up to 5 for severe with psychotic features) [50]. The Massachusetts General Hospital Staging Model (MGH-s) [51] conceptualizes TRD as a continuous scale based on prior treatment failures with each unsuccessful antidepressant trial contributing one point, while a failure of ECT is weighted as equivalent to three antidepressant failures. The resulting score serves as a quantitative indicator of TRD severity.

In conclusion, a clear and consistent definition of TRD remains lacking. Although the term "response" refers to symptomatic improvement, it does not necessarily indicate the complete remission of symptoms or restoration of pre-morbid functioning [40]. Definite standardized criteria for TRD are crucial for much needed research results that can provide sufficient comparability and generalizability that would allow further advances. This lack of uniformity also complicates attempts at meta-analytical synthesis. Future investigations would greatly benefit from adopting standardized staging frameworks for TRD, such as those proposed by CANMAT, WFSBP, or the Maudsley Staging Model, which would allow more robust cross-study comparisons and facilitate replication.

Moreover, key contributors to TRD, such as chronic medical conditions, substance use, anxiety disorders, and personality disorders, were not consistently addressed in the studies reviewed. These gaps underscore the need for standardized research protocols to enhance the reliability and comparability of future findings. Altogether, the integration of genetic data with clinical assessments holds promise for identifying individuals at increased risk of TRD, facilitating earlier and more targeted therapeutic strategies. For example, individuals homozygous for *MTHFR* variants may benefit from early supplementation with L-methylfolate as a mean to mitigate TRD risks. Addressing genetically mediated metabolic disturbances may support a more personalized treatment, potentially improving clinical outcomes and reducing the burden of TRD.

A significant limitation of this systematic review is the absence of a meta-analysis, which limits the ability to quantitatively synthesize the findings from the included studies. This decision was determined due to the heterogeneity across studies, particularly regarding definitions and assessments of TRD, and drug treatment regimens.

Conclusion

This review highlights a potential association between the *MTHFR* 677C>T and 1298A>C genetic variants and TRD, emphasizing their role in folate metabolism, neurotransmitter synthesis, and therapeutic response. Incorporating genetic information into precision psychiatry may enhance treatment efficacy, with L-methylfolate supplementation offering potential benefits, particularly in individuals carrying the homozygous genotypes for these variants. All in all, it is crucial to distinguish the contribution of the MTHFR variants to MDD susceptibility from their influence on antidepressant treatment outcomes. Given the heterogeneity in study designs and TRD definitions, standardized methodologies are essential to enable robust meta-analyses and support the translation of findings into clinical practice. In summary, current evidence suggests that MTHFR variants may play a role in susceptibility to TRD, particularly within specific subpopulations. These associations, however, remain tentative and require validation in well-designed studies that apply standardized TRD definitions. Until such criteria are consistently adopted, the contribution of MTHFR variants to TRD should be considered as a possible, but not yet established, risk factor.

Statement of Ethics

A Statement of Ethics is not applicable because this study is based exclusively on published literature.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Data Availability Statement

The data that support the findings of this study are openly available in Figshare at https://doi.org/10.6084/m9.figshare.2869087, reference number [2869087].

Author Contributions

JBM: conceptualization of the work, analysis and interpretation, writing and reviewing the manuscript; CECO: analysis and interpretation, writing and reviewing the manuscript; DFA: data acquisition, analysis or interpretation; writing and reviewing the manuscript; LMV: data acquisition, analysis, writing the manuscript; NJE: data acquisition, analysis or interpretation, writing the manuscript; EMVR data acquisition, analysis or interpretation, writing and reviewing the manuscript; SOVN: conceptualization of the work, analysis and interpretation, writing and reviewing the manuscript.

All authors approved the final version of the manuscript and agreed to be responsible for all aspects of the work.

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Figure Legends

Fig. 1. Flow diagram of study selection.

Fig. 2. Risk of bias graph of included studies across multiple methodological domains. Each domain was represented as a percentage, indicating the proportion of studies that achieved a low, unclear, or high risk of bias.

Fig. 3. Risk of bias summary of methodological quality among the included studies.

Fig. 4. Proposed biochemical and epigenetic pathway linking *MTHFR* gene variants to treatment-resistant depression (TRD).

Variants in the *MTHFR* (677C>T and 1298A>C) lead to reduced enzymatic activity and impaired conversion of 5,10-methylenetetrahydrofolate (5,10-MTF) to 5-methyltetrahydrofolate (5-MTHF). This deficiency alters the methionine cycle, resulting in elevated homocysteine (Hcy) levels and a decreased S-adenosylmethionine (SAM) and S-adenosylhomocysteine (SAH) (SAM/SAH) ratio. These changes are associated with epigenetic dysregulation, including global DNA hypomethylation, altered histone acetylation, and abnormal methylation of neurotransmission-related genes. Multiple modulators (body mass index, folate intake, psychiatric comorbidities, and inflammation markers) interact with MTHFR activity, contributing to these alterations. The resulting dysregulation affects the expression of neuropsychiatrically relevant genes (e.g., those involved in neuroplasticity and mood regulation), ultimately leading to poor antidepressant response and persistent depressive symptoms characteristic of treatment-resistant depression.

Abbreviations: MTHFR: methylenetetrahydrofolate reductase; THF: tetrahydrofolate; 5,10-MTF: 5,10-methylenetetrahydrofolate; 5-MTHF: 5-methyltetrahydrofolate; Hcy: homocysteine; SAM: S-adenosylmethionine; SAH: S-adenosylhomocysteine.

Table 1. Characteristics of the selected studies used in the systematic review include population sample, type of assessment, methods, study design, results, limitations, and clinical practice.

Study	Population and Sample size (n)	Methods	Study design	Results	Limitations	Clinical Practice
Duprey, 2016 [19]	USA; N=29 cases of TRD Patients' characteristics are not available	● Genotyping of *MTHFR* 677 C>T.	Cross-sectional	● Seventy-six percent of TRD cases tested positive for the *MTHFR* 677 T>C T allele. ● Among the positive cases, 77% were heterozygous (CT), while 23% were homozygous (TT), yielding a prevalence ratio of 3.4:1. ● TRD patients have a 74% likelihood of carrying the *MTHFR* 677T>C variants.	● A small sample size is a limitation. Additionally, age, race, and ethnicity were not considered in the sample selection. ● The absence of a control group limits the analysis. Although it is hypothesized that the prevalence of the *MTHFR* mutation is higher in TRD compared to non-TRD and the general population, this assumption was not formally assessed. ● The specific classes of antidepressants to which patients were resistant are not reported.	Genotype-based treatment strategies are essential for TRD, given the high prevalence of the heterozygous *MTHFR* variant, which influences treatment decisions.
Jamerson et al., 2013 [23]	USA; N=106 controls. N=198 MDD patients. Only Caucasian with age >60y were included (mean age 67.6y; gender: 42.3% male/ 57.7% female).	● Genotyping was conducted for 15 genetic variants, including *MTHFR* 1298A>C and 677C>T. ● Logistic regression models were used to examine associations between genetic variants adjusting for relevant covariates.	Cross-sectional	● The *MTHFR* A1298C variant achieved a borderline significant association with remission status, where individuals with the AC genotype were more likely to be in remission compared to those with the AA genotype.	● A small sample size, which limited the power to identify genotype associations. ● It was based on a retrospective analysis of antidepressant treatment response, which may have been influenced by prior treatment success and medication tolerance. ● There was no serum measure of folate status, which would have aided in understanding the relationship between diet, folate metabolism genes, and depression.	Folate metabolism genes may play a key role in response to antidepressants *MTHFR* variant A1298C also has a significant effect on enzyme activity and individuals who were heterozygotes were more likely to be in remission.
Lok et al., 2014 [20]	United Kingdom; N=137 MDD patients (mean age 46.4y; Gender 26% female/ 74% male).	● Genotyping of *MTHFR* 677 C>T, and dichotomized into "T	Case-control	● The depressed state had higher Hcy and lower vitamin B6 than the remitted state of depression (euthymic)	● Treatment resistance was measured through episode recurrence – at least 2 episodes in the last five years.	MDD patients who were taking antidepressants and had higher Hcy and lower B6

	N= 76 controls (mean age 44.7y; Gender 33% female/ 66% male).	carriers" and "non T carriers" groups. . ● Propensity scores were used to correct for multiple confounders.		● *MTHFR* 677 C>T genotype was 45% more prevalent in MDD patients than in controls, but not statistically significant.	● Data on diet, vitamin, and other supplementations were not available at the time of sampling, potentially affecting results.	and B12 had more non-remitted depressive states.
Mischoulon et al., 2012 [24]	USA; N=224 MDD patients (mean age 39y; gender 52% female/ 48% male). The ethnic distribution was 83% Caucasian, 7% Black, 2% Hispanic, 1% Asian/Pacific Islander, 7% self-describing as other ethnic data.	● Genotyping was performed for *MTHFR* 1298A>C and 677C>T. ● Logistic regression and non-parametric tests were used to evaluate associations between genetic status and treatment response.	Open clinical trial	● The *MTHFR* 677C>T variant had no significant effect on plasma folate and homocysteine levels and did not significantly influence the antidepressant response.	● Insufficient power to detect differences with smaller effect sizes, which may not be clinically meaningful. ● Key findings are derived from an open-label treatment sample, making the results susceptible to placebo effects.	Individuals with the *MTHFR* 677C>T variant appear to have no added risk of non-response to SSRI antidepressants compared to those without the variant.
Nielsen et al., 2015 [21]	Italy; N=613 MDD patients (mean age 56.3y; gender 67.5% female / 32,5% male) TRD:389 (63,5%) and no-TRD: 224 (36,5%) N=463 controls (mean age 46.7y; gender: 55.5% female/ 44,5% male)	● Genotyping was performed for *MTHFR* 1298A>C and 677C>T. ● Linkage disequilibrium analysis and permutation tests were conducted for multiple testing corrections, while logistic regression was used to evaluate associations between variants and treatment response.	Case-control	● No found differences in genotype and allele distributions of *MTHFR* variants between MDD patients and controls, nor significant associations with treatment response. ● CC homozygotes (1298 A>C) were more frequent in female MDD patients, indicating a higher genetic risk for depression.	● Findings may be influenced by environmental confounding factors, which were minimized but not eliminated. ● Folate and homocysteine levels were not measured, preventing correlation with genetic and transcriptional data.	A greater vulnerability for MDD in women with *MTHFR* 1298 CC genotype together with a genetic vulnerability to develop depression. No significant effects with response to treatment. Several variables, such as medication, dietary intake, smoking, physical problems, and socio-demographic factors could have strong effects on folate variation.
Shen et al., 2014 [26]	China; N= 368 patients with MDD (mean age 51.4y; 75.5% female/ 54.5%	● Genotyping was performed for *MTHFR* 677C>T.	Case-control	● The T allele of the *MTHFR* 677 C>T variant has a significant association with MDD.	● There is a disequilibrium in age and gender between the case and control groups, which may affect the study's accuracy.	Individually, MHTFR 677 C>T variant is not associated with MDD; however, MDD is associated with the COMT

	male) N=219 controls (mean age 44.4y; 63.5 female/ 35.5 male)			• There was no association between gene variant and treatment response	• Although statistical analysis controlled for age and gender, a larger sample size is needed for more reliable results	Met/Val and MTHFR C/T genotypes.
Yuan et al., 2020 [25]	China; N=281 MDD patients (mean age 38.1y; 37% female, 63% male).	• Genotyping was performed for *MTHFR* 1298A>C and 677C>T. • Logistic regression was used to analyze interactions between genotypes, haplotypes, and factors such as gender and drug type in relation to treatment outcomes.	Open clinical trial	• Individually, the variants 677 C>T and 1298 A>C showed no significant association with response to antidepressant treatment. • The haplotypes C-A of 677 C>T and 1298 A>C were associated with better antidepressant effects in the whole group, and male or SNRI treated subgroup.	• The absence of a placebo control group makes it challenging to exclude the influence of non-pharmaceutical factors.	Genetic variants in homocysteine and lipid metabolism systems are associated with antidepressant response. Higher folate concentrations may enhance antidepressant efficacy, particularly in male patients with specific haplotypes

Abbreviations: TRD: Treatment-Resistant Depression; MDD: Major depressive disorder;; *MTHFR*: Methylenetetrahydrofolate reductase; MADRS: Montgomery-Asberg Depression Rating Scale; SSRI, Selective Serotonin Reuptake Inhibitor antidepressant; Hcy: Homocysteine; HDRS: Hamilton Depression Rating Scale; PCR; Polymerase chain reaction; COMT: catechol-O-methyltransferase; SNRI: Serotonin and Norepinephrine Reuptake Inhibitor antidepressant;

Table 2. Treatment Resistant Depression (TRD) definitions and its characteristics across studies.

Study	TRD definition	Standardized scales	Number of failed medication trials	Antidepressant class/ drug	Treatment duration	Observations
Duprey, 2016 [19]	Local service protocol for TRD - not described	DSM 5 - diagnostic criteria	Not reported	Not reported	Not reported	Compares the frequency of *MTHFR* 677C>T in TRD sample versus literature data on MDD
Jamerson et al., 2013 [23]	MADRS score > 15 after 12 weeks of antidepressant use	MADRS	One trial	SSRI/paroxetine, citalopram, fluoxetine, escitalopram, sertralina.	12 weeks	Evaluated 15 genetic variants, not only *MTHFR* 677C>T and 1298A>C
Lok et al., 2014 [20]	History of 2 depressive episodes in the last 5 years	SCID-I	One trial	Different classes - 64% of the sample were on SSRI use	Not reported	No clear associations, except for higher homocysteine and lower vitamin B_6 during the depressed state.
Mischoulon et al., 2012 [24]	Lack of treatment response was defined as less than 50% improvement in HDRS score compared to baseline.	HDRS	One trial	SSRI/fluoxetine	12 weeks	A subset of 52 subjects underwent fluoxetine treatment
Nielsen et al., 2015 [21]	Failure to respond to two or more adequate trials of two or more different classes of antidepressants and to an adequate trial of a tricyclic drug.	SCID-I	Two or more trials + 1 tricyclic drug trial	Tricyclic trial + various other classes of antidepressant	Not specified in the model used by the authors - Thase and Rush Staging Method; presumably, minimum time of 4-6 weeks	The Thase and Rush Staging Method only considers switching antidepressants but not combination and augmentation trials
Shen et al., 2014 [26]	Lack of treatment response was defined as less than 50% improvement in HDRS score compared to baseline and nonremitters if participants reported a HDRS score of 48 or higher at endpoint	HDRS	One trial	SSRI or SNRI or TCA or other antidepressant or combination of medication	6 weeks	No association between gene variants and treatment response
Yuan et al., 2020 [25]	Response was defined as a reduction of at least 50% in the HDRS total score after 6 weeks of treatment, while "remission" was defined as a total HDRS score ≤ 7 points after 8 weeks of treatment.	HDRS	One trial	SSRI or SNRI	6 weeks for response and 8 weeks for remission	Genetic variants in homocysteine and lipid metabolism systems are associated with antidepressant response, particularly for the interactions of certain genes with gender or drug type.

Abbreviations: TRD: Treatment Resistant Depression); DSM-5: Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition; *MTHFR*: Methylenetetrahydrofolate reductase; MDD: Major Depressive Disorders; MADRS: Montgomery-Asberg Depression Rating Scale; HDRS: Hamilton Depression Rating Scale; reaction; SCID-I: Structured Clinical Interview for DSM, 4th edition.

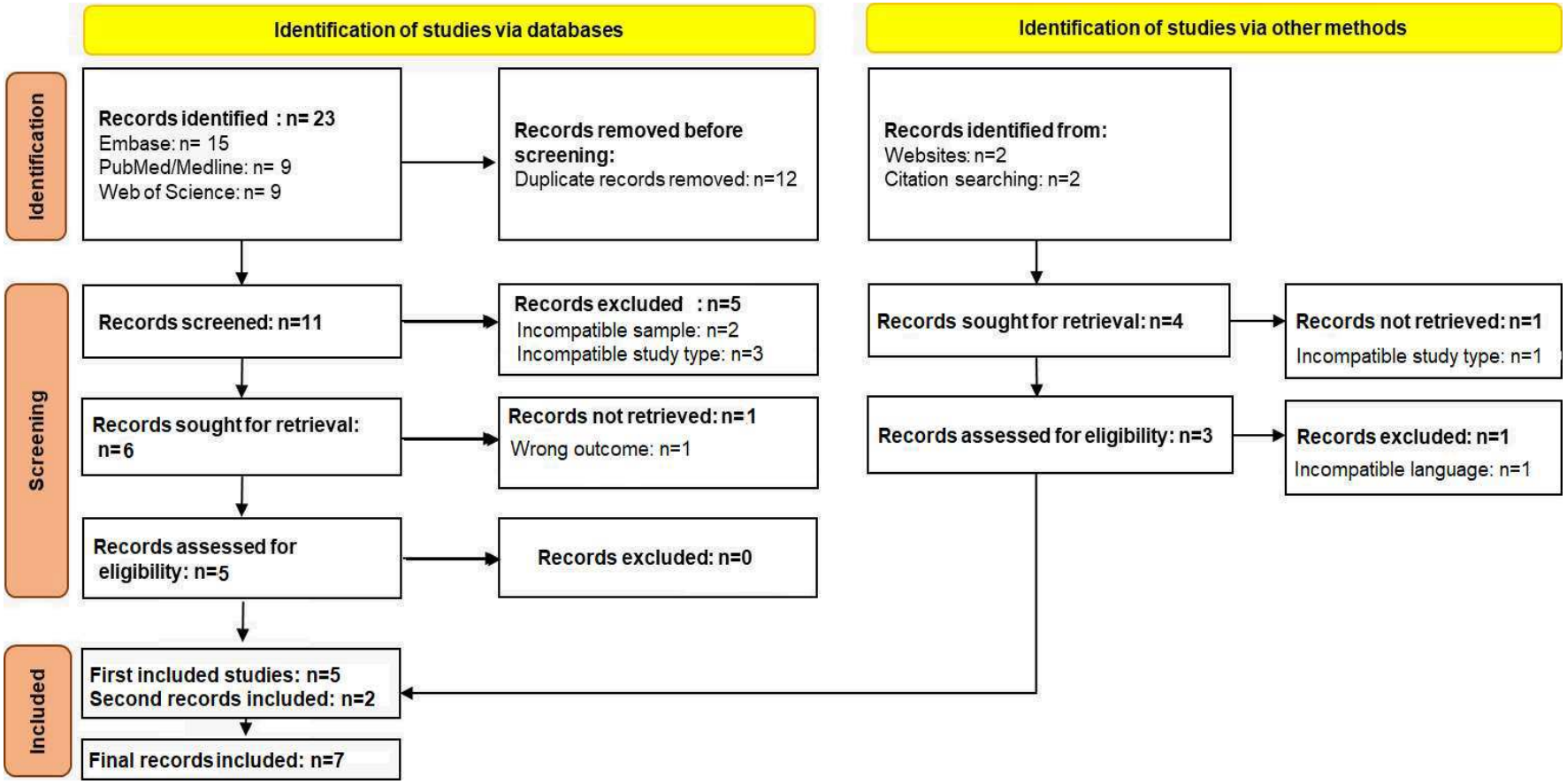
Table 3. Allele frequencies distribution of variants i*n MHTFR* (677 C>T and 1298 A>C) in each study.

Study	Population and Sample Size	rs1801133 (677 C>T)	rs1801131 (1298 A>C)
Duprey, 2016 [19]	USA; N=29 cases of MDD TRD	Genotype: • TT: 17.3% • CT: 58.6% • CC: 24.2% Allele frequency: • C: 46.5% / T: 53.5%	Not analyzed
Jamerson et al., 2013 [23]	USA; N=304 (106 controls and 198 MDD patients);	Genotype: • CC: 41.12% • CT: 46.38% • TT: 12.5% Allele Frequency: • C: 64.21% / T: 35.79%	Genotype: • AA: 47.02% • AC: 44.04% • CC: 8.94%. Allele Frequency: • A: 69.04% / C: 30.96%
Lok et al., 2014 [20]	United Kingdom; N=137 MDD patients N= 76 controls	Genotype in MDD: CC: 46,6% CT: 41,2% TT: 12.3%. Allele Frequency in MDD C: 67,2% T: 32,8% Genotype in controls: CC: 44,1% CT: 47,4% TT: 8,5%. Allele Frequency in controls C: 67,9% T: 32,1%	Not analyzed
Mischoulon et al., 2012 [24]	USA; N= 194 MDD patients The ethnic distribution was 83% Caucasian, 7% Black, 2% Hispanic, 1% Asian/Pacific Islander, 7% self-describing as other or not provide ethnic data	Genotype: • TT: 11.0% • TC: 47.0% • CC: 41.0% Allele frequency*: C: 71.5% / T: 28.5%	Not analyzed
Nielsen et al., 2015 [21]	Italy; N=613 MDD patients TRD:389 (63,5%) and no-TRD: 224 (36,5%) N=463 controls	Genotype in MDD: • CC: 31.0% • CT: 48.62% • TT: 20.4%. Allele Frequency in MDD • C: 55.3% / T: 44.7% Genotype in controls: • CC: 28.5% • CT: 50.0% • TT: 21.5%. Allele Frequency in controls • C: 53.5% / T: 46.5%	Genotype in MDD: • CC: 9.6% • AC: 42.4% • AA: 48.0%. Allele Frequency in MDD • C: 30.8% / A: 69.2% Genotype in controls: • CC: 7.3% • AC: 42.6% • AA: 50.1%. Allele Frequency in MDD • C: 28.6% / A: 71.4%
Shen et al., 2014 [26]	China; N = 368 patients with MDD	Genotype in MDD: • CC: 23.9% • CT: 70.4%	Not analyzed

	N = 219 controls	• TT: 5.7%. Allele Frequency in MDD • C: 59.1% / T: 40.9% Genotype in controls: • CC: 51.6% • CT: 41.6% • TT: 6.8%. Allele Frequency in controls • C: 72.4% / T: 27.4%	
Yuan et al., 2020 [25]	China; N=281 MDD patients	Genotype: • TT: 18.4% • TC: 49.3% • CC: 32.3% Allele frequency: • C: 58.0% / T: 42.0%	Genotype: • CC: 0.0% • AC: 32.4% • AA: 67.6%. Allele Frequency: • C: 16.2% / A: 83.2%

MDD: Major depressive disorder MTHFR: Methylenetetrahydrofolate reductase; All studies evaluated the Hardy-Weinberg equilibrium of variants, except Mischoulon et al 2012.

Figure 1


Identification of studies via databases
Identification of studies via other methods
Identification
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Embase: n= 15
PubMed/Medline: n= 9
Web of Science: n= 9
Records removed before screening:
Duplicate records removed: n=12
Records identified from:
Websites: n=2
Citation searching: n=2
Screening
Records screened: n=11
Records excluded : n=5
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Incompatible study type: n=3
Records sought for retrieval: n=4
Records not retrieved: n=1
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Records not retrieved: n=1
Wrong outcome: n=1
Records assessed for eligibility: n=3
Records excluded: n=1
Incompatible language: n=1
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Records excluded: n=0
Included
First included studies: n=5
Second records included: n=2
Final records included: n=7

Figure 2

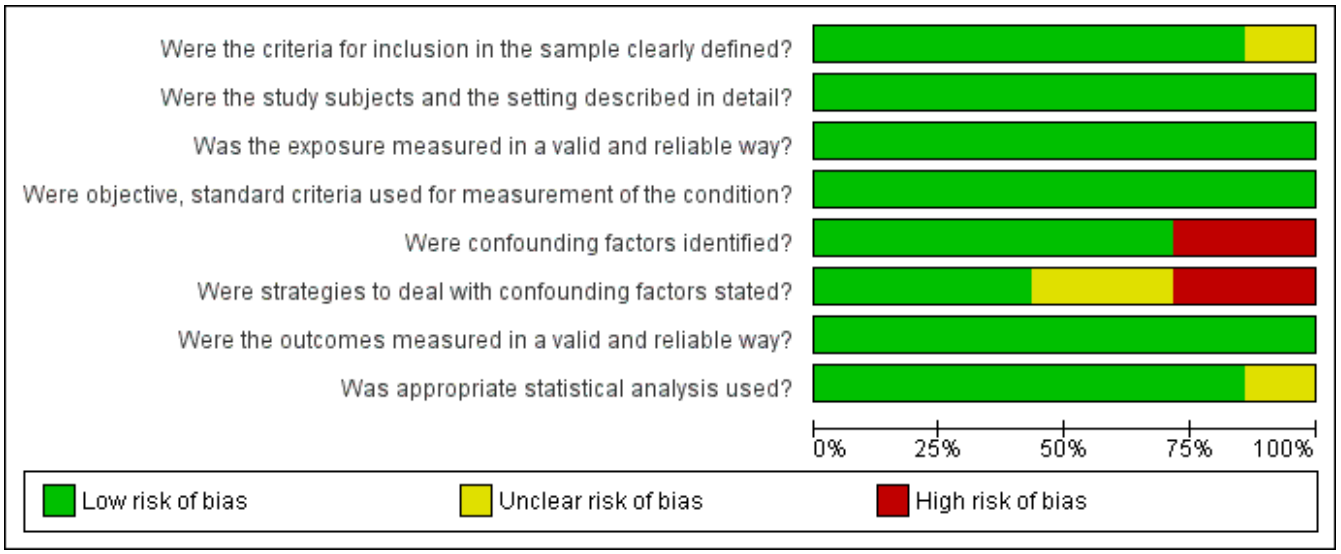
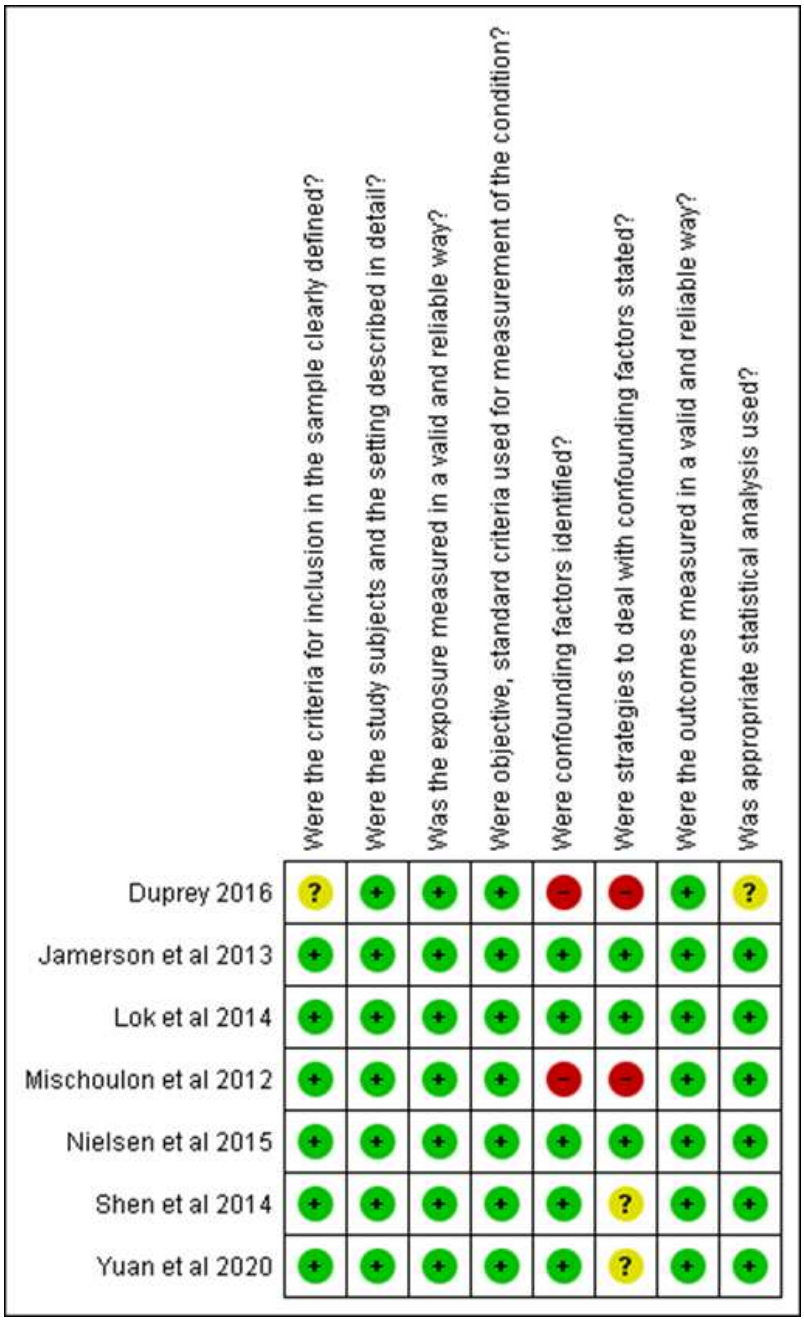

Were the criteria for inclusion in the sample clearly defined?
Were the study subjects and the setting described in detail?
Was the exposure measured in a valid and reliable way?
Were objective, standard criteria used for measurement of the condition?
Were confounding factors identified?
Were strategies to deal with confounding factors stated?
Were the outcomes measured in a valid and reliable way?
Was appropriate statistical analysis used?
0%
25%
50%
75%
100%
Low risk of bias
Unclear risk of bias
High risk of bias

Figure 3


Were the criteria for inclusion in the sample clearly defined?
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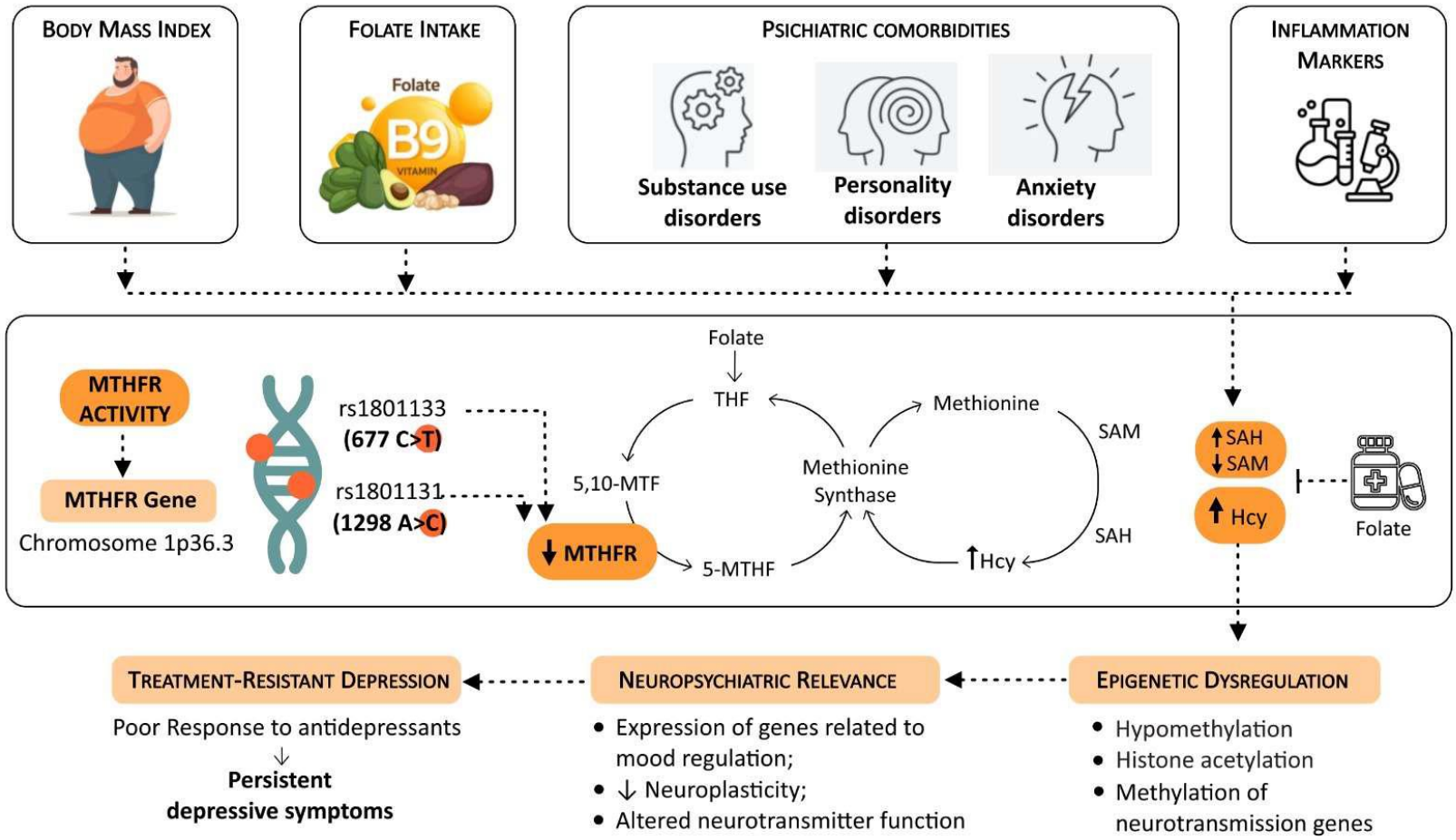
Were confounding factors identified?
Were strategies to deal with confounding factors stated?
Were the outcomes measured in a valid and reliable way?
Was appropriate statistical analysis used?
Duprey 2016
Jamerson et al 2013
Lok et al 2014
Mischoulon et al 2012
Nielsen et al 2015
Shen et al 2014
Yuan et al 2020

Figure 4



References
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Li L, et al., 2024 [28]
Shelton RC, et al., 2015 [39]
Cui L, et al., 2024 [52]

5.2 ARTIGO 2

Validation and adaptation of the Brazilian version of the Massachusetts General Hospital Treatment Response Questionnaire

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ABSTRACT

Introduction: Treatment-resistant depression (TRD) affects approximately one third of patients with major depressive disorder (MDD) and poses significant challenges in both clinical and research settings. The Massachusetts General Hospital Antidepressant Treatment Response Questionnaire (MGH-ATRQ) is a self-rated instrument developed to identify antidepressant treatment response and TRD cases.

Objective: To translate, culturally adapt, and validate the MGH-ATRQ for use in the Brazilian population.

Methods: The cross-cultural adaptation and validation process included translation, back-translation, development of a pre-final version, pretesting, and field testing in a clinical sample (n = 156). Diagnostic accuracy, Cohen's kappa coefficient, sensitivity, specificity, positive predictive value, and negative predictive value were calculated. Additional measures included the Hamilton Depression Rating Scale ($HDRS_{17}$), Medication Adherence Rating Scale (MARS), Adverse Childhood Experiences Questionnaire (ACE), and Sheehan Disability Scale (SDS) to assess convergent validity.

Results: The MGH-ATRQ accurately classified individuals as TRD compared with standard clinical criteria, demonstrating 88.89% sensitivity and 97.56% specificity. TRD cases showed greater depressive severity, higher functional impairment, lower medication adherence, and higher rates of adverse childhood experiences.

Conclusions: The MGH-ATRQ Brazilian Portuguese version is a valid instrument to detect patients with TRD and could be a useful tool to aid both clinical decision-making and the standardization of research protocols in MDD.

Keywords: Treatment Resistant Depression, Validation Study, Major Depressive Disorder, Refractory Depression.

List of abbreviations: TRD - Treatment-Resistant Depression, **MDD** - Major Depressive Disorder, **MGH-ATRQ** - Massachusetts General Hospital Antidepressant Treatment Response Questionnaire, **$HDRS^{17}$** - 17-item Hamilton Depression Rating Scale, **SDS** - Sheehan Disability Scale, **MARS** - Medication Adherence Rating Scale, **ACE** -Adverse Childhood Experiences, **DSM-5** - Diagnostic and Statistical Manual of Mental Disorders – Fifth Edition, **ICD-11** - International Classification of Diseases – 11th Edition, **SCID-5**: Structured Clinical Interview for DSM-5, **ReBec**:

Brazilian Registry of Clinical Trials, **UEL**: State University of Londrina, **PROAP**: Post-Graduation Support Program, **ROC** - Receiver Operating Characteristic, **SD**: Standard Deviation, **PR** - Paraná (Brazilian state abbreviation), **CAAE** – Ethical Appreciation Presentation Certificate, **BT** - Back Translation,

T1 / T2 / T12 - Translation versions of the questionnaire (initial and synthesized), **BT1 / BT2 / BT12** -Back-translation versions (initial and synthesized), **MDD-TRD**: Major Depressive Disorder with Treatment Resistance, **WHO** - World Health Organization, **R Core Team** - Group responsible for the R statistical software, **PROAP 2020** - Postgraduate Support Program (2020 edition).

1. INTRODUCTION

Major Depressive Disorder (MDD) is a very impairing and prevalent condition still in need for better treatment outcomes globally[1,2]. Moreover, a significant number of individuals with MDD who manage to get proper medical treatment will still not achieve sufficient clinical improvement, that is, will present treatment-resistant depression (TRD)[3].

Despite many definitions, TRD has been described as failure to respond to 2 or more antidepressant trials at a therapeutic dose and adequate duration[4], which seems to encompass 15-30% of all depressive episodes[5]. Also, TRD has been associated with many clinical characteristics, such as chronic and persistent symptoms of low mood, repeated depressive episodes, functional impairment, poor quality of life, suicide ideation and attempts and self-injurious behavior[6,7].

Among many challenges in assessing TRD, pseudo-resistance factors can contribute to a misleading situation of apparent resistance to antidepressant treatment, for instance, some individuals may report poor response to a specific antidepressant agent while not achieving proper use criteria in terms of therapeutic dosage and treatment duration[8].

More recently it has been suggested that measuring only response to pharmacological treatment would be an oversimplification to a complex scenario in TRD[9] and psychological and sociocultural factors must also be considered when evaluating MDD treatment response as well as psychiatric comorbidities and differential diagnoses that can contribute to poor response rates[10].

Research implications of TRD involve difficulties in a consensus for its definition and outcome measures that can be applied in a standardized manner so that research findings can be translated into clearer treatment guidelines[11,12].

In short, the need to determine whether a person has indeed engaged in one or more antidepressant trials for the minimum time and dosage needed to qualify their depression as TRD seems to be particularly important in both clinical and research settings[13]. Standardized self-rated scales such as the Massachusetts General Hospital Antidepressant Treatment Response Questionnaire (MGH-ATRQ) can be a valuable and easy tool to assess TRD[14].

The primary objective of this study was to adapt and validate the MGH-ATRQ for use in a Brazilian population. The secondary aim of our project was to compare clinical characteristics among TRD and non-TRD patients in MDD treatment.

2. METHODS

Study design

The present study was a cross-cultural translation and adaptation of the MGH-ATRQ into a Brazilian Portuguese language version.

The MGH-ATRQ is a self-report questionnaire that assesses treatment resistance in MDD and defines 6 weeks on an adequate dose of antidepressant medication as a valid antidepressant trial. It also provides specific operational criteria for adequate dosage for each of the commonly used antidepressants[9].

The cross-cultural adaptation was performed according to the following steps[15], also summarized in Figure 1:

(1) Two bilingual translators whose native language is Portuguese produced two separate versions of the instrument in this language: versions T1 and T2.

(2) The two versions were synthesized into a final Portuguese MGH-ATRQ version (T12) by a medical researcher with access to the two initial translators to exchange information.

(3) The MGH-ATRQ Portuguese T12 version was back translated into English (BT version) by two bilingual translators with English as their native language (BT1 and BT2 versions), independently. The new version in English (BT12) was synthesized by an outside observer with both medical knowledge and linguistic background along with the research team in an expert committee.

(4) The pre-final version of the Brazilian Portuguese MGH-ATRQ was applied in a small sample of 30 subjects for initial field test.

(5) The six versions (T1, T2, T12, BT1, BT2, BT12) were sent to the author of the original English version, so he could authorize the start of the validation process in Brazilian Portuguese.

(6) The questionnaire was carried out in 156 MDD outpatients in maintenance treatment also using standard definition for TRD as failure to achieve at least 50% symptom reduction after two well established antidepressant treatment courses of evidence based acceptable dose and duration according to medical records for comparison purposes[4,12].

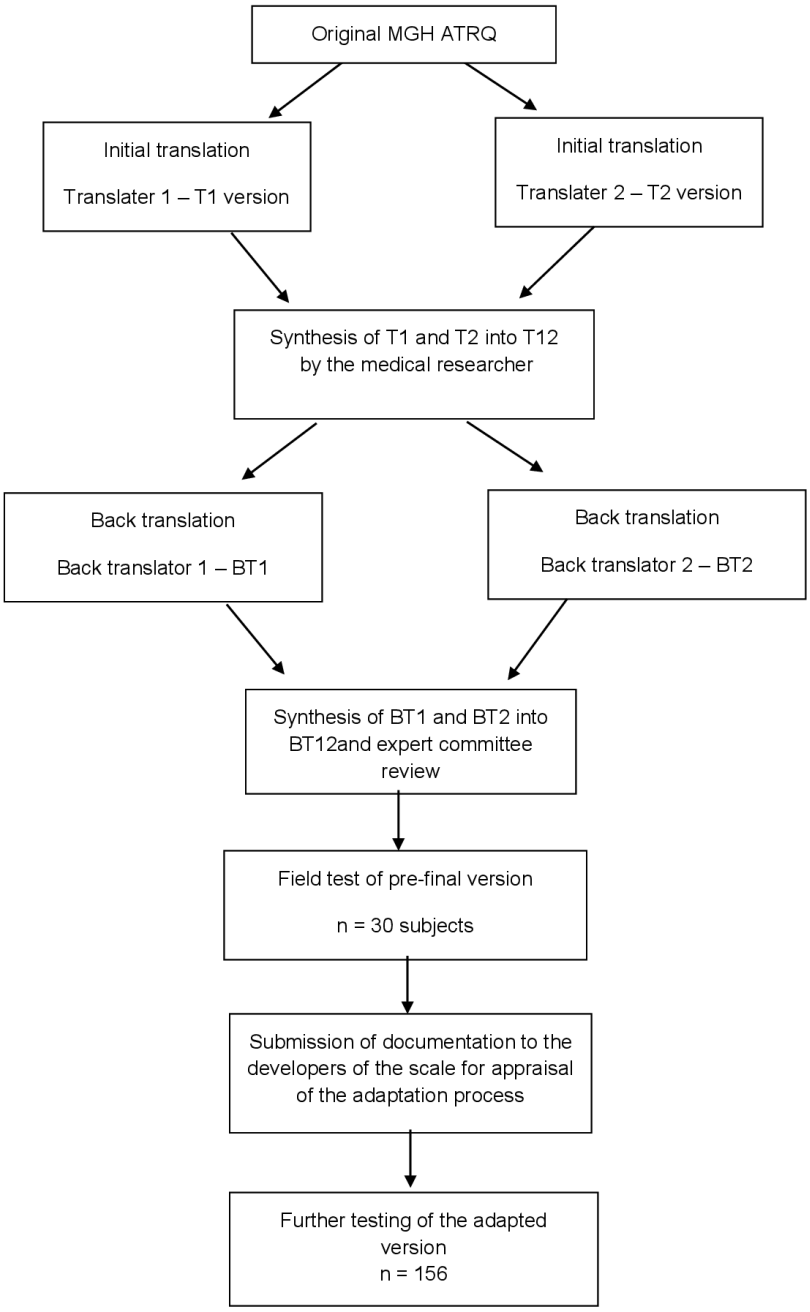

Figure 1. Overall Design of the study.

Participant recruitment and eligibility criteria

The outpatients were recruited from 2 private psychiatric clinics enrolled in the research, in the city of Londrina, Brazil in the period of July 2022 through December of 2024. Eligible patients were required to meet Diagnostic and Statistical Manual of Mental Disorders-5th Edition (DSM-5) diagnostic criteria for MDD without psychotic features through the Structured Clinical Interview for DSM-5 (SCID 5), translated to Portuguese[16] and International Classification of Diseases-11th edition (ICD-11) criteria[17]. Other inclusion criteria were age between 18 and 65 years (inclusive), both genders. The exclusion criteria were a) cognitive deficit preventing the full understanding of both the informed consent form and the assessment questions; b) depressive disorder due to another medical condition and c) substance/medication-induced depressive disorder.

Ethical compliance

The study protocol was registered in a database of clinical research studies (Brazilian Registry of Clinical Trials - ReBec) under the number RBR-3yt263y and was approved by local Ethics Committee (Research Ethics Committee of UEL: **CAAE** 03628120900005231). Participants who met the eligibility criteria received a detailed explanation about the protocol and provided electronic consent according to the declaration of Helsinki. They were informed they could withdraw from the study at any time without consequence and anonymity was guaranteed.

Sample size

The sample size of 156 subjects was performed using the formula described in Sample Size Calculation Guide according to Negida, Fahim and Negida[18] considering sensitivity = 0.9, specificity = 0.9, prevalence of TRD as 30% of MDD cases and 0.123 the maximum acceptable width of the 95% confidence interval.

Assessments

Clinical and Sociodemographic Assessments

All participants were assessed through a semi-structured questionnaire to gather socio-demographic and clinical characteristics, including age, level of education, work and marital status, and medical comorbidities.

Psychopharmacological treatment was recorded through MGH-ATRQ as well as treatment improvement in participants´ perspective, which was used to stratify patients as TRD if they reported symptom reduction of 49% or less after two adequate antidepressant trials for the current depressive episode and non-TRD for a symptom reduction of 50 % or more after one or two adequate antidepressant trials during current depressive episode. For comparison, we considered standard

definition of TRD as two failures to achieve significant improvement (≥50 %) after two acceptable dose and duration antidepressant trials according to medical records.

Hamilton Depression Rating Scale

The severity of depression among participants was measured by the 17-item Hamilton Depression Rating Scale ($HDRS_{17}$) translated and adapted for the Brazilian population[19,20].

Sheehan Disability Scale

The Sheehan Disability Scale (SDS) is a self-report inventory to assess impaired functioning in the following domains: work/school, social life, family life/home responsibilities and all items are scored on a 0-10 analogue scale, where 0 represents no impairment and 10 the highest level of impairment[21,22]. Two additional items assess the degree to which symptoms affect productivity as days lost (how many days in the last week did your symptoms cause you to miss school or work or leave you unable to carry out your normal daily responsibility) and underproductive days (how many days in the last week did you feel so impaired by your symptoms, that even through you went to school or work , your productivity was reduced).

Medication Adherence Rating Scale

Treatment adherence and adverse effects were determined by the ten items of the Medication Adherence Rating Scale (MARS)[23,24]. Participants answered to the statements in the questionnaire by choosing the answer which best described their behavior or attitude towards their medication treatment.

Adverse Childhood Experience History

Childhood trauma and stress exposure before the age of 18 were assessed using the 10-item version of the Adverse Childhood Experiences (ACE) Questionnaire[25,26]. The ACE is a standardized self-report instrument developed to evaluate exposure to potentially traumatic experiences during childhood and adolescence. It comprises 10 items covering three main domains: abuse (emotional, physical, and sexual), neglect (emotional and physical), and household dysfunction (including parental separation or divorce, domestic violence, substance abuse, mental illness, and incarceration of a household member). Each affirmative response is scored as one point, yielding a total score ranging from 0 to 10, with higher scores indicating greater exposure to adverse experiences.

Statistical analysis

The quantitative variables are described using means followed by the standard deviation, and for the qualitative variables the frequencies are presented followed by the percentages. To

compare the quantitative variables among the groups (TRD based on standard criteria or TRD based on MGH-ATRQ) we used t-test or Wilcoxon test, and for the qualitative variables the Chi-square test or Fisher exact test. The significance level used was 0.05, and if the p-value is < 0.05 there is significant difference. For the validation of the MGH-ATRQ (compared to the standard criteria) were calculated the accuracy, kappa coefficient, sensitivity, specificity, positive predictive value, and negative predictive value. All analyses were performed using software R Core Team (2023)[27].

3. RESULTS

Sample

A total of one hundred and fifty-six outpatients with MDD joined the study with sociodemographic and clinical characteristics presented in Table 1.

Table.1 Sociodemographic and clinical characteristics.

Variable	Sample n = 156
TRD based on standard criteria n (%)	
Yes	31 (19.87%)
No	125 (80.13%)
TRD based on MGH ATRQ; n (%)	
Yes	32 (20.51%)
No	124 (79.49%)
Female gender; n (%)	106 (67.95%)
Age; mean (SD)	43.63 (12.01)
Stable relationship; n (%)	97 (62.18%)
Currently employed; n (%)	114 (73.08%)
Ethnicity n (%)	
White	136 (87.18%)
Black	4 (2.56%)
Asian	8 (5.13%)
Other	8 (5.13%)
Years of education; mean (SD)	18.31 (4.46)
MDD age of onset; mean (SD)	25.40 (11.50)
Treatment gap; mean (SD)	3.80 (7.26)
$HDRS_{17}$; mean (SD)	10.46 (6.18)

Abbreviations: TRD: treatment-resistant depression; MGH-ATRQ: Massachusetts General Hospital Antidepressant Treatment Response Questionnaire; SD: standard deviation; $HDRS_{17}$: 17-item Hamilton Depression Rating Scale; MDD: Major Depressive Disorder.

Our sample had predominantly the following characteristics: female (67.95 %), in a stable relationship (62.18%), white ethnicity (87.18%), and currently employed (73.08%). Also, the analyses of quantitative variables show a mean age of 43.63 years (SD of 12.01 years), 18.31 mean years of education (± 4.46), MDD mean age of onset of 25.40 (± 11.50), treatment gap - defined as the number of years between the onset of depressive symptoms and the beginning of pharmacological treatment. - of 3.80 (± 7.26) and $HDRS_{17}$ mean score of 10.46 (± 6.18). Also, Table 1 presents the percentage of TRD patients in our sample, with 19.87% of TRD based on standard criteria and 20.51% based on MGH-ATRQ.

The diagnostic validity of the Brazilian Portuguese version of the MGH-ATRQ was evaluated by comparing its classification of TRD with the standard clinical criteria established through medical record review. Table 2 presents the cross-classification of participants according to both standard classification and measured by the MGH-ATRQ.

Table 2. TRD and not-TRD based on standard criteria versus TRD and not-TRD based on MGH-ATRQ.

MGH ATRQ	Standard criteria		Total
	TRD	not-TRD	
TRD	30	1	31 (19.9%)
not-TRD	2	123	125 (80.1%)
Total	32 (20.5%)	124 (79.5%)	156 (100.0%)

Abbreviations: TRD- treatment-resistant depression; MGH-ATRQ - Massachusetts General Hospital Antidepressant Treatment Response Questionnaire.

Among the total sample (n = 156), 30 patients were identified as TRD by both approaches, while 123 were consistently classified as non-TRD. Only one participant was labelled as TRD by the MGH-ATRQ but not by the standard definition, and two participants were classified as non-TRD by the MGH-ATRQ despite meeting standard TRD criteria. These results indicate a sensitivity of 93.75% and a specificity of 99.19%, positive predictive value of 96.77%, negative predictive value of 98.40%, accuracy of 98.08 % and Kappa coefficient of 94,03%.

On Table 3 the results of treatment adherence are presented for both TRD based on standard criteria and TRD based on MGH-ATRQ compared to the non-TRD group.

Table 3. Medication Adherence Rating Scale (MARS) results in Treatment Resistant Depression (TRD) based both on standard criteria and on MGH-ATRQ.

Variable	Answer	TRD based on standard criteria			TRD based on MGHATRQ		
		Non-TRD	TRD	p-value	Non-TRD	TRD	p-value
1.Do you ever forget to take your medication?	Yes	96 (77.4%)	27 (84.4%)	0.39	97 (77.6%)	26 (83.9%)	0.44
	No	28 (22.6%)	5 (15.6%)		28 (22.4%)	5 (16.1%)	
2.Are you careless at times about taking your medication?	Yes	25 (20.2%)	11 (34.4%)	0.09	26 (20.8%)	10 (32.3%)	0.18
	No	99 (79.8%)	21 (65.6%)		99 (79.2%)	21 (67.7%)	
3.When you feel better, do you sometimes stop taking your medication?	**Yes**	**8 (6.5%)**	**8 (25.0%)**	**< 0.01**	**8 (6.4%)**	**8 (25.8%)**	**< 0.01**
	No	**116 (93.5%)**	**24 (75.0%)**		**117 (93.6%)**	**23 (74.2%)**	
4.Sometimes if you feel worse when you take the medication, do you stop taking it?	**Yes**	**13 (10.5%)**	**12 (37.5%)**	**< 0.01**	**14 (11.2%)**	**11 (35.5%)**	**< 0.01**
	No	**111 (89.5%)**	**20 (62.5%)**		**111 (88.8%)**	**20 (64.5%)**	
5.I take my medication only when I am sick	Yes	2 (1.6%)	0 (0.0%)	0.99	2 (1.6%)	0 (0.0%)	0.99
	No	122 (98.4%)	32 (100.0%)		123 (98.4%)	31 (100.0%)	
6. It is unnatural for my mind and body to be controlled by medication	Yes	24 (19.4%)	9 (28.1%)	0.28	25 (20.0%)	8 (25.8%)	0.48
	No	100 (80.6%)	23 (71.9%)		100 (80.0%)	23 (74.2%)	
7.My thoughts are clearer on medication	Yes	100 (80.6%)	26 (81.2%)	0.94	101 (80.8%)	25 (80.6%)	0.98
	No	24 (19.4%)	6 (18.8%)		24 (19.2%)	6 (19.4%)	

8.By staying on medication, I can prevent getting sick	Yes	96 (77.4%)	21 (65.6%)	0.17	96 (76.8%)	21 (67.7%)	0.30
	No	28 (22.6%)	11 (34.4%)		29 (23.2%)	10 (32.3%)	
9. I fell weird, like a 'zombie' on medication	Yes	6 (4.8%)	3 (9.4%)	0.39	6 (4.8%)	3 (9.7%)	0.30
	No	118 (95.2%)	29 (90.6%)		119 (95.2%)	28 (90.3%)	
10. Medication makes me feel tired and sluggish	Yes	20 (16.1%)	9 (28.1%)	0.12	20 (16.0%)	9 (29.0%)	0.10
	No	104 (83.9%)	23 (71.9%)		105 (84.0%)	22 (71.0%)	

Abbreviations: MARS: Medication Adherence Rating Scale; TRD- treatment-resistant depression; MGH ATRQ - Massachusetts General Hospital Antidepressant Treatment Response Questionnaire.

Compliance = No to questions 1-6, 9-10; and Yes to questions 7-8.

There is significant difference between TRD and non-TRD in both groups. Specifically, individuals with TRD were more likely to discontinue their antidepressant medication when they felt better or when they experienced worsening of symptoms after taking it. Based on standard TRD criteria, 25.0% of patients with TRD reported stopping medication upon symptom improvement, compared to 8.5% of non-TRD patients ($p < 0.01$), and 37.5% reported discontinuing when they felt worse, compared to 10.5% of non-TRD patients ($p < 0.01$). Similar results were observed when TRD was defined according to the MGH-ATRQ, with higher rates of discontinuation among TRD participants both when feeling better (25.8% vs. 6.4%, $p < 0.01$) and when feeling worse after medication intake (35.5% vs. 11.2%, $p < 0.01$).

Table 4 summarizes the comparisons between patients with TRD and non-TRD based on standard criteria and based on MGH-ATRQ.

Table 4. Comparisons between TRD patients and non-TRD based on standard criteria and on MGH-ATRQ

Variables	TRD based on standard criteria			TRD based on MGH-ATRQ		
	Non-TRD	TRD	p-value	Non-TRD	TRD	p-value
Age	43.04 (12.19)	45.94 (11.19)	0.26	43.02 (12.06)	46.10 (11.67)	0.20
MDD age of onset	25.76 (12.09)	23.59 (8.74)	0.65	25.95 (12.10)	23.16 (8.47)	0.50
Age in which started MDD treatment	29.23 (11.38)	29.06 (10.63)	0.99	29.33 (11.40)	28.65 (10.47)	0.83

Treatment gap for MDD	3.37 (6.44)	5.47 (9.78)	0.35	3.38 (6.41)	5.48 (9.96)	0.60
$HDRS_{17}$	**8.84 (5.22)**	**16.75 (5.62)**	**< 0.01**	**8.94 (5.31)**	**16.61 (5.67)**	**< 0.01**
BMI	27.18 (5.56)	27.39 (5.35)	0.91	27.11 (5.49)	27.67 (5.59)	0.72
SDS - Work/ School	**1.73 (2.51)**	**4.78 (3.58)**	**< 0.01**	**1.71 (2.50)**	**4.94 (3.53)**	**< 0.01**
SDS - Social Life	**2.85 (3.06)**	**5.19 (3.11)**	**< 0.01**	**2.90 (3.08)**	**5.03 (3.16)**	**< 0.01**
SDS - Family Life	**1.94 (2.69)**	**3.78 (3.68)**	**< 0.01**	**1.88 (2.67)**	**4.06 (3.60)**	**< 0.01**
SDS – Lost days	**0.42 (1.44)**	**3.63 (7.94)**	**< 0.01**	**0.42 (1.43)**	**3.74 (8.04)**	**< 0.01**
SDS - Underproductive days	**2.99 (4.24)**	**8.28 (7.65)**	**< 0.01**	**2.87 (3.94)**	**8.94 (7.96)**	**< 0.01**
ACE	**2.06 (1.82)**	**2.91 (2.10)**	**0.03**	2.11 (1.87)	2.74 (2.02)	0.11

Abbreviations**:** TRD: treatment-resistant depression, MDD: major depressive disorders; MGH ATRQ: Massachusetts General Hospital Treatment Response Questionnaire; BMI: Body mass index**;** $HDRS_{17}$: 17-item Hamilton Depression Rating Scale; SDS: Sheehan Disability Scale, ACE: Adverse Childhood Experiences.

No significant differences were observed between TRD and non-TRD groups regarding current age, age at MDD onset, age at treatment initiation, treatment gap, or body mass index (BMI).

On the other hand, TRD patients exhibited significantly higher depressive symptom severity and greater functional impairment compared to non-TRD participants. Based on standard TRD criteria, the TRD group had higher mean scores on the 17-item Hamilton Depression Rating Scale ($HDRS_{17}$) (15.75 ± 6.28 vs. 8.84 ± 5.22, $p < 0.01$). Functional impairment, assessed using the Sheehan Disability Scale (SDS), was also more pronounced among TRD patients across all domains: work/school (2.56 ± 1.99 vs. 1.73 ± 1.78, $p < 0.01$), social life (5.78 ± 1.93 vs. 2.85 ± 2.06, $p < 0.01$), family life (5.13 ± 2.12 vs. 2.84 ± 2.00, $p < 0.01$), lost days (1.59 ± 1.73 vs. 0.42 ± 1.44, $p < 0.01$), and unproductive days (2.91 ± 2.91 vs. 2.06 ± 1.82, $p = 0.03$). When TRD was defined using the MGH ATRQ, similar differences were observed. TRD participants presented higher $HDRS_{17}$ scores (16.61 ± 6.57 vs. 8.94 ± 5.31, $p < 0.01$) and significantly greater disability across all SDS domains: work/school (2.67 ± 1.75 vs. 1.71 ± 1.59, $p < 0.01$), social life (6.04 ± 1.36 vs. 3.00 ± 2.00, $p < 0.01$), family life (5.36 ± 1.64 vs. 3.01 ± 1.93, $p < 0.01$), lost days (1.94 ± 1.94 vs. 0.28 ± 1.43, $p < 0.01$), and unproductive days (2.74 ± 2.02 vs. 2.11 ± 1.87, $p < 0.01$).

Importantly, patients with TRD reported statistically significant higher scores on the Adverse Childhood Experiences (ACE) questionnaire compared to non-TRD participants when defined by standard criteria (2.91 ± 2.10 vs. 2.06 ± 1.82, $p = 0.03$). Nevertheless, this difference did not reach

statistical significance when TRD was defined by the MGH ATRQ ($p = 0.09$).

4. DISCUSSION

The primary objective of this work was to validate the Brazilian Portuguese version of the MGH-ATRQ for identifying TRD. Our results support its implementation as a reliable and accurate instrument that can operationalize TRD diagnoses in both clinical and research settings, improving comparability and consistency of future findings.

Indeed, the lack of uniform criteria for TRD is a major obstacle in the literature[28-30]. Many studies use differing thresholds — number of failed trials, duration, dosage adequacy — making cross-study comparisons difficult and potentially misclassifying pseudo-resistance due to poor adherence or suboptimal dosing as true resistance. The validated Portuguese MGH-ATRQ helps mitigate this inconsistency, by providing explicit criteria for adequate trials and enabling self-reported standardization that correspond to medical records review.

Beyond its methodological relevance, our clinical findings also provide convergent evidence for the instrument's validity. Participants classified as TRD exhibited significantly greater depressive severity and higher functional impairment across all domains (work/school, family, social life) in both standard and MGH-ATRQ definitions. These results align with prior literature indicating that TRD is associated with a higher burden of illness and reduced quality of life[31-34].

Medication adherence behaviors differed markedly between groups. TRD patients were more likely to discontinue medication when feeling better or worse after intake, both under standard and MGH-ATRQ definitions ($p < 0.01$). This underlines the importance of discriminating "true" pharmacological resistance from treatment nonresponse caused by poor adherence. Although the MGH-ATRQ stipulates minimum dose and duration for a trial to be considered valid, these adherence differences may still influence apparent resistance and must be accounted for in both clinical assessments and research[9,35-36].

We also found that TRD participants reported significantly higher scores on the Adverse Childhood Experiences (ACE) questionnaire compared to non-TRD subjects when TRD was defined by standard criteria ($p = 0.03$). Although this link between childhood adversity and poor antidepressant response is well documented, our findings serve as replication in a Brazilian clinical sample and reinforce the external validity of our data[37-38]. Early-life stress might predispose individuals to treatment resistance through mechanisms such as HPA-axis dysregulation, increased proinflammatory signaling, impaired neuroplasticity, and maladaptive epigenetic changes[39-42]. Hence, ACE may act as a vulnerability factor interacting with behavioral (e.g., adherence) and clinical variables to sustain depressive symptoms despite adequate treatment.

Collectively, these findings underscore that TRD is a multidimensional phenomenon, influenced by biological, psychological, and behavioral factors. The validated Brazilian MGH ATRQ offers a structured and standardized approach to identify TRD cases more reliably, which is crucial given the complexity of treatment resistance. Accurate classification is the first step toward tailored management, more rigorous trials, and better comparability across studies.

This study has limitations. First, our definition of TRD encompassed only pharmacological response, excluding psychotherapy strategies or neuromodulation. Second, participants were recruited from private psychiatric clinics, which may limit the generalizability of the findings to populations treated in public health settings or with different socioeconomic backgrounds. Third, although the sample size was adequate for validation purposes, larger and more diverse samples will be important in future studies to further confirm the psychometric robustness and external validity of the Brazilian Portuguese version of the MGH-ATRQ.

In conclusion, the Brazilian Portuguese version of the MGH-ATRQ proved to be a valid and reliable instrument for diagnosing TRD. More importantly, by providing a standardized and replicable tool, it has the potential to enhance diagnostic consistency, facilitate multicenter research comparisons, and support better clinical decision-making in MDD. Adoption of such a tool is essential in a field where heterogeneity of definitions has hampered progress.

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Disclosure

The authors report no conflict of interest.

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5.3 ARTIGO 3

Methylenetetrahydrofolate reductase variants, predicted enzymatic activity, and their associations with depression severity, adverse childhood experiences, and treatment resistance in major depressive disorder

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The data that support the findings of this study are openly available in Figshare at

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ABSTRACT

Background: Variants of the methylenetetrahydrofolate reductase (*MTHFR*) gene have been associated with depression severity and treatment resistance, potentially through impaired one-carbon metabolism. However, the clinical relevance of predicted MTHFR enzymatic activity for symptom burden, functional impairment, suicidality, and adverse childhood experiences (ACEs) in major depressive disorder (MDD) remains insufficiently characterized.

Methods: This cross-sectional observational study included 78 adult outpatients with DSM-5–diagnosed MDD who had available pharmacogenetic testing for *MTHFR* 677C>T and 1298A>C variants. Predicted MTHFR enzymatic activity was estimated based on the combined functional impact of the 677C>T and 1298A>C genotypes, and participants were classified into preserved (>50%) or reduced (≤50%) enzymatic activity groups. Depressive severity was assessed using the 17-item Hamilton Depression Rating Scale (HDRS-17). Functional impairment, medication adherence, treatment characteristics, lifetime course variables, suicidality, and ACEs were evaluated using standardized instruments. Groups were compared using appropriate statistical tests.

Results: Patients with reduced predicted MTHFR enzymatic activity (≤50%) exhibited a more severe clinical profile, including higher depressive symptom severity (HDRS-17: 12.1 ± 6.8 vs 9.1 ± 5.0; $p = 0.04$), a greater frequency of recurrent depressive episodes (≥3 episodes: 86.2% vs 63.3%; $p = 0.04$), more suicide attempts (24.1% vs 6.1%; $p = 0.03$), and higher use of antipsychotic augmentation (27.6% vs 8.2%; $p = 0.04$). Functional impairment across work/school, social, and family domains was significantly worse in the low-activity group (all $p \leq 0.05$). Rates of high ACEs exposure (ACEs ≥ 4) did not differ between the groups (24.5% vs 27.6%; $p = 0.76$). Genotype and allele analyses showed an enrichment of the 677T and 1298C alleles among individuals with reduced enzymatic activity (both $p < 0.01$). Higher ACEs scores were associated with greater depressive severity across subgroups, particularly among patients with reduced MTHFR activity and treatment-resistant depression.

Conclusions: Reduced predicted MTHFR enzymatic activity was associated with greater depressive severity, functional impairment, suicidality, and treatment complexity in MDD, independent of medication adherence and overall ACEs burden. Functional stratification based on predicted MTHFR activity may help identify clinically vulnerable subgroups and refine prognostic assessment in MDD.

Keywords: MTHFR; major depressive disorder; pharmacogenetics, treatment-resistant depression, adverse childhood experiences

Significant Outcomes:

Reduced predicted MTHFR enzymatic activity (≤50%) was associated with greater depressive severity, functional impairment, suicidality, and treatment complexity in patients with major depressive disorder, identifying a clinically vulnerable subgroup.

Differences in clinical severity and functional outcomes between MTHFR activity groups were observed despite comparable exposure to adverse childhood experiences, suggesting a biologically mediated vulnerability rather than differential early-life stress burden.

Stratification based on predicted MTHFR enzymatic activity may complement clinical assessment by helping to identify patients at higher risk of severe and recurrent depressive phenotypes.

1.Introduction

Major depressive disorder (MDD) is a common, functional impairing disorder, ranked as a leading cause of global disability.[1] Despite various antidepressant options, many patients respond only partially or relapse frequently, leading to ongoing impairment and increased risk for chronic issues.[2] Treatment-resistant depression (TRD), usually defined as inadequate response to two antidepressant trials[3], poses particular clinical challenges, with greater symptoms, higher healthcare use, and significant social consequences[4]. Not achieving remission results in persistent symptoms, poor functioning, and increased suicidal behaviors in depressed individuals[5].

MDD is estimated to have a heritability rate of 40%, indicating that genetics play a significant role in both risk and prognosis[6]. One of the genetic mechanisms associated with MDD risk and poorer clinical outcomes is the methylenetetrahydrofolate reductase (MTHFR) enzyme gene variants, particularly the 677C>T (rs1801133) and 1298A>C (rs1801131) [7-8]. MTHFR is a crucial enzyme in the folate-mediated one-carbon (1-C) metabolism, which is a fundamental pathway in the generation of methyl groups for methylation of DNA, proteins, phospholipids, and neurotransmitters[9], as well as in the regulation of oxidative stress and neuroplasticity[10]. MTHFR converts 5,10-methylenetetrahydrofolate to 5-methyltetrahydrofolate, which is essential for the methylation of homocysteine to methionine. Functional genetic variants such as 677C>T (rs1801133) and 1298A>C (1801131) can reduce enzymatic activity, disrupt folate metabolism, and lead to elevated homocysteine levels, which have been implicated in depressive pathology[11-12]. Previous genetic association studies and meta-analysis, and more recent systematic reviews have explored the relationship between *MTHFR* variants and MDD risk, symptom severity, and antidepressant response[13-17]. Despite strong biological plausibility, these associations remain inconsistent across populations.

Epigenetic regulation in MDD is influenced by environmental stressors such as childhood adversity and recent life stress, which have biological effects[18-19]. These effects include DNA methylation, histone modification, noncoding RNA activity, RNA modification, and changes to chromatin remodeling factors. Such epigenetic modifications contribute to abnormal neuroendocrine

responses, impaired neuroplasticity, disrupted neurotransmission, and neuroglia dysfunction, all of which play a role in the pathophysiology of MDD[20].

Although both environmental stressors and genetic factors contribute to the complex nature of MDD, much of the current research has examined diagnostic links or genotype frequencies without considering how the predicted functional effects of these genetic variants relate to important clinical outcomes like symptom severity, recurrence, suicidality, or everyday functioning. As a result, it is still uncertain whether estimates of MTHFR enzyme activity can identify meaningful subgroups within MDD patients who differ in treatment responses and daily functioning.

2. Aims of the study

Hence, the aims of the present study are to examine whether predicted MTHFR enzymatic activity correlates with the severity of depression, multiple adverse childhood experiences (ACEs) and treatment-resistant depression in MDD outpatients receiving standard psychiatric care. The study also aims to assess how *MTHFR* variants influence depression severity, recurrence, suicidal behavior, ACEs, and functioning based on differing enzyme activity levels.

3. Materials and Methods

3.1. Study design and setting

This was a cross-sectional observational study with retrospective clinical data abstraction, conducted with a convenience sample of 78 adult outpatients receiving routine psychiatric care at two private outpatient clinics in the city of Londrina, Brazil, between 2023 and 2025.

3.2. Participants and procedure

Participants were eligible if they:

(1) were ≥18 years old;

(2) fulfilled DSM-5 diagnostic criteria[6] for MDD confirmed by a psychiatrist through the Structured Clinical Interview for DSM-5 (SCID 5), translated to Portuguese[21]; and

(3) had available genetic testing for *MTHFR* genetic variants in their medical records.

Patients with bipolar disorder, psychotic disorders, or neurocognitive disorders were excluded. Demographic and clinical data were obtained through structured interviews and medical record review.

3.3. Genotyping

Peripheral blood or saliva samples were collected for genomic DNA extraction, and genotyping had been conducted as part of routine clinical care in certified laboratories using commercially available assays. Only individuals with complete and unambiguous genotype information for both variants were included in the present analyses. Genotyping focused on two functional variants of the *MTHFR* gene: 677C>T (rs1801133) and 1298A>C (rs1801131). Genotypes were categorized as homozygous wild-type, heterozygous, or homozygous variants for each variant. Quality control procedures included verification of genotype consistency and assessment of Hardy–Weinberg equilibrium (HWE) for each variant.

Prediction of MTHFR enzymatic activity

Predicted enzymatic activity was derived by combining the functional effects attributed to the 677C>T (rs1801133) and 1298A>C (rs1801131) variants, according to previously published and widely used models of relative enzyme activity. These models consider the wild-type genotype (677 CC and 1298 AA) as the reference condition (100% activity) and assign decreasing levels of predicted activity according to the presence and combination of variant alleles, according to Table 1. Predicted enzymatic activity values represent approximate estimates derived from previously published genotype–function models[22-23] and are expressed relative to the wild-type genotype (677CC/1298AA). These values reflect estimated residual enzyme activity relative to the wild-type genotype. The cutoff of ≤50% was applied as an operational threshold for stratified analyses.

3.4. Clinical assessments

Diagnosis for MDD was based on the Structured Clinical Interview for DSM-5[6] Axis I (SCID-I), clinical version, translated and validated for the Portuguese language[21].

Depressive symptom severity was assessed using the 17-item Hamilton Depression Rating Scale (HDRS-17) validated for Brazilian Portuguese[24-25] administered by trained clinicians.

Medication adherence and adverse effects were determined by the ten items of the Medication Adherence Rating Scale[26] (MARS), validated for the Portuguese language[27]. Treatment history, number of previous depressive episodes, suicide attempts, psychiatric comorbidities, and current pharmacotherapy were extracted from both medical records and clinical interview.

Functional outcomes

Functional impairment was evaluated using the Sheehan Disability Scale (SDS)[28], which assesses impairment in work/school, social life, and family/home responsibilities. All items are scored on a 0-10 analogue scale, where 0 represents no impairment and 10 the highest level of impairment. Two additional items assess the degree to which symptoms affect productivity as days lost (how many days in the last week did your symptoms cause you to miss school or work or leave you unable to carry out your normal daily responsibility) and underproductive days (how many days in the last week did you feel so impaired by your symptoms, that even through you went to school or work , your productivity was reduced).

History of Adverse Childhood Experiences (ACEs)

ACEs[29] are traumatic and stressful experiences that represent a deviation from the expected environment and require adaptation, such as childhood maltreatment and family dysfunction, that occur before the age of 18.

The analysis included ten types of conventional ACEs, including physical abuse, sexual abuse, emotional abuse, physical neglect, emotional neglect, household suicidal attempt, parental conflict, parental separation/divorce, parental problematic drinking, and parental incarceration measured by the Adverse Childhood Experiences Questionnaire translated for the Portuguese Language[30-31].

Definition of Treatment-Resistant Depression

Treatment-Resistant Depression (TRD) was defined according to standard clinical criteria, i.e., inadequate response to at least two antidepressant trials of adequate dose and duration[32-33], as documented in medical records.

3. 5 Statistical Analyses

Continuous variables are presented as mean and standard deviation, and categorical variables as absolute number (n) and percentage (%). Comparisons between the higher-activity and lower-activity MTHFR groups were conducted using Student's t test or the Mann–Whitney U test for continuous variables, and the χ^2 test or Fisher's exact test for categorical variables, as appropriate.

A linear regression model was fitted including HDRS-17 and ACEs variables, along with treatment resistance status and predicted MTHFR enzymatic activity. Odds ratios (ORs) with corresponding 95% confidence intervals were calculated when applicable. The significance level considered was 0.05, and p values < 0.05 were considered statistically significant. Statistical analyses were conducted using R software (R Core Team, 2026)[34].

3.6 Ethical considerations

The study protocol was registered in a database of clinical research studies (Brazilian Registry of Clinical Trials - ReBec) under the number RBR-3yt263y and was approved by local Ethics Committee (Research Ethics Committee of UEL: CAAE 03628120900005231). Participants who met the eligibility criteria received a detailed explanation about the protocol and provided electronic consent according to the declaration of Helsinki. They were informed they could withdraw from the study at any time without consequence and anonymity was guaranteed.

4. Results

A total of 78 patients with MDD were included and based on predicted MTHFR enzymatic activity, 49 (62.8%) were classified as having preserved MTHFR enzymatic activity (>50%) and 29 (37.2%) as having reduced MTHFR enzymatic activity (≤50%).

Patients with ≤50% MTHFR activity exhibited a more severe clinical profile (Table 2). This group reported a higher number of depressive episodes (≥3 episodes: 86.2% vs 63.3%; p = 0.04; OR = 3.63; 95% CI = 1.18–13.80) and greater depressive severity as assessed by the HDRS-17 (12.1 ± 6.8 vs 9.1 ± 5.0; p=0.04, with OR = 4.20; 95% CI = 1.03–18.76 for HDRS-17 ≥ 17). Suicide attempts were also more frequent among patients with reduced MTHFR activity (24.1% vs 6.1%; p = 0.03; OR = 4.88; 95% CI = 1.23–24.35). In addition, these patients more often required antipsychotic augmentation as part of their pharmacological treatment (27.6% vs 8.2%; p = 0.04; OR = 4.29; 95% CI = 1.21–17.58).

Functional impairment, as assessed by the SDS, was significantly worse across all domains, including work/school, social and family life, lost days, and underproductive days (all p ≤ 0.05).ACEs did not differ between groups stratified by predicted MTHFR enzymatic activity. High ACEs burden (ACE ≥ 4) was observed in 24.5% of participants with MTHFR activity >50% and in 27.6% of those with MTHFR activity ≤50%, whereas ACE <4 was present in 75.5% and 72.4% of the groups, respectively (p = 0.76). These findings indicate that early-life stress exposure was comparable between enzymatic activity groups.

Medication adherence is presented in Table 3, and it did not differ significantly between groups. Across all MARS items, the proportions of patients reporting non-adherent behaviors were similar among those with preserved (>50%) and reduced (≤50%) MTHFR enzymatic activity (all p > 0.05). These findings suggest that the more severe clinical profile observed in the low-activity group cannot be attributed to poorer treatment adherence.

Genotype distribution, genetic models, and allele frequencies of the *MTHFR* 677C>T and 1298A>C variants are presented in Table 4. For the 677C>T variant, the codominant model showed a predominance of heterozygous CT individuals (62.8%), followed by CC homozygotes (29.5%), whereas TT homozygosity was uncommon (7.7%). Similarly, for the 1298A>C variant, heterozygous

AC genotypes were frequent (46.2%), with AA homozygotes representing 50.0% of the sample and CC homozygosity observed in only 3.8% of participants.

Under the dominant model, most patients carried at least one variant allele for both genetic variants (677C>T: CT+TT = 70.5%; A1298C: AC+CC = 50.0%). In contrast, the recessive model revealed a low prevalence of homozygous genotypes for the minor allele in both variants. The overdominant model further highlighted the high frequency of heterozygous states, supporting the notion that partial reductions in MTHFR enzymatic activity are more common than complete loss of function.

Allele frequency analysis demonstrated a substantial presence of functionally relevant alleles in the sample, with the T allele accounting for 39.1% of 677C>T alleles and the C allele representing 26.9% of 1298A>C alleles. Taken together, the genotype distribution and genetic models indicate that the majority of patients carried heterozygous variants of *MTHFR* 677C>T and/or 1298A>C, suggesting partial rather than complete reductions in enzymatic activity.

Based on this genetic background, participants were subsequently classified according to their predicted MTHFR enzymatic activity, integrating the combined functional impact of both genetic variants. This functional stratification enabled the evaluation of clinical, functional, and treatment-related outcomes according to biologically meaningful differences in enzyme activity, rather than isolated genotype categories. Genotype distributions differed markedly between groups (Table 5). The T allele of *MTHFR* 677C>T and the C allele of 1298A>C were significantly more frequent among patients with enzymatic activity ≤50% (both $p < 0.01$). Allelic analyses showed increased odds of low enzymatic activity for the 677T allele (OR = 4.21; 95% CI = 2.11–8.42) and for the 1298C allele (OR = 2.73; 95% CI = 1.32–5.65; both $p < 0.01$). Patients with enzymatic activity ≤50% showed a significantly higher frequency of the T allele in 677C>T and the C allele in 1298A>C compared with those with activity >50%, indicating an enrichment of risk alleles among individuals with lower predicted MTHFR function. When allele frequencies were compared between groups, individuals with MTHFR activity ≤50% showed a significantly higher prevalence of risk alleles. The T allele of 677C>T was associated with a four-fold increase in odds of belonging to the low-activity group (OR

= 4.21; 95% CI = 2.11–8.42; p < 0.01). Similarly, the C allele of 1298A>C was more frequent among patients with reduced enzymatic activity (OR = 2.73; 95% CI = 1.32–5.65; p < 0.01). Taken together, these findings indicate a clear enrichment of *MTHFR* risk alleles in subjects with predicted lower enzymatic function.

A linear regression model (Table 6) was fitted with HDRS-17 as the response variable and ACEs, TRD, and predicted MTHFR enzymatic activity as explanatory variables. Higher ACEs scores were associated with greater depression severity, as reflected by increased HDRS-17 scores. TRD patients consistently exhibited higher HDRS-17 values. Specifically, HDRS-17 scores were highest among individuals with TRD and predicted MTHFR activity ≤50%, followed by TRD with MTHFR activity >50%, non-TRD with MTHFR activity ≤50%, and non-TRD with MTHFR activity >50%, as shown in Figure 1. Notably, lower predicted MTHFR enzymatic activity (≤50%) was associated with greater depression severity across ACEs levels, suggesting a potential interaction between early-life stress, MTHFR-related metabolic vulnerability, and clinical severity.

5. Discussion

In our study, the predicted reduced MTHFR enzymatic activity group was associated with greater depressive severity, higher frequency of recurrent episodes, more suicide attempts, and greater functional impairment across occupational, social, and family domains. These findings suggest that MTHFR-related reductions in one-carbon metabolism may be associated with clinical complexity and poorer psychosocial outcomes in MDD.

Previous studies have reported inconsistent and often modest associations between individual MTHFR variants and depressive outcomes, including treatment resistance, particularly when the 677C>T or 1298A>C variants are analyzed in isolation[20,35,36]. Several investigations have failed to demonstrate significant effects, highlighting important gaps and heterogeneity in the literature. In contrast, our approach considered the combined functional impact of the two most widely studied MTHFR variants, which is biologically more plausible given their cumulative influence on enzymatic activity, homocysteine metabolism, and methyl donor availability[8,37,38]. Consistent with this framework, the T allele of 677C>T and the C allele of 1298A>C were strongly associated with

the low predicted enzymatic activity group in our sample, reinforcing their clinical relevance when evaluated in combination. Individuals carrying these variants have been shown to present higher risk of recurrent depression, cognitive impairment, and poorer antidepressant response [11,13,39] — particularly in the presence of nutritional deficiency or medical comorbidity.

A particularly relevant observation in our study is that worse outcomes were not explained by poor adherence, despite considerable non-adherence rates in our sample comparable to many previous studies in MDD[40]. Patients with reduced MTHFR activity exhibited greater use of antipsychotics as an augmentation strategy in pharmacological treatment, which can be interpreted as an indirect marker of treatment resistance given that augmentation is not the first option in treatment guidelines for MDD [32,33]. These results suggest that the increased use of antipsychotic augmentation in individuals with lower MTHFR activity may serve as a proxy for treatment resistance, in line with previous evidence indicating that dysfunction in folate-dependent pathways may contribute to inadequate antidepressant response[17]. Importantly, differences in self-reported medication adherence were not observed between activity groups; however, adherence was assessed using a self-report instrument, and confounding related to treatment exposure or clinical decision-making cannot be excluded.

In the present study, reduced predicted MTHFR enzymatic activity was associated with a higher prevalence of suicide attempts. This finding aligns with the hypothesis that impairments in one-carbon metabolism may contribute to neurobiological vulnerability underlying suicidality in MDD[41]. Reduced MTHFR activity can lead to alterations in folate availability, homocysteine accumulation, and downstream effects on monoamine synthesis, methylation capacity, and neuroplasticity, all of which have been implicated in affective dysregulation and suicidal behavior. These results support the notion that MTHFR-related metabolic vulnerability may represent a contributing biological substrate for suicidality in a subset of patients with more severe or recurrent depressive phenotypes, and a higher burden of suicide attempts — variables often interpreted as indirect markers of a more complex course of illness[35,42,43].

Biologically, decreased MTHFR activity may contribute to depression through converging pathways[44-46]. Impaired folate metabolism reduces S-adenosylmethionine availability, influences DNA methylation patterns, alters monoamine synthesis, and may enhance vulnerability to stress-related epigenetic reprogramming. Elevated homocysteine, frequently observed in carriers of low-activity variants, promotes oxidative stress, endothelial dysfunction, and neuroinflammation — mechanisms that have been repeatedly implicated in depression severity, suicidality, and poor treatment response. These interactions may help explain why individuals with reduced enzymatic activity experience not only more symptoms, but also greater functional disability.

From a clinical perspective, our results support the concept that evaluating one-carbon metabolism may provide additional insight into patient stratification in depression. Identification of individuals with genetically determined reductions in MTHFR activity could inform early preventive strategies, nutritional optimization (including folate status), and a more personalized treatment approach [47,48]. Importantly, such findings should not be interpreted deterministically: MTHFR is one element within a complex network of biological, psychosocial, and environmental factors. Nonetheless, incorporating metabolic markers into assessment frameworks may help refine prognostic evaluation and avoid attributing refractoriness solely to adherence or psychological traits.

Although genotype-based models are essential for describing genetic distributions, they may be insufficient to capture the clinical heterogeneity associated with *MTHFR* variants. In this context, a functional approach based on predicted enzymatic activity appears more clinically informative, as it integrates the cumulative impact of multiple genotypes on folate metabolism. From a clinical perspective, the predominance of heterozygous genotypes suggests that most patients do not exhibit complete enzymatic deficiency, but rather intermediate reductions in MTHFR activity, which may still be sufficient to influence symptom severity, functional impairment, and treatment response. Accordingly, stratifying patients based on predicted MTHFR enzymatic activity, rather than individual genetic variants alone, may provide a more biologically coherent framework for investigating clinical correlates of depression, including functional outcomes and treatment resistance. This approach may help reconcile inconsistencies across previous studies that focused exclusively on single

MTHFR variants, highlighting the importance of functional interpretations when translating genetic findings into clinical practice.

Importantly, the rates of ACEs - 24.5 % in the preserved MTHFR enzymatic activity group and 27.6 % in the reduced MTHFR enzymatic activity group – were similar to previous MDD studies[49,50] and did not differ significantly between groups, indicating comparable exposure to early-life stress. This finding suggests that the observed differences in depressive severity, functional impairment, and treatment complexity associated with MTHFR enzymatic reduction are unlikely to be driven by differential childhood adversity. Instead, these results support a biologically mediated vulnerability related to impaired one-carbon metabolism and methylation capacity, which may independently contribute to poorer clinical and functional outcomes in MDD.

While overall exposure to ACEs did not differ significantly between groups stratified by MTHFR enzymatic activity, this does not preclude a modulatory role of early-life stress on clinical expression. As illustrated in Figure 1, higher ACEs scores were associated with increased depressive severity across subgroups, with a steeper gradient observed among individuals with reduced MTHFR enzymatic activity. This pattern suggests that, although childhood adversity was comparable at the group level, impaired one-carbon metabolism may amplify the clinical impact of stress exposure, acting as a biological vulnerability factor that heightens sensitivity to environmental insults[51-52]. In this context, MTHFR enzymatic reduction appears to modify the relationship between early adversity and depressive severity, rather than serving as a proxy for differential stress exposure itself. These findings suggest that reduced predicted MTHFR enzymatic activity may amplify the clinical impact of ACEs on depression severity, particularly among patients with TRD, reinforcing the relevance of gene–environment interactions in the clinical heterogeneity of MDD.

Previous studies suggest that ACEs are associated with an increased likelihood of TRD, potentially through long-lasting effects on neurodevelopment, stress responsivity, and inflammatory pathways [53-56]. In parallel, functional variants of the *MTHFR* gene, such as 677C>T, have been linked to reduced methylation capacity and altered one-carbon metabolism[45], mechanisms that may influence neuroplasticity and stress regulation. Rather than acting independently, these biological

and environmental factors may converge to increase vulnerability to more severe and recurrent depressive phenotypes, particularly those less responsive to standard treatments. Importantly, this convergence should be interpreted as a biologically plausible gene–environment interplay, rather than a deterministic pathway.

Consistent with this framework, prior clinical studies have shown that individuals exposed to childhood trauma are more likely to develop chronic or treatment-resistant forms of depression, with greater symptom severity and recurrence[57,58]. Evidence also suggests that genetic vulnerability related to *MTHFR* variants may modulate the long-term impact of early-life stress on mood regulation and illness course[52]. Together, these findings support the hypothesis that impaired one-carbon metabolism may heighten sensitivity to environmental stressors, thereby amplifying depressive burden and recurrence, without implying direct causality.

From a clinical perspective, the assessment of ACES and genetic factors related to folate metabolism may contribute to a more nuanced understanding of heterogeneity within TRD. However, such information should be integrated cautiously, recognizing that MTHFR represents one component within a complex network of biological, psychosocial, and environmental determinants. While adjunctive strategies targeting trauma or nutritional status have shown promise in selected contexts[58,59], further prospective and interventional studies are required before definitive treatment recommendations can be established.

This study has limitations that should be acknowledged. The convenience sample and cross-sectional design preclude causal inference and may limit generalizability. Enzymatic activity was inferred from genotype rather than measured directly, and homocysteine or folate levels were not systematically assessed. TRD classification relied on clinical chart review, which, although ecologically valid, may underestimate previous adequate pharmacological trials. Finally, the sample was recruited from specialized outpatient settings, which may limit generalizability to community populations, and the sample size restricts exploration of more complex interactions.

Despite these limitations, the study adds clinically relevant evidence that predicted reductions in MTHFR enzymatic activity are associated with more severe depressive symptoms and greater functional impact, independent of treatment adherence.

Taken together, our findings support the relevance of gene–environment interactions in MDD, suggesting that variation in predicted MTHFR enzymatic activity may be associated with clinical severity and prognostic features, particularly in the context of ACEs. However, given the cross-sectional design, these findings should be interpreted as associative rather than causal. Future longitudinal studies integrating genetic, metabolic, and epigenetic markers are warranted to clarify causal pathways and to determine whether targeted interventions may modify risk trajectories in vulnerable individuals.

Conflict of Interest

The authors report no conflict of interest.

Data Availability

The data that support the findings of this study are openly available in Figshare at DOI: 10.6084/m9.figshare.31082350

Author Contributions

JBM and SOVN designed the study, evaluated the scales, and drafted the manuscript; DA and EMVR handled genotyping interpretation and reviewed the manuscript, and MUR performed the statistical analysis. All authors participated in interpreting the results, which were then critically reviewed for significant intellectual content by other contributors. Every author approved the final version of the manuscript before submission.

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Table 1. Predicted MTHFR enzymatic activity according to combined *MTHFR* 677 C>T and 1298 A>C genotypes in patients with major depressive disorders

677 C>T genotype	1298 A>C genotype	Estimated enzymatic activity (%)	Functional category
CC	**AA**	**~100%**	**Preserved (>50%)**
CT	**AA**	**~70%**	**Preserved (>50%)**
TT	**AA**	**~30%**	**Reduced (≤50%)**
CC	**AC**	**~70%**	**Preserved (>50%)**
CC	**CC**	**~60%**	**Preserved (>50%)**
CT	**AC**	**~50%**	**Reduced (≤50%)**
TT	**AC**	**~30%**	**Reduced (≤50%)**
CT	**CC**	**~40%**	**Reduced (≤50%)**
TT	**CC**	**~30%**	**Reduced (≤50%)**

Predicted MTHFR enzymatic activity was derived from the combined functional effects of the *MTHFR* 677 C>T (rs1801133) and 1298 A>C (rs1801131) variants, according to previously validated enzymatic models[22,23]. Briefly, each variant contributes independently to reductions in MTHFR catalytic activity, and their combined genotype determines overall functional capacity. Combined genotypes were used to estimate individual enzymatic activity and to classify participants into functional categories. Participants were stratified into two groups based on predicted enzymatic activity: preserved activity (>50%) and reduced activity (≤50%).

Abbreviations: *MTHFR*: Methylenetetrahydrofolate reductase; for the *MTHFR* 677 C>T: CC: homozygous genotype for the major C allele; CT: heterozygous genotype; TT; homozygous genotype for the minor T allele; AA: homozygous genotype for the major A allele; AC: heterozygous genotype; CC; homozygous genotype for the minor C allele.

Table 2. Sociodemographic and clinical characteristics of patients with major depressive disorders according to their predicted MTHFR enzymatic activity

Variable	MTHFR activity > 50 (n=49)	MTHFR activity ≤ 50 (n=29)	p-value*
Female sex	35 (71.4%)	16 (55.2%)	0.145
Stable relationship	33 (67.3%)	18 (62.1%)	0.474
Ethnicity			0.180
White	46 (93.9%)	24 (82.8%)	
Black	0 (0.0%)	1 (3.4%)	
Asian	2 (4.1%)	1 (3.4%)	
Other	1 (2.0%)	3 (10.3%)	
Years of education	19.14 (4.38)	17.48 (3.81)	0.06
Currently employed	37 (75.5%)	24 (82.8%)	0.57
Age at first depressive episode	25.37 (12.24)	21.69 (7.90)	0.32
Treatment resistant depression	8 (16.3%)	9 (31.0%)	0.13
Number of depressive episodes			**0.04**
≤ 2	**18 (36.7%)**	**4 (13.8%)**	
≥ 3	**31 (63.3%)**	**25 (86.2%)**	
HDRS-17	**9.14 (5.02)**	**12.14 (6.75)**	**0.04**
Current medication use			
SSRIs	21 (42.9%)	15 (51.7%)	0.44
SNRIs	24 (49.0%)	12 (41.4%)	0.52
Other ADs	11 (22.4%)	9 (31.0%)	0.40
Antipsychotics	4 (8.2%)	8 (27.6%)	0.04
Suicide attempt (Yes)	**3 (6.1%)**	**7 (24.1%)**	**0.03**
Sheehan Disability Scale (SDS)			
SDS - Work/ School	**1.65 (2.72)**	**3.93 (2.89)**	**< 0.01**
SDS - Social life	**2.22 (2.82)**	**4.00 (3.31)**	**0.01**
SDS - Family Life	**1.59 (2.68)**	**2.83 (3.02)**	**0.04**
SDS – Lost days	**0.94 (4.40)**	**1.55 (4.09)**	**0.03**
SDS -Under productive days	**2.96 (5.01)**	**6.24 (6.25)**	**<0.01**
ACEs			0.76
< 4	37 (75.5%)	21 (72.4%)	

≥ 4	12 (24.5%)	8 (27.6%)

Categorical variables were expressed as absolute number (n) and percentage (%); Continuous variables were expressed as mean and standard deviation. Abbreviations:
MTHFR: Methylenetetrahydrofolate reductase; ; HDRS-17: Hamilton Depression Rating Scale; SSRIs: Selective Serotonin Reuptake Inhibitor antidepressants; SNRI: Serotonin and Norepinephrine Reuptake Inhibitor antidepressants; Other ADs: Other Antidepressants; SDS: Sheehan Disability Scale; ACEs: Adverse Childhood Experiences.*p-value were calculated using Student's t test or the Mann–Whitney U test for continuous variables, and the χ^2 test or Fisher's exact test for categorical variables.

Table 3. Medication Adherence Rating Scale (MARS) of the patients with major depressive disorders according to their predicted MTHFR enzymatic activity

Question	Answer	MTHFR activity > 50 (n=49)	MTHFR activity ≤ 50 (n=29)	p-value*
1.Do you ever forget to take your medication?	Yes	36 (73.5%)	25 (86.2%)	0.26
	No	13 (26.5%)	4 (13.8%)	
2.Are you careless at times about taking your medication?	Yes	9 (18.4%)	7 (24.1%)	0.54
	No	40 (81.6%)	22 (75.9%)	
3.When you feel better, do you sometimes stop taking your medication?	Yes	3 (6.1%)	4 (13.8%)	0.41
	No	46 (93.9%)	25 (86.2%)	
4.Sometimes if you feel worse when you take the medication, do you stop taking it?	Yes	7 (14.3%)	3 (10.3%)	0.74
	No	42 (85.7%)	26 (89.7%)	
5.I take my medication only when I am sick	Yes	0 (0.0%)	1 (3.4%)	0.37
	No	49 (100.0%)	28 (96.6%)	
6. It is unnatural for my mind and body to be controlled by medication	Yes	8 (16.3%)	9 (31.10%)	0.13
	No	41 (83.7%)	20 (69.0%)	
7.My thoughts are clearer on medication	Yes	42 (85.7%)	21 (72.4%)	0.15
	No	7 (14.3%)	8 (27.6%)	
8.By staying on medication, I can prevent getting sick	Yes	41 (83.7%)	20 (69.0%)	0.13
	No	8 (16.3%)	9 (31.0%)	

9. I felt weird, like a 'zombie' on medication	Yes	2 (4.1%)	3 (10.3%)	0.35
	No	47 (95.9%)	26 (89.7%)	
10. Medication makes me feel tired and sluggish	Yes	8 (16.3%)	7 (24.1%)	0.4
	No	41 (83.7%)	22 (75.9%)	

Abbreviations: *MTHFR*: Methylenetetrahydrofolate reductase; MARS: Medication Adherence Rating Scale. Higher percentages reflect endorsement of each behavior. Group comparisons were performed item-wise (all $p > 0.05$).
*p-value obtained in the χ^2 test or Fisher's exact test

Table 4. Genotype distribution, genetic models, and allele frequencies for *MTHFR* 677C>T and 1298A>C in patients with major depressive disorders (n = 78)

	***MTHFR* 677 C>T**			***MTHFR* 1298 A>C**		
Genetic Model	**Genotype**	**n**	**%**	**Genotype**	**n**	**%**
Codominant	CC	23	29.5	AA	39	50.0
	CT	49	62.8	AC	36	46.2
	TT	6	7.7	CC	3	3.8
Dominant	CC	23	29.5	AA	39	50.0
	CT + TT	55	70.5	AC + CC	39	50.0
Recessive	CC + CT	72	92.3	AA + AC	75	96.2
	TT	6	7.7	CC	3	3.8
Overdominant	CC + TT	29	37.2	AA + CC	42	53.8
	CT	49	62.8	AC	36	46.2
Allele frequency	C	95	60.9	A	114	73.1
	T	61	39.1	C	42	26.9

Abbreviations: *MTHFR*: Methylenetetrahydrofolate Reductase

Table 5. Genotype and allele distributions of *MHTFR* variants in patients with major depressive disorders stratified by predicted MTHFR enzymatic activity.

Variant	Genotype / Allele	MTHFR activity > 50 (n=49)	MTHFR activity ≤ 50 (n=29)	p-value*
677 C>T	**CT**	26 (53.1%) a**	23 (29.3%) b	< 0.01
	TT	0 (0.1%) a	6 (20.7%) b	
	CC	23 (46.9%) a	0 (0.0%) b	
	Allele C	72 (73.5%) a	23 (39.7%) b	
	Allele T	26 (26.5%) a	35 (60.3%)	< 0.01
1298 A>C	**AC**	13 (26.5%) a	23 (79.3%) b	< 0.01
	CC	3 (6.1%) a	0 (0.0%) a	
	AA	33 (67.3%) a	6 (20.7%) b	
	Allele A	79 (80.6%) a	35 (60.3%) b	< 0.01
	Allele C	19 (19.4%) a	23 (39.7%) b	

Abbreviations: *MTHFR*: Methylenetetrahydrofolate reductase; for the *MTHFR* 677 C>T: CC: homozygous genotype for the major C allele; CT: heterozygous genotype; TT; homozygous genotype for the minor T allele; AA: homozygous genotype for the major A allele; AC: heterozygous genotype; CC; homozygous genotype for the minor C allele. Odds ratios (ORs) were calculated comparing allele frequencies between groups (≤50% vs. >50% enzymatic activity). For *MTHFR* 677C>T, the T allele was associated with increased odds of low enzymatic activity (OR = 4.21; 95% CI = 2.11–8.42; p < 0.01). For 1298A>C, the C allele also showed higher odds of low activity (OR = 2.73; 95% CI = 1.32–5.65; p < 0.01).

*p-value obtained in the χ^2 test or Fisher's exact test
** Percentages followed by the same letter do not differ significantly among groups, whereas those followed by different letters indicate significant differences.

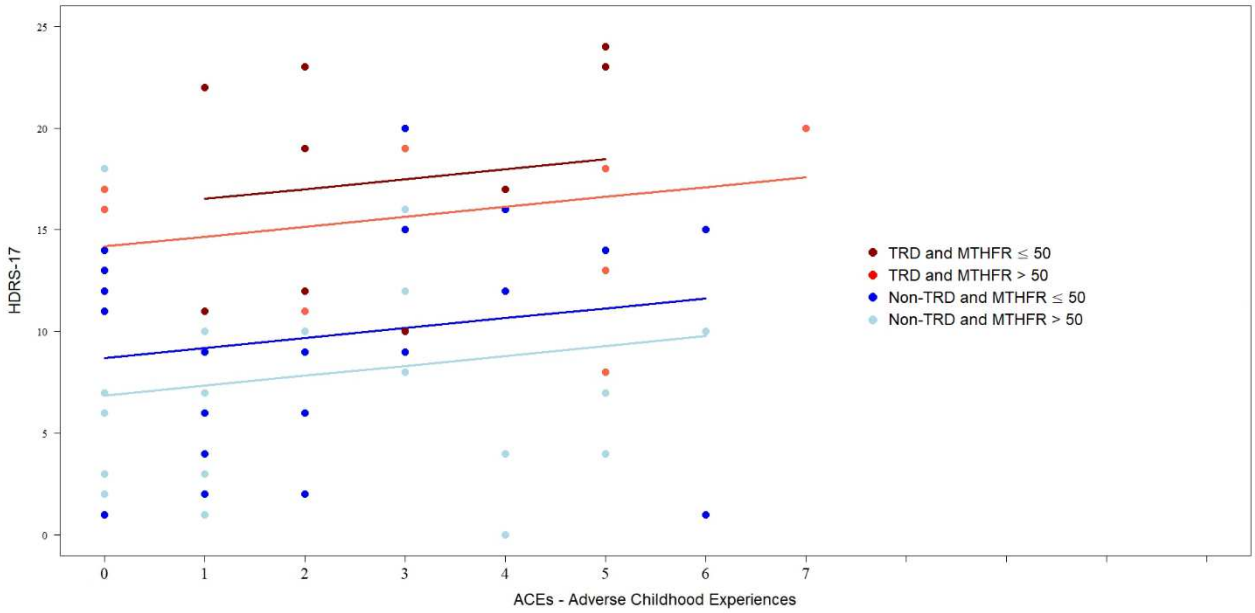

Figure 1. Association between adverse childhood experiences (ACEs) and depressive symptom severity (HDRS-17), stratified by treatment resistance status (TRD vs non-TRD) and predicted MTHFR enzymatic activity (>50% vs ≤50%). Scatter plots depict individual data points with fitted regression lines illustrating trends within each subgroup. Higher ACEs scores were associated with greater depressive severity across groups, with consistently higher HDRS-17 scores observed among patients with TRD, particularly those with lower predicted MTHFR enzymatic activity (≤50%).

Abbreviations: ACEs, adverse childhood experiences; HDRS-17, 17-item Hamilton Depression Rating Scale; MTHFR, methylenetetrahydrofolate reductase; TRD, treatment-resistant depression; non-TRD, non–treatment-resistant depression; MTHFR enzymatic activity ≤50%, reduced predicted enzymatic activity; MTHFR enzymatic activity >50%, preserved predicted enzymatic activity.

5.4 ARTIGO 4

Training Healthcare Professionals in the Epigenetics of Depression: A Training of Trainers and Case-Based Learning Experience

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ABSTRACT

Depression is a complex condition shaped by dynamic interactions between genetic vulnerability, environmental exposures, and epigenetic mechanisms. This experience report describes a pilot educational intervention designed to train healthcare professionals in the epigenetics of Depression using a Training of Trainers (ToT) model combined with case-based learning (CBL). The epigenetics module was delivered as part of a broader training program in mental disorders, and the epigenetics component consisted of an interactive session integrating theoretical instruction, a structured clinical case, guided discussion questions, and learning objectives focused on gene–environment interactions, adverse childhood experiences (ACEs), lifestyle factors, and pharmacogenetic considerations. A total of 47 healthcare professionals from diverse disciplines participated in the program. Qualitative outputs indicated that participants developed an expanded understanding of depression. Reports suggested increased sensitivity to non-specific clinical presentations, such as somatic complaints and functional impairment, and greater awareness of how life history and contextual factors may contribute to depressive vulnerability. This experience suggests that ToT and CBL-based educational strategies may support the dissemination of epigenetic knowledge among healthcare professionals and promote its application in practice. Future studies incorporating structured quantitative assessments are needed to evaluate educational outcomes and long-term impact.

Keywords: Epigenetics; Training of Trainers; Major Depressive Disorder; Healthcare Professionals; Health Education.

1. INTRODUCTION

Major Depressive Disorder (MDD) is a multifactorial condition involving a complex interplay between genetic variants and the environment, with disrupting gene expression and consequent clinical outcomes, such as early age of illness onset, poor treatment response, and other clinical variables[1-4]. This aligns with emerging perspectives on precision medicine in neuropsychiatry, which emphasize the importance of integrating genetic, environmental, and lifestyle factors for personalized treatment planning.[5-7]. Environmental stressors, particularly adverse childhood

experiences and recent life stress, can be mediated, at least in part, through epigenetic mechanisms[8]. Alterations in DNA methylation, histone modifications, and noncoding RNA expression can induce persistent changes in gene regulation, thereby contributing to dysregulation of neuroendocrine function, impaired neuroplasticity, altered neurotransmission, and neuroglial dysfunction—processes central to the pathophysiology of MDD[9-11]. The heritability estimate of MDD is 40.0%[12-14], suggesting that environmental factors account for a substantial proportion of risk for development and prognosis. of MDD.

Understanding epigenetic mechanisms is essential for healthcare professionals, particularly in relation to MDD. There is growing interest in the co-occurrence of adverse childhood experiences (ACEs) such as child abuse and neglect as a plausible mediating mechanism linking early adversity to depressive symptoms in young adulthood[15]. DNA methylation, a key epigenetic process, is influenced by chronic stress and early-life trauma, both of which have been linked to increased vulnerability to MDD[16,17]. The stress-diathesis model, widely used in suicide research, further illustrates how genetic susceptibility interacts with environmental stressors[18]. Adverse childhood experiences—including emotional, physical, and sexual abuse, as well as neglect—may define ecophenotypic variants of depression, underscoring the need for early recognition and preventive strategies[19]. Importantly, the epigenetic consequences of childhood trauma may contribute to treatment resistance in adults with MDD[20]. The association between MDD and ACEs has increasingly focused on epigenetic mechanisms, particularly DNA methylation, which represents the most extensively studied modification linking childhood trauma to long-term psychopathology[21-23].

The education on the epigenetics of MDD could prepare health professionals to teach others about how epigenetic mechanisms, particularly DNA methylation, influence gene expression and disease susceptibility.

Training of Trainers (ToT) programs use methods such as interactive sessions, experiential learning, multimedia resources, real clinical case, and practical exercises[24,25]. This approach has been often utilized to address workforce shortages in scenarios where urgent care was needed, such

as war zones, epidemics, low-income countries, by upskilling staff, improving their performance, commitment, and retention[26-28].

This pilot experience aims to describe the development and implementation of an Epigenetics of Depression module embedded within a broader mental health training program for healthcare professionals, focusing on knowledge dissemination and perceived applicability in clinical practice.

2. MATERIALS AND METHODS

2.1 Educational Program Context

The educational intervention described in this study was part of a broader continuing education program entitled “Educate to Prevent: Focus on Mental Health”, delivered in the city of Londrina, Brazil from March to July 2025. This structured program comprised of 13 thematic classes and a total workload of 72 hours. The course addressed major mental disorders, diagnostic frameworks, psychosocial determinants, and translational approaches to mental health care. The Epigenetics of Depression module analyzed in this manuscript was delivered during the first week of the program and represented one specific component within this comprehensive educational initiative.

2.2 Description of the Epigenetics of Depression Module

The Epigenetics of Depression module aimed to introduce healthcare professionals to gene–environment interactions, adverse childhood experiences (ACEs), and epigenetic mechanisms involved in vulnerability to depression. The module emphasized translational concepts relevant to clinical practice, including stress-related epigenetic regulation, neuroplasticity, and implications for prevention and personalized care. It was designed as an introductory component of the broader course, serving as a conceptual foundation for subsequent discussions on mental health disorders.

2.3 The TOT Model

The module was developed according to the Training of Trainers (ToT) educational model[29], which focuses on capacity building and knowledge dissemination through trained healthcare

professionals. Within this framework, participants were encouraged not only to acquire conceptual knowledge but also to develop skills to share this information within their professional and community settings. The ToT approach prioritizes scalability, sustainability, and community impact, particularly in contexts with limited access to specialized mental health education[30].

The ToT model assesses the impact of a training program by establishing learning outcomes and employing a “learning-by-doing” approach. Healthcare professionals trained through this model develop skills to teach others about depression epigenetics within their communities, and the process concludes with a report documenting competency transfer. Our course intended to develop skills and knowledge by mentoring healthcare professionals to teach others through resources such as online materials on the platform and participate in instructor-led online classes.

Participants analyzed a clinical case to understand how ACEs can impact gene expression and increase depression risk later in life. The program emphasized practical application, with tutors-professors and postgraduate students guiding participants in both theoretical and hands-on settings. Trained healthcare professionals were expected to share their knowledge within their communities, enhancing understanding of epigenetic changes related to stress response and depression.

2.4 Case-based learning (CBL)

CBL is a healthcare training method that uses real or simulated patient scenarios to teach clinical reasoning and decision-making skills[31]. By analyzing case studies, professionals can actively apply theoretical knowledge to realistic situations, improving their problem-solving abilities. This approach promotes critical thinking, strengthens patient assessment, and supports retention and professional competence[32].

CBL was implemented through the discussion of a structured clinical case of recurrent depression that was assessed using an integrated clinical framework that combined psychiatric diagnosis, psychosocial history, and pharmacogenetic information. Beyond the diagnosis of recurrent major depressive disorder, the case description included: (i) assessment of adverse childhood experiences (ACESs) using the Adverse Childhood Experiences Questionnaire; (ii) evaluation of pharmacogenetic markers related to antidepressant response and one-carbon

metabolism through genetic variants of *MTHFR*[33]; and (iii) functional and clinical characteristics relevant to treatment complexity.

The clinical case was intentionally designed as a pedagogical tool to translate epigenetic concepts into clinical reasoning. In the educational context, epigenetics was presented not as a laboratory-based assessment, but as a conceptual framework to understand how environmental exposures, such as ACEs, may interact with genetic vulnerability to influence depression severity, chronicity, and treatment response. The clinical case was used to exemplify this gene–environment interaction, integrating childhood trauma with pharmacogenetic and metabolic susceptibility.

Specific learning objectives included: (i) recognizing how ACEs may induce epigenetic vulnerability through altered DNA methylation capacity; (ii) understanding how reduced predicted MTHFR (methylenetetrahydrofolate reductase) enzymatic activity may amplify stress-related biological susceptibility; and (iii) integrating genetic, environmental, and lifestyle factors into individualized treatment planning. During case discussions, participants were encouraged to apply these concepts to real clinical scenarios from their own practice, fostering reflective learning and practical knowledge transfer.

Description of the clinical case

The clinical case involved a 42-year-old female physiotherapist, currently unemployed, married, and mother of a three-year-old child, presenting with a five-year history of anxiety and depressive symptoms.

History of Present Illness: The patient reported that her paternal grandfather passed away five years ago, triggering panic attacks. She was initially treated with Duloxetine, which alleviated her symptoms, but discontinued the medication due to side effects (decreased libido and weight gain). Three years ago, she experienced postpartum depression and resumed Duloxetine alongside psychotherapy, with partial improvement. She stopped the medication again due to intolerance to side effects. Over the past six months, she reported worsening fatigue, low energy, excessive self-demand, persistent sadness, irritability, social isolation, and somatic anxiety symptoms (shortness

of breath, tachycardia, and initial insomnia). She denied suicidal ideation or prior suicide attempts and noted that she had never achieved full remission of depressive symptoms.

Past Medical History: Type I diabetes mellitus (diagnosed at age 12) and hypothyroidism secondary to Hashimoto's thyroiditis.

Personal and Childhood History: Raised primarily by her paternal grandparents due to parental separation, with intermittent contact with both parents. During childhood, she exhibited perfectionist tendencies and high self-demand. She sought psychological counseling at age 16 to cope with diabetes management.

Family History: Father with alcohol dependence disorder (abstinent for several years) and mother undergoing treatment for obsessive-compulsive disorder (OCD).

Lifestyle and Habits: No substance use reported; sedentary lifestyle.

The patient filled in the Patient Health Questionnaire-9 (PHQ-9)[34,35], an easy and useful instrument for making criteria-based diagnoses of depression in a primary care context, as follows in Table 1.

Early Detection of Adverse Childhood Experiences (ACEs)

Beyond detection of signs and symptoms of depression, it was necessary to understand the role of personal history of childhood trauma.

The Adverse Childhood Experiences (ACEs) Questionnaire is a widely used screening instrument for the early identification of childhood trauma and household adversity and has been validated to the Portuguese language[36,37]. The 10-item short form assesses five types of maltreatment—physical abuse, emotional abuse, sexual abuse, physical neglect, and emotional neglect—and five types of household dysfunction.

A cumulative score of four or more affirmative ("Yes") responses indicates a significantly increased risk for serious long-term health, social, and functional impairments.

Key Components of the ACE Questionnaire are described below:

Maltreatment:

- Emotional abuse: Being insulted, sworn at, humiliated, or threatened with physical harm.
- Physical abuse: Being slapped, pushed, pulled, hit, or injured by a caregiver or household member.
- Sexual abuse: Experiencing sexualized touching, fondling, or attempted or completed intercourse.
- Physical neglect: Lack of adequate food, shelter, clean clothing, or physical protection.
- Emotional neglect: Absence of affection, emotional support, or a sense of being valued and loved.

Household Dysfunction:

- Domestic violence: Mother or stepmother treated violently by a partner.
- Substance abuse: Living with someone who abused alcohol or illicit drugs.
- Mental illness: A household member who was depressed, mentally ill, or suicidal.
- Parental separation or divorce: Disruption of the caregiving environment due to separation.
- Incarcerated household member: A family member who was imprisoned during childhood.

Scoring and Clinical Implications

Each of the 10 categories is scored dichotomously (1 point for “Yes,” 0 for “No”), regardless of the frequency or severity of exposure. Higher cumulative ACE scores are strongly associated with increased risk of adverse adult outcomes, including cardiovascular disease, cancer, stroke, substance use disorders, and mental health conditions. Individuals with ACEs scores of four or higher demonstrate approximately a 12-fold increased risk of suicide attempts and a seven-fold increased risk of alcoholism[38].

The patient´s answers to the Adverse Childhood Experiences Questionnaire are presented in Table 2.

After this initial assessment, she began to be followed up as an outpatient for Recurrent Depressive Disorder and Generalized Anxiety Disorder.

A pharmacogenetic report was presented as an illustrative case example (Figure 1) to support discussion on gene–environment interactions, epigenetic mechanisms, and individualized clinical reasoning. The subject in this clinical case had a 60.0% MTHFR enzymatic deficiency, carrying MTHFR 677 C>T and 1298 A>C genetic variants, in addition to a childhood maltreatment history. This case exemplifies the precision medicine approach in neuropsychiatry, where genetic markers are considered alongside environmental factors to inform treatment decisions[7]. Research shows that variants in *MTHFR* combined with experiences of multiple childhood maltreatment, significantly contribute to more recurrent depression[33] and that this subset of MDD patients could benefit from supplemental use of L-methyl folate 15mg per day[39].

In this clinical case, new therapeutic strategies were considered following a pharmacogenetic testing displayed in Figure 1. The patient had already undergone various psychopharmacological regimens; however, she did not exhibit the expected therapeutic response and treatment adherence due to intolerance and adverse side effects. Notably, she also had drug metabolism alterations confirmed in the cytochrome P450 system genes that could explain these tolerability difficulties.

Following the results of the pharmacogenetic test, the combination of methyl folate (15 mg/day) with escitalopram (15 mg/day) resulted in a significant improvement in functionality, allowing the patient to resume social activities, practice physical exercise and improve family relationships.

This case reported an individual who carried genetic variants in *MTHFR* (677C>T and 1298A>C) and who had experienced childhood maltreatment, and exposure to other contextual stressors with major risk factors for the development of depression. In addition, MTHFR enzymatic activity reduction was probably associated with increased folate deficiency and increased homocysteine levels, and when combined with childhood trauma could increase risk of MDD recurrence as well as the development of more severe depressive symptoms[19,40].

Accumulating evidence suggests that *MTHFR* variants may contribute to vulnerability profiles associated with depression severity and recurrence[41], particularly when combined with environmental, nutritional, or clinical factors, rather than acting as independent predictors.

Furthermore, for individuals with depression who carry *MTHFR* variants, clinicians may develop specific clinical treatment strategies, such as folate or methyl folate supplementation to improve depressive symptoms[42].

2.5 Participants

A total of 47 healthcare professionals from the local community participated in the training course. Participants represented diverse professional backgrounds, including family physicians, nurses, psychologists, social workers, and nutritionists. Participants were recruited from different healthcare settings and represented varying levels of professional experience. The training was offered as part of a voluntary continuing education initiative from HUTEC - foundation that manages research projects, continuing education programs, and the provision of services in various fields of knowledge in Londrina, Brazil - and no formal baseline assessment of prior knowledge was conducted.

2.6 Educational Materials and Knowledge Dissemination

Educational materials included live online classes, structured case discussions, and an e-book developed by the teaching team. The e-book contained a dedicated chapter on Epigenetics of Depression and adverse childhood experiences, designed to support knowledge consolidation and subsequent dissemination. The training also explicitly addressed common misconceptions about epigenetics, reinforcing that epigenetic mechanisms should not be interpreted as deterministic or used as standalone diagnostic tools, but rather as complementary concepts within an integrative clinical framework.

In line with the ToT model, participants were encouraged to adapt and share the acquired knowledge within their professional networks and community contexts.

At the end of the module, participants received structured discussion questions focused on risk factors, treatment adherence, genetic variants, and integrative care in depression to stimulate critical reflection, clinical reasoning, and translation of epigenetic concepts into real-world practice. These educational materials are publicly available on Figshare (DOI: https://doi.org/10.6084/m9.figshare.30068353).

Participants were expected to be able to:

(i) identify key clinical and psychosocial factors involved in major depressive disorder with medical and psychosocial comorbidities;

(ii) evaluate strategies to improve adherence to pharmacological treatment;

(iii) understand the impact of genetic variants—particularly those affecting folate metabolism—on antidepressant metabolism and treatment response; and

(iv) apply an integrative treatment model incorporating biological, psychological, and social dimensions of care.

Knowledge consolidation and post-training evaluation occurred through a reflective learning process. Participants were encouraged to apply the discussed concepts in their own clinical or community settings and, in subsequent weekly sessions of the broader training program, to share real-life cases, professional experiences, and challenges encountered in practice.

2.7 Faculty and Tutors Involved in the Training Program

The Epigenetics of Depression module was delivered by a multidisciplinary teaching team composed of four instructors with complementary expertise. The faculty included: (1) a senior psychiatrist and faculty member from the Department of Clinical Medicine and Psychiatry at the State University of Londrina (UEL), with extensive experience in mood disorders and clinical teaching; (2) a doctoral candidate in Health Sciences (Psychiatry) at State University of Londrina (UEL), with research focus on treatment-resistant depression, genetic variants of *MTHFR*, and epigenetic mechanisms; (3) a faculty member from the Department of Pharmaceutical and Pharmacological

Sciences, contributing expertise in pharmacogenetics, drug metabolism, and molecular mechanisms relevant to antidepressant response; and (4) a faculty member from the Department of Pediatrics, providing perspectives on developmental vulnerability, early-life stress, and adverse childhood experiences.

This interdisciplinary composition was intentionally designed to integrate clinical psychiatry, molecular and pharmacological mechanisms, developmental perspectives, and translational research, aligning with the program's objective of bridging epigenetic theory and real-world clinical practice[43].

2.8 Ethical Considerations

This educational initiative was conducted in accordance with ethical principles for educational research. Participation was voluntary, and no identifiable personal or clinical data were collected for research purposes.

3. RESULTS

3.1. Educational Outputs

Participants completed applied learning activities in the form of reflective reports or case reports, designed to integrate epigenetic concepts into real-world clinical, academic, or personal contexts.

Learning objectives and guided discussion questions were provided to support critical analysis of clinical cases, gene–environment interactions, and integrative treatment strategies.

Submissions were uploaded to the course platform within a defined period and reviewed by instructors. In subsequent weekly meetings, participants engaged in collective discussions, during which they presented real cases encountered in their workplace settings and reflected on how the newly acquired knowledge informed clinical reasoning and interdisciplinary collaboration. These outputs aimed to promote conceptual understanding, clinical reasoning, and interdisciplinary dialogue rather than rote knowledge acquisition.

3.2. Evidence of Knowledge Application and Dissemination

Evidence of knowledge application and dissemination emerged through an iterative, formative assessment process embedded in the course structure (Figure 2). Following the epigenetics module, participants applied acquired knowledge to their professional settings, bringing real clinical cases and practical experiences to subsequent weekly sessions.

Group discussions facilitated collective reflection on how epigenetic mechanisms—such as DNA methylation pathways, early-life stress, and metabolic vulnerability—could inform patient assessment, treatment planning, and preventive strategies. Instructor feedback and peer exchange supported the expansion of clinical perspectives and adaptation of concepts to diverse healthcare contexts.

This cyclical process of application, reflection, feedback, and discussion demonstrated active knowledge transfer beyond the classroom environment. Participants were able to contextualize epigenetic concepts within their own practice settings. The interdisciplinary group of health care professionals approach is particularly valuable given the growing evidence that lifestyle-oriented medical interventions can reduce the incidence and severity of depression through epigenetic mechanisms.

Among the different modules offered throughout the training program, the chapter dedicated to depressive disorders stood out for its broad applicability across participants' diverse professional and social contexts. The content addressed clinical aspects of depressive disorders, differentiation between sadness and depressive episodes, risk factors, warning signs, referral pathways, and the importance of qualified listening and stigma reduction. At the end of the module, participants were invited to complete a knowledge transfer activity, applying the acquired concepts to real-life professional or interpersonal situations.

As an illustrative example of the submitted activities, a primary healthcare professional reported reassessing the clinical approach to a patient who frequently attended the health unit with nonspecific somatic complaints. Following the training, the participant expanded the clinical

assessment to include targeted questions about mood, sleep, anhedonia, and hopelessness, identifying symptoms compatible with a moderate depressive episode. The report highlighted that, prior to the training, clinical management had been limited to investigation of organic causes; after the course, the professional implemented appropriate referral, improved clinical documentation, and coordinated care with the local psychosocial healthcare network.

Beyond individual clinical practice, the participant described sharing this experience during a multidisciplinary team meeting, reframing recurrent somatic complaints as potential manifestations of unrecognized psychological distress. This discussion led to the joint development of strategies for depressive symptom screening within the primary care unit and strengthened interprofessional collaboration among nursing, medical, and social work staff. The participant emphasized that the main learning outcome was a shift in professional posture—from an exclusively symptom-focused approach to an expanded, patient-centered perspective attentive to subjective dimensions of suffering and comprehensive care.

In another report, a social worker described applying the acquired knowledge in a non-institutional context, recognizing persistent signs of social withdrawal and hopelessness in a close acquaintance. The training facilitated a more confident and empathetic approach, enabling validation of the individual's distress without judgment and encouragement to seek professional mental health support.

Collectively, these examples illustrate that the knowledge transfer activity extended beyond the academic setting, promoting concrete changes in professional practice and interpersonal relationships. Group discussion of these reports in subsequent sessions supported critical reflection on interventions, exchange of strategies among participants, and reinforcement of ethical, humanized approaches to depressive disorders. Figure 3 summarizes the conceptual framework used during the training sessions to support discussion on gene–environment interactions, epigenetic mechanisms, and the role of pharmacogenetics in individualized depression care.

Across these reports, participants emphasized that exposure to epigenetic concepts contributed to a broader clinical perspective on depression. By understanding how life experiences, chronic stress, and environmental factors can influence biological vulnerability, healthcare professionals reported increased awareness that depressive presentations may emerge beyond classical diagnostic complaints. This perspective supported a more integrative clinical reasoning, in which somatic complaints, general medical conditions, and psychosocial stressors were recognized as potential indicators of underlying depressive processes, rather than isolated or purely organic phenomena.

4. DISCUSSION

This experience report enhances our understanding of how a ToT model combined with CBL can train healthcare professionals to acquire knowledge about depression epigenetics to train others. As artificial intelligence applications continue to transform mental health care through mood tracking and treatment personalization, healthcare professionals will need even stronger foundational knowledge in epigenetics to effectively interpret and apply these emerging technologies[44].

Rather than evaluating clinical outcomes, the present study focuses on educational processes, knowledge application, and dissemination strategies within a structured mental health training program. Although no formal longitudinal follow-up was conducted, the educational design encouraged continued application of the content through structured knowledge-transfer activities, peer discussions in subsequent course modules, and reflection on real-world professional experiences. These elements supported ongoing engagement with the concepts beyond the initial session, while long-term educational outcomes remain a target for future research.

MDD is a complex condition of both genetic and environmental factors, with an interplay between them[45]. Furthermore, research found a positive correlation between genetics and environmental factors such as adverse childhood experiences, and stress can influence susceptibility for developing depression later in life[2,4].

The clinical case enabled participants to explore epigenetic and environmental mechanisms in individuals with recurrent depressive episodes. Twin and molecular genetic studies indicate that

depression has a moderate heritable component, with heritability estimates commonly around 30–40%[12-14,23], while also underscoring its polygenic architecture and contributions of environmental exposures.

These factors, including early life stress, trauma, and other adverse experiences, can alter gene expression by modifying DNA histone proteins, leading to long-lasting changes in brain function and behavior[22,43]. Epigenetic mechanisms such as alterations in chromatin structure, histone modifications, DNA modifications, noncoding RNA regulation, and RNA modifications may contribute to the progression of MDD in response to stressful experiences and adverse environmental exposures[46], as postulated in Figure 4.

Although the presence of *MTHFR* variants is often discussed within a pharmacogenetic framework, their relevance in this case extends to epigenetic regulation[47]. Reduced predicted MTHFR enzymatic activity compromises the availability of methyl groups required for one-carbon metabolism, which directly impacts DNA methylation processes. DNA methylation is a core epigenetic mechanism involved in gene expression regulation, neuroplasticity, and stress responsivity. Therefore, in the context of early-life adversity, impaired methylation capacity may represent a biological pathway linking genetic vulnerability to epigenetic dysregulation and increased susceptibility to depressive episodes.

Meanwhile, ACEs are linked to a higher risk of health problems, which involves sustained activation of the stress response system, and have a role in the mediation of epigenetics mechanisms. Traumatic experiences during childhood can cause changes in the limbic-hypothalamic-pituitary-adrenal axis, resulting in increased levels of catecholamines (“fight or flight” response), cortisol, and proinflammatory cytokines and cascading effects[24]. Childhood maltreatment affects the physiological response and activity of the HPA axis[48]. Childhood trauma might modulate epigenetic pathways through methylation changes in genes, and is associated with glucocorticoid-mediated stress response, which may lead to accelerated epigenetic aging process in later life[49]. The mechanisms of ACEs may modulate epigenetic altering the function of the HPA axis and

glucocorticoid receptor gene that can trigger DNA methylation patterns being a likely way early life events have long-term effects[16].

Emerging evidence indicates that an unhealthy lifestyle may be associated with alterations in epigenetic processes linked to depression. Emerging evidence indicates that an unhealthy lifestyle may be associated with alterations in epigenetic processes linked to depression[50]. This research highlights how lifestyle choices involving diet, physical activity, sleep, social relationships, and stress influence epigenetic processes positively or negatively, and thereby play a significant role in determining whether one does or does not suffer from depression.

Socially negative lifestyle factors, such as childhood adversity, childhood sexual abuse, and social rejection were found to be associated with genetic hypermethylation and single-nucleotide polymorphism patterns that increase production of pro-inflammatory mediators, downregulate anti-inflammatory markers, and alter the expression of opioid and glucocorticoid receptors involved in the stress response[8,51,52].

Growing evidence indicates that lifestyle-based psychoeducation can substantially contribute to the primary prevention of depressive disorders, particularly when healthcare professionals are systematically trained to promote core pillars of mental health such as restorative sleep, balanced nutrition, regular physical activity, and social connectedness[53,54]. These lifestyle domains influence molecular pathways involved in stress responsivity, inflammation, mitochondrial function, and epigenetic regulation, which are all implicated in the onset and progression of depression. Training healthcare professionals to integrate these principles into clinical practice may enhance early identification of at-risk individuals, strengthen protective factors[55], and foster beneficial epigenetic modifications that support neuroplasticity and emotional regulation[56-58]. As illustrated in Figure 5, lifestyle-oriented psychoeducation provides a low-cost, scalable, and biologically informed strategy to mitigate vulnerability and reduce the incidence of depressive symptoms at the population level.

From an educational perspective, the clinical case functioned as a translational tool, allowing participants to connect molecular mechanisms with real-world clinical scenarios encountered in their own professional settings. The reflective questions and applied tasks encouraged participants to

identify epigenetic risk factors, discuss integrative treatment strategies, and critically reflect on how lifestyle, psychosocial context, and biological vulnerability interact in depression. The introduction of epigenetic concepts appeared to function as a conceptual bridge between biological vulnerability and lived experience. Rather than focusing on molecular mechanisms in isolation, participants were encouraged to understand epigenetics as a framework that links environmental exposures, stress, and life history to clinical manifestations of depression. This approach may explain why healthcare professionals reported greater sensitivity to nonspecific presentations, such as somatic complaints or functional impairment, and a broader recognition of depression risk beyond strict diagnostic criteria. By framing depressive disorders within an epigenetic and biopsychosocial model, participants reported greater attention to contextual factors, improved clinical questioning, and more appropriate referrals within psychosocial care networks. Although patient outcomes were not directly assessed, such changes in professional behavior represent meaningful practice-level outcomes with potential downstream effects on patient care.

The field of epigenetics in mental health continues to evolve rapidly, with several recent publications offering valuable insights that complement our findings. Recent work on precision medicine approaches in neuropsychiatry highlights the growing importance of integrating genetic, environmental, and lifestyle factors for personalized treatment planning.[7] Additionally, emerging research on artificial intelligence applications in mood disorders suggests new frontiers for predicting treatment response and monitoring epigenetic changes[44]. These developments reinforce the value of training healthcare professionals in epigenetics, as they will need to interpret increasingly complex biological data in clinical practice.

This experience report has several limitations. First, the absence of a standardized baseline knowledge assessment limits the ability to quantify learning gains. Second, educational outcomes were primarily assessed through reflective reports, case discussions, and observed application in professional contexts, which may be subject to reporting bias. Third, the sustainability and long-term impact of knowledge dissemination were not systematically evaluated.

Despite the positive educational outcomes, potential barriers to implementing similar training programs should be acknowledged, including time constraints, variability in baseline knowledge, and limited institutional support. Integrating complex epigenetic concepts into routine clinical practice may also require ongoing reinforcement.

Future studies should incorporate mixed-method evaluation frameworks to assess educational effectiveness more rigorously.

Cultural considerations are particularly relevant for educational interventions in mental health[58]. Although the training was implemented within a specific regional and cultural context, the program was designed to be adaptable to different healthcare settings. The emphasis on case-based learning, reflective discussions, and community-oriented knowledge transfer allows content to be contextualized according to local sociocultural realities, healthcare resources, and professional roles. Nevertheless, the present study did not formally evaluate cultural adaptations across diverse settings, which represents an important direction for future implementations and research.

5. CONCLUSIONS

This experience report suggests that a ToT and CBL approach incorporating epigenetic concepts into mental health education is feasible and may support healthcare professionals in broadening their understanding of gene–environment interactions in depression. While the findings are exploratory and based on qualitative educational outputs, they indicate potential for knowledge dissemination and reflective practice, warranting further evaluation using structured outcome measures. By supporting healthcare professionals in identifying adverse life events within their communities and contextualizing these factors within epigenetic frameworks, such initiatives may contribute to early recognition of vulnerability and inform preventive and supportive strategies to mitigate the long-term impact of childhood trauma.

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Disclosure of statement

The authors report there are no competing interests to declare.

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Data Availability Statement

The datasets generated and analyzed during the current study are available in the Figshare repository. All data are openly accessible at DOI: 10.6084/m9.figshare.30068353.

Data Deposition

Data supporting this study has been deposited in the Figshare repository under the DOI 10.6084/m9.figshare.30068353.

Author Contributions

JBM: conceptualization of the work, data acquisition, analysis, interpretation, writing and reviewing the manuscript. DFA: conceptualization of the work, analysis or interpretation, writing and reviewing the manuscript, analysis and interpretation. RMM: conceptualization of the work, analysis and interpretation. EMVR: analysis, interpretation and reviewing the manuscript. RCBRM: writing and reviewing the manuscript, analysis and interpretation SOVN: conceptualization of the work, analysis, interpretation, writing and reviewing the manuscript. All authors approved the final version of the manuscript and agreed to be responsible for all aspects of the work.

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Table 1: Patient Health Questionnaire-9 (PHQ-9) answers from the case study.

How often have you been bothered by the following in the past 2 weeks?	Not at all	Several days	More than half of the days	Nearly every day
1 - Little interest or pleasure in doing things?				X

2 - Feeling down, depressed, or hopeless?				X
3 - Trouble falling or staying asleep, or sleeping too much?			X	
4 - Feeling tired or having little energy?				X
5 - Poor appetite or overeating?		X		
6 - Feeling bad about yourself - or that you are a failure or have let yourself or your family down?				X
7 - Trouble concentrating on things, such as reading the newspaper or watching television?			X	
8 - Moving or speaking so slowly that other people could have noticed? Or so fidgety or restless that you have been moving a lot more than usual?		X		
9 - Thoughts that you would be better off dead, or thoughts of hurting yourself in some way?	X			

Table 2: The Adverse Childhood Experiences Questionnaire answers from the case study.

Ask	Answer
1. Did either your parents or other adults in the home frequently or very frequently: offend, insult, belittle, humiliate you? Or act in a way that made you fear being physically harmed?	Yes
2. Did a parent or other adult in the home frequently or very frequently: push, grab, slap, or throw objects at you? Or ever hit you in a way that left marks or physical injuries?	No
3. Has any adult or person at least 5 years older ever: touched or fondled you or caused you to touch their body in a sexual way? Or attempted to have or had oral, anal or vaginal sex with you?	No
4. Did you often or very often feel that: No one in your family loved you or thought you were important or special? Or that your family members did not care about each other's well-being, did not feel close to each other, or did not support each other?	Yes
5. Did you often or very often feel that: You didn't have enough to eat, had to wear dirty clothes, and had no one to protect you? Or were your parents too drunk or on drugs to take care of you or take you to the doctor if you needed them?	Yes

6. Did your parents ever separate or divorce?	Yes
7. Your mother or stepmother: Was she often or very often pushed, grabbed, slapped, or had objects thrown at her? Or was she sometimes, often, or very often kicked, bitten, punched, or hit with heavy objects?	No
8. Have you lived with someone who suffered from drinking or alcoholism, or who used illicit drugs?	Yes
9. Have you lived with someone who was depressed, had a psychiatric problem, or attempted suicide?	Yes
10. Have any family members been arrested?	No

Figure 1. Pharmacogenetic profile of the patient illustrating genotypes and predicted phenotypes for antidepressant response and metabolism.

Pharmacogenetics tests

Response and toxicity genes	Genotype	Phenotype
HTR2A (rs7997012)	A/A	Favorable response
SLC6A4	L/C	Favorable response
MTHFR (rs1801131)	A/A	60.0% reduction
MTHFR (rs1801133)	T/T	

Drug class	Use as directed in the prescribing information Minimal or no gene-drug interaction	Use with caution Moderate gene-drug interaction	Use with caution and close attention or consider an alternative drug Significant gene-drug interaction
Antidepressants		Amitriptyline	
		Citalopram	
		Clomipramine	
		Desipramine	
		Doxepin	
		Duloxetine	
		Escitalopram	
		Fluoxetine	
	Amoxapine	Fluvoxamine	
		Imipramine	
		Mirtazapine	
		Nortriptyline	
		Paroxetine	
		Protriptyline	
		Sertraline	
		Trimipramine	
		Venlafaxine	
		Vortioxetine	

Metabolism genes	**Genotype**	**Phenotype**
CYP2C9	*1/*2	Intermediate metabolizer
CYP2C9 (rs1057910)	A/A	Normal metabolizer
CYP2C19	*1/*2	Intermediate metabolizer
CYP2D6	*1/*5	Intermediate metabolizer

Escitalopram: Reduced metabolism. The applicable guideline from the Clinical Pharmacogenetics Implementation Consortium (CPIC) still recommends initiating therapy with the standard starting dose. There is evidence of a favorable response to treatment.

CYP2C19, SLC6A4, HTR2A – High level of scientific evidence

Figure 2. Knowledge transfer and formative assessment cycle used in the Epigenetics of Depression training module.

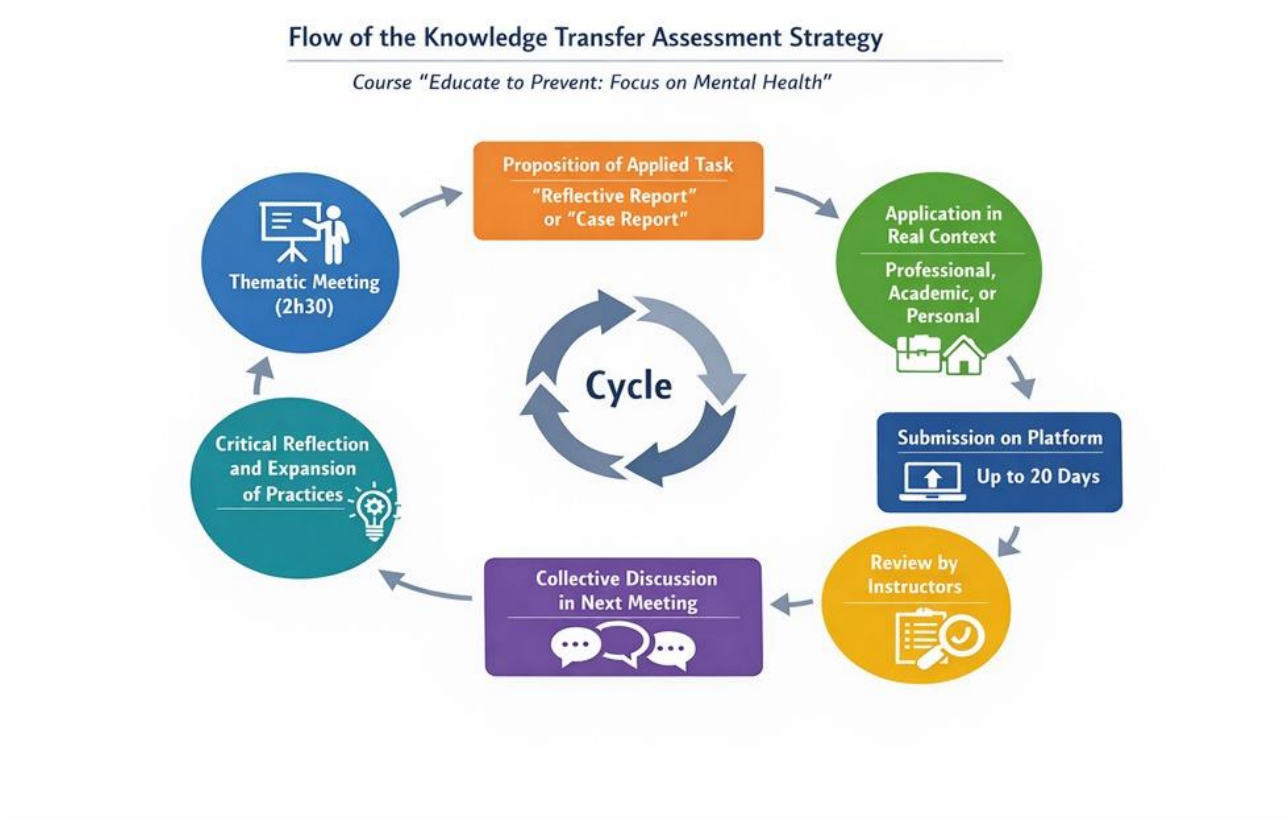


Figure 3. Healthcare professionals train their communities. Integration of epigenetic and pharmacogenetic insights into the clinical management of Major Depressive Disorder (MDD).

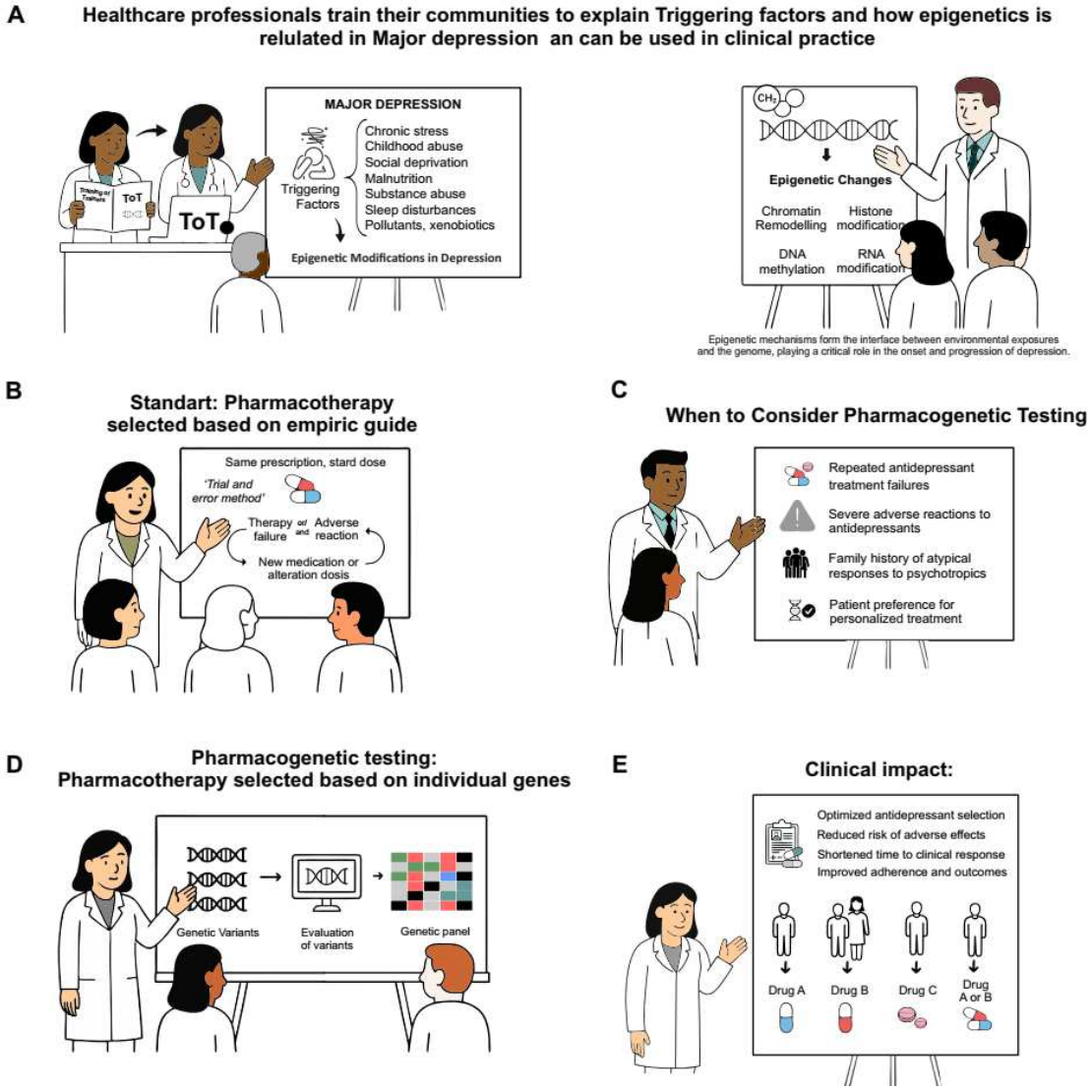


Figure 4. Conceptual model illustrating how early-life stress may influence depressive vulnerability through epigenetic regulation.

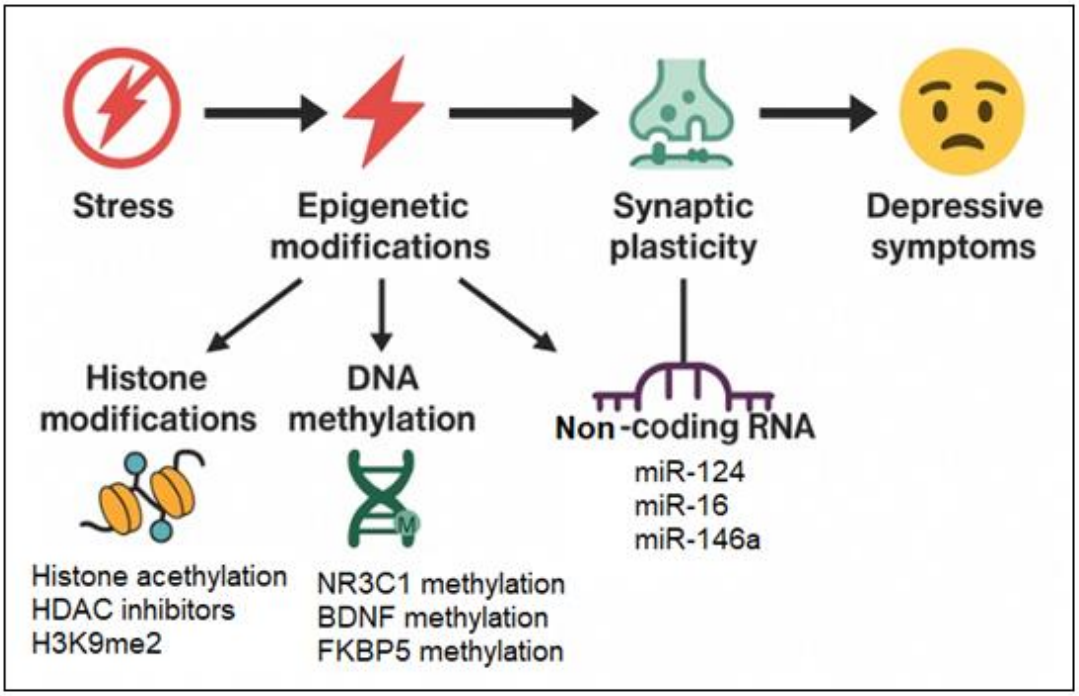
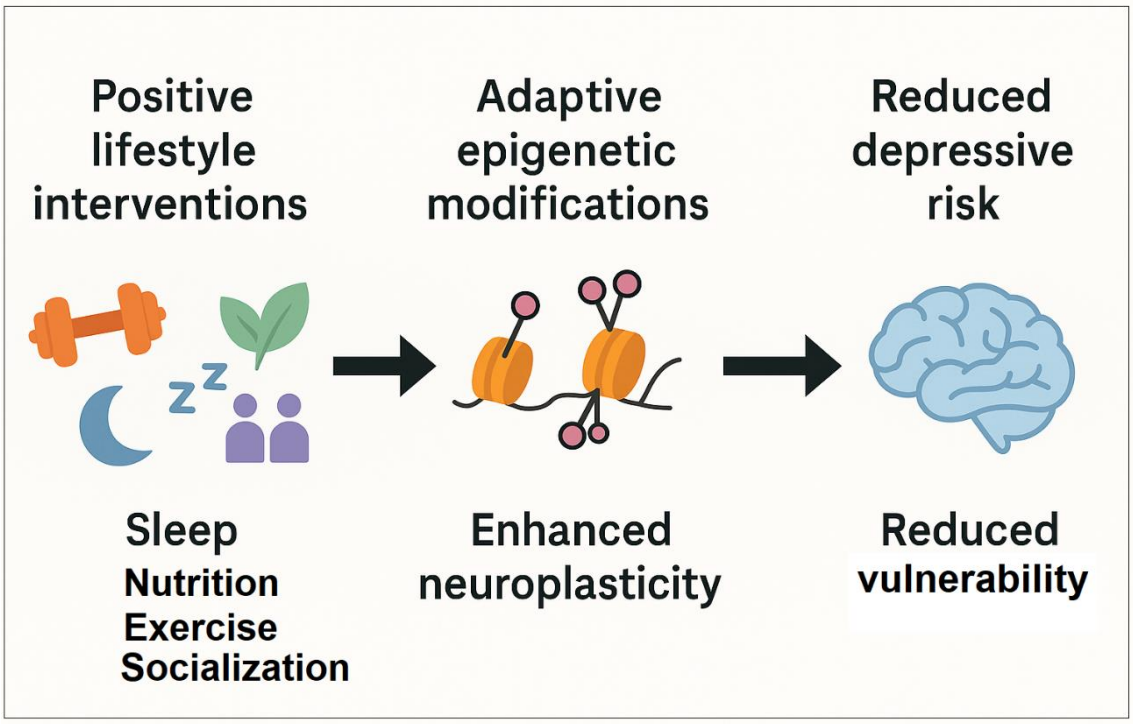


Figure 5. Conceptual model illustrating how positive lifestyle interventions may induce beneficial epigenetic modifications that support mental health and reduce depressive vulnerability.



Figures legends.

Figure 1.

This figure illustrates a pharmacogenetic report used as an educational resource during the case-based learning component of the training program. The report summarizes variants in pharmacodynamic genes (HTR2A, SLC6A4) and pharmacokinetic genes (CYP2C9, CYP2C19, CYP2D6), as well as folate-related variants (MTHFR C677T and A1298C).

The combined MTHFR genotype indicates reduced predicted enzymatic activity, which was discussed in the training context as a potential modifier of one-carbon metabolism and DNA methylation capacity, supporting the conceptual link between genetic vulnerability and epigenetic mechanisms. Pharmacokinetic results classify the patient as an intermediate metabolizer for CYP2C9, CYP2C19, and CYP2D6, while pharmacodynamic findings suggest a potentially favorable response to selective serotonin reuptake inhibitors (SSRIs).

Importantly, this pharmacogenetic profile was not used as a prescriptive clinical tool, but rather as a didactic example to illustrate how genetic, environmental, and clinical information can be integrated to support individualized and biologically informed clinical reasoning within the epigenetics education framework.

Abbreviations: CPIC, Clinical Pharmacogenetics Implementation Consortium; CYP, cytochrome P450; CYP2C9, cytochrome P450 family 2 subfamily C member 9; CYP2C19, cytochrome P450 family 2 subfamily C member 19; CYP2D6, cytochrome P450 family 2 subfamily D member 6; HTR2A, 5-hydroxytryptamine receptor 2A gene; MTHFR, methylenetetrahydrofolate reductase; SLC6A4, solute carrier family 6 member 4 (serotonin transporter gene).

Genotype notation: A, C, G, and T represent nucleotide alleles; homozygous genotypes are indicated by duplicate letters (e.g., A/A, T/T), and heterozygous genotypes by mixed alleles (e.g., A/T). L and S represent the long and short alleles of the SLC6A4 promoter polymorphism (5-HTTLPR).

Star allele notation: CYP genotypes are represented using star alleles (e.g., *1, *2, *5), where each star allele corresponds to a known functional variant. Diplotypes (e.g., *1/*2, *1/*5) are used to infer pharmacokinetic phenotypes (e.g., normal, intermediate, or poor metabolizer).

Figure 2. Following the thematic session, participants were assigned an applied task (reflective report or case report) aimed at integrating epigenetic concepts into real-world clinical, academic, or personal contexts. Submissions were uploaded to the educational platform within up to 20 days and reviewed by instructors. In subsequent meetings, collective discussions were conducted, promoting critical reflection, expansion of clinical practices, and peer learning. This iterative cycle emphasized formative evaluation and real-world knowledge application rather than formal pre- and post-training testing.

Figure 3. This figure presents a conceptual and educational framework used during the training sessions to illustrate how genetic, environmental, and clinical factors may be integrated in the understanding and management of major depressive disorder (MDD).

(A) Healthcare professionals engage in community education to recognize early-life stressors and adverse experiences that may influence gene expression through epigenetic mechanisms.

(B) Standard antidepressant treatment is discussed as frequently relying on a trial-and-error process, which may be associated with variable efficacy and tolerability.

(C) Pharmacogenetic testing is presented as a potential supportive tool in selected clinical scenarios, such as repeated treatment failure, significant adverse effects, atypical family treatment responses, or patient interest in individualized care.

(D) Gene-informed strategies are explored as a means to support clinical reasoning regarding antidepressant selection and dosing, based on individual genetic profiles.

(E) Within an educational context, these approaches are discussed in relation to potential clinical benefits, including improved treatment tolerability, enhanced adherence, and more efficient symptom management.

Importantly, this framework was used for educational purposes only, aiming to support reflective clinical reasoning and understanding of precision psychiatry concepts, rather than to establish prescriptive clinical recommendations.

Figure 4. Adverse childhood experiences (ACEs) are associated with epigenetic modifications, including histone modifications, DNA methylation changes, and alterations in non-coding RNA pathways, which may influence synaptic plasticity and stress responsivity and contribute to vulnerability to depressive phenotypes.
This schematic integrates evidence from preclinical and translational studies and is intended as a conceptual illustration of putative biological pathways, rather than a direct or deterministic causal representation.

Abbreviations: ACE, adverse childhood experiences; BDNF, brain-derived neurotrophic factor; DNA, deoxyribonucleic acid; FKBP5, FK506-binding protein 5; HDAC, histone deacetylase; H3K9me2, histone 3 lysine 9 demethylation; miR-16, microRNA-16; miR-124, microRNA-124; miR-146a, microRNA-146a; NR3C1, nuclear receptor subfamily 3 group C member 1 (glucocorticoid receptor gene); RNA, ribonucleic acid.

Figure 5. Lifestyle-related factors—such as restorative sleep, balanced nutrition, regular physical activity, and social connectedness—are discussed as potential modulators of molecular pathways involved in stress responsivity and neuroplasticity.

Within an educational context, these behaviors are presented as being associated with adaptive epigenetic processes, including histone acetylation, modulation of DNA methylation patterns, and regulation of microRNAs, which may support neuronal resilience and emotional regulation.

This figure was used to illustrate how lifestyle-oriented strategies could represent low-cost and scalable approaches for mental health promotion and primary prevention, rather than as prescriptive therapeutic recommendations.

6. CONCLUSÕES

Através desta pesquisa em DRT com abordagens multidimensionais que englobaram variantes genéticas de *MTHFR*, mecanismos epigenéticos, características clínicas e aspectos psicossociais, foi possível constatar que:

As variantes do *MTHFR* podem desempenhar um papel na suscetibilidade à DRT, porém sua contribuição deve ser considerada como a de um possível fator de risco ainda não estabelecido devido a dificuldades de não padronização metodológica na literatura científica disponível.

A validação da versão em português brasileiro do MGH-ATRQ permite sua implementação como um instrumento confiável que pode operacionalizar a detecção de DRT tanto em contextos clínicos quanto de pesquisa, melhorando a comparabilidade e a consistência de achados futuros.

Em nossa amostra de 156 pacientes com TDM, os casos de DRT apresentaram maior gravidade depressiva, menor adesão à medicação e maiores taxas de ACEs. Quanto a prejuízos funcionais, o grupo DRT apresentou maior comprometimento funcional em todos os itens avaliados: trabalho/escola, vida social, vida familiar, dias de ausência do trabalho/escola e dias improdutivos.

A redução da atividade enzimática prevista da MTHFR (≤50%) em nossa amostra de 78 pacientes com teste genético de variantes de *MTHFR* foi associada a maior gravidade de sintomas depressivos, maior número de episódios depressivos, maior número de tentativas prévias de suicídio e uso de antidepressivos potencializado com uso de antipsicóticos atípicos, o que sugere ser um sinal de maior complexidade do tratamento medicamentoso. Diferenças na gravidade clínica e nos desfechos funcionais entre os grupos de atividade da MTHFR foram observadas apesar da exposição comparável a ACEs e níveis comparáveis de adesão relatada ao tratamento medicamentoso , sugerindo uma vulnerabilidade biologicamente mediada em vez de uma carga diferencial de estresse no início da vida.

A abordagem ToT com CBL é viável para a transmissão de conceitos epigenéticos na educação em TDM, e pode auxiliar profissionais de saúde a ampliar sua compreensão das interações gene-ambiente deste transtorno, com possível contribuição para o reconhecimento precoce da vulnerabilidade e fundamentar estratégias preventivas e de apoio para a comunidade.

7. CONSIDERAÇÕES FINAIS

A DRT representa um dos maiores desafios contemporâneos da psiquiatria, tanto pelo impacto clínico e funcional nos indivíduos acometidos quanto pelas limitações dos modelos tradicionais de diagnóstico e tratamento. Ao longo desta tese, buscou-se explorar a DRT a partir de uma perspectiva multidimensional, integrando evidências genéticas, epigenéticas, clínicas e psicossociais, com o objetivo de contribuir para uma compreensão mais abrangente e translacional desse fenômeno complexo.

Os achados apresentados nos quatro artigos que compõem esta tese reforçam a heterogeneidade da DRT e evidenciam que a resistência ao tratamento não pode ser compreendida exclusivamente como falha terapêutica farmacológica.

A revisão sistemática demonstrou que variantes genéticas do gene *MTHFR*, particularmente 677C>T e 1298A>C, têm sido consistentemente associadas à DRT, sugerindo que alterações no metabolismo do folato e nos processos de metilação podem desempenhar papel relevante na vulnerabilidade biológica à resistência ao tratamento.

A validação transcultural da escala Massachusetts General Hospital Antidepressant Treatment Response Questionnaire (MGH-ATRQ) para o português brasileiro representa uma contribuição metodológica importante, ao disponibilizar um instrumento padronizado, confiável e clinicamente aplicável para a avaliação da resistência ao tratamento em pacientes com TDM. Esse achado fortalece a capacidade de identificação e estratificação de pacientes com DRT no contexto clínico e de pesquisa no Brasil, reduzindo ambiguidades conceituais e favorecendo comparabilidade entre estudos.

O terceiro artigo aprofundou a análise clínica ao demonstrar que a atividade enzimática predita da MTHFR se associa a maior gravidade depressiva, maior recorrência, maior complexidade terapêutica e pior funcionalidade, independentemente da exposição a experiências adversas na infância. Esse achado é particularmente relevante, pois sugere que a redução da atividade enzimática da MTHFR pode constituir um fator biológico independente de vulnerabilidade, modulando a expressão clínica da depressão e contribuindo para desfechos menos favoráveis. Ao mesmo tempo, a ausência de diferenças significativas entre os grupos quanto à frequência de experiências adversas na infância reforça a hipótese de que fatores genéticos e metabólicos podem atuar de forma autônoma ou interativa, sem determinismo causal simplista.

No quarto artigo, a abordagem educacional baseada no modelo Training of Trainers (ToT) evidenciou o potencial da psicoeducação em psiquiatria de precisão como estratégia de prevenção primária e promoção de saúde mental. Ao capacitar profissionais de saúde para compreender e disseminar conhecimentos sobre epigenética da depressão, experiências

adversas na infância e fatores ambientais modificáveis, o estudo amplia o foco da psiquiatria para além do tratamento farmacológico, incorporando ações de base comunitária, baixo custo e alto potencial de impacto populacional.

De forma integrada, os resultados desta tese sustentam a noção de que a DRT emerge da convergência entre predisposição genética, alterações epigenéticas induzidas por estressores ao longo da vida, características clínicas específicas e fatores psicossociais. Essa interação dinâmica desafia modelos lineares de causalidade e reforça a necessidade de abordagens personalizadas, que considerem não apenas sintomas, mas também trajetórias de vida, funcionamento global e vulnerabilidades biológicas subjacentes.

Do ponto de vista clínico, os achados apontam para a relevância da avaliação do metabolismo de um carbono, da história de estresse precoce e da funcionalidade como componentes essenciais na estratificação de pacientes com depressão. A identificação de indivíduos com atividade reduzida da MTHFR pode auxiliar na tomada de decisões terapêuticas mais precoces e individualizadas, incluindo estratégias de suplementação específica e maior vigilância quanto à recorrência e ao risco suicida. Ressalta-se, contudo, que tais achados não devem ser interpretados de forma determinística, mas inseridos em um modelo biopsicossocial ampliado.

Entre as limitações desta tese, destacam-se o delineamento transversal de parte dos estudos, o uso de amostras de conveniência e a impossibilidade de estabelecer relações causais diretas entre variáveis genéticas, epigenéticas e desfechos clínicos. Ainda assim, a convergência dos achados entre os diferentes artigos fortalece a plausibilidade dos modelos propostos e abre caminhos para investigações longitudinais futuras.

Em síntese, esta tese contribui para o avanço do conhecimento sobre a DRT ao integrar múltiplos níveis de análise — do molecular ao psicossocial — e ao propor uma visão mais abrangente, preventiva e personalizada do cuidado em saúde mental. Espera-se que esses achados possam subsidiar futuras pesquisas, informar a prática clínica e fomentar políticas de saúde que valorizem intervenções baseadas em evidências biológicas, educacionais e comunitárias, ampliando o alcance e a efetividade do cuidado em depressão.

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APÊNDICE A

Termo de Consentimento Livre e Esclarecido - TCLE ELETRÔNICO

Você está sendo convidado (a) a participar da pesquisa: Adaptação transcultural e validação da versão brasileira do Massachusetts General Hospital Antidepressant Treatment History Questionnaire (MGHATRQ) e características clínicas associadas à depressão refratária coordenada pela doutoranda Juliana Brum Moraes e sua orientadora Professora Dra. Sandra Odebrecht Vargas Nunes na Clínica Heber Vargas. O objetivo da pesquisa é adaptar e validar o MGHATRQ, uma escala de autoavaliação usada para determinar a resistência ao tratamento em Transtorno Depressivo Maior, para uma população brasileira. Sua participação é importante e se dará da seguinte forma: 1. Após seu atendimento clínico haverá a oferta para sua participação do estudo; caso você concorde, disponibilize seu *email ou whatsapp*; 2. Através desse *email ou whatsapp* você receberá um link para ser acessado por você com esse Termo de Consentimento Livre e Esclarecido (TCLE – online) e outro link para o questionário da pesquisa online. O questionário será constituído por dados sociais e clínicos e por 4 escalas que avaliam sintomas depressivos e de adesão ao tratamento (verificar o uso e cuidados com sua medicação); o tempo em média para responder a esse questionário e escalas será de 20 minutos. Exames laboratoriais disponíveis em prontuário médico serão coletados também. Por sua colaboração, você receberá um livro digital com informações sobre psicoeducação e estilo de vida saudável.

Esclarecemos que sua participação é totalmente voluntária, podendo recusar-se a participar, ou mesmo desistir a qualquer momento, sem que isto acarrete qualquer ônus ou prejuízo a você e seu tratamento. Esclarecemos, também, que as informações serão utilizadas somente para os fins deste estudo e serão tratadas com o mais absoluto sigilo e confidencialidade, de modo a preservar sua identidade. Esclarecemos ainda, que você não pagará e nem será remunerado(a) pela participação. Garantimos, no entanto, que todas as despesas decorrentes da pesquisa serão ressarcidas, quando devidas e decorrentes especificamente de sua participação. Os benefícios esperados serão que as intervenções digitais com educação em saúde vão contribuir adesão ao tratamento, favorecer o seu automonitoramento de sinais e sintomas, autocuidados, melhorar sua qualidade de vida e te ajudar a ter um estilo de vida mais saudável. Quanto aos riscos, se, em algum momento. perceber que pode ter apresentado alterações emocionais relativas às perguntas das escalas (questionário), pode entrar em contato com seu médico, o qual providenciará atendimento médico sem custos. Caso tenha dúvidas, ou necessite de maiores esclarecimentos, poderá nos contatar: Juliana Brum Moraes, endereço Clínica Heber Vargas , Rua João Wycliff, 111 salas 2608 e 2607. Telefone:43-988106336, email: julianabrumpsiq@gmail.com e/ou Sandra Odebrecht Vargas Nunes, CRM 7100-PR. Rua João Wycliff, 111, 26 andar, SALA 2604 fone 3328-8210, 98824-6138, email: **sandranunes@sercomtel.com.br** ou procurar o Comitê de Ética em Pesquisa Envolvendo

Seres Humanos da Universidade Estadual de Londrina, situado junto ao prédio do LABESC – Laboratório Escola, no Campus Universitário, telefone 3371-5455, e-mail: cep268@uel.br.

Disponível em: https://forms.gle/YghnSPpkdiSZhGFL9

APÊNDICE B

VERSÃO TRADUZIDA E ADAPTADA DE MCH-ATRQ PARA O PORTUGUÊS DO BRASIL

MASSACHUSETTS GENERAL HOSPITAL (MGH) QUESTIONÁRIO DE RESPOSTA AO TRATAMENTO COM ANTIDEPRESSIVOS (ATRQ)

(População Não-Geriátrica: 18 a 64 anos de idade)

Nota: A dose terapêutica mínima para cada antidepressivo na Seção I é baseada em informações de bula, literatura relevante e consulta com médicos especialistas.

Seção I. Fármacos antidepressivos

Instruções:

1. Por favor **assinale (√)** os nomes de qualquer medicamento que o participante fez uso desde o início do **EPISÓDIO ATUAL** de depressão.
2. Por favor **assinale (√)** se a dosagem diária do medicamento foi **igual ou maior que a dose terapêutica mínima** por no mínimo 6 semanas.
3. Apenas para os que utilizaram a dose terapêutica mínima por pelo menos 6 semanas, indique o percentual (%) de melhora no quadro depressivo relatado pelo participante quando ele sentiu que o tratamento funcionou melhor.
4. Se o participante inicialmente sentiu uma melhora ≥50% e então perdeu esta resposta (tolerância/taquifilaxia), este medicamento não será contabilizado como uma tentativa falha de tratamento antidepressivo.

Antidepressivos tricíclicos

Nome genérico	Administrado durante o episódio ATUAL de depressão (√)	Utilizou esta dose* por *pelo menos 6 semanas?* (√)		Apenas para os que utilizaram a dose terapêutica mínima por pelo menos 6 semanas: Baseado no feedback do participante, indique o percentual (%) de melhora no quadro depressivo relatado por ele quando o tratamento funcionou melhor. A. De 75% a 100% B. De 50% a <75% C. De 26% a <50% D. ≤ 25%
doxepina		150mg/d		
clomipramina		150mg/d		
amoxapina		150mg/d		
amitriptilina		150mg/d		
maprotilina		150mg/d		
desipramina		150mg/d		
nortriptilina		75 mg/d		
trimipramina		150mg/d		
imipramina		150mg/d		
protriptilina		30mg/d		

pipofezina		150mg/d		
noxiptilina		100mg/d		

* Se a dose estiver abaixo do mínimo necessário, níveis sanguíneos dentro do índice terapêutico do antidepressivo também são aceitáveis.

Inibidores da Monoaminoxidase (IMAOs)

Nome genérico	Administrado durante o episódio ATUAL de depressão (√)	Utilizou esta dose* por *pelo menos 6 semanas?* (√)		Apenas para os que utilizaram a dose terapêutica mínima por pelo menos 6 semanas: Baseado no feedback do participante, indique o percentual (%) de melhora no quadro depressivo relatado por ele quando o tratamento funcionou melhor. A. De 75% a 100% B. De 50% a <75% C. De 26% a <50% D. ≤ 25%
isocarboxazida		30mg/d		
fenelzina		45mg/d		
tranilcipromina		30mg/d		
adesivo de selegilina		6 mg/24h		
moclobemida		300 mg/d		
pirlindol		200 mg/d		

Inibidores Seletivos da Recaptação de Serotonina (ISRSs)

Nome genérico	Administrado durante o episódio ATUAL de depressão (√)	Utilizou esta dose* por *pelo menos 6 semanas?* (√)		Apenas para os que utilizaram a dose terapêutica mínima por pelo menos 6 semanas: Baseado no feedback do participante, indique o percentual (%) de melhora no quadro depressivo relatado por ele quando o tratamento funcionou melhor. A. De 75% a 100% B. De 50% a <75% C. De 26% a <50% D. ≤ 25%
fluvoxamina		50mg/d		
paroxetina		20/25mg/d		
fluoxetina		20 mg/d		
sertralina		50 mg/d		
citalopram		20mg/d		
escitalopram		10 mg/d		

Inibidores da Recaptação de Serotonina e Noradrenalina (IRSNs)

Nome genérico	Administrado durante o episódio ATUAL de depressão (√)	Utilizou esta dose* por *pelo menos 6 semanas?* (√)		Apenas para os que utilizaram a dose terapêutica mínima por pelo menos 6 semanas: Baseado no feedback do participante, indique o percentual (%) de melhora no quadro depressivo relatado por ele quando o tratamento funcionou melhor. A. De 75% a 100% B. De 50% a <75% C. De 26% a <50% D. ≤ 25%
venlafaxina / venlafaxina XR		75 mg/d		
duloxetina		60mg/d		
desvenlafaxina		50mg/d		
milnaciprano		100mg/d		
levomilnaciprano		40mg/d		

Outros antidepressivos

Nome genérico	Administrado durante o episódio ATUAL de depressão (√)	Utilizou esta dose* por *pelo menos 6 semanas?* (√)		Apenas para os que utilizaram a dose terapêutica mínima por pelo menos 6 semanas: Baseado no feedback do participante, indique o percentual (%) de melhora no quadro depressivo relatado por ele quando o tratamento funcionou melhor. A. De 75% a 100% B. De 50% a <75% C. De 26% a <50% D. ≤ 25%
trazodona		300mg/d		
bupropiona		300mg/d		
mirtazapina		15 mg/d		
mianserina		30 mg/d		
opipramol		150 mg/d		
nefazodona		300 mg/d		
agomelatina		25 mg/d		
tianeptina		37,5 mg/d		
reboxetina		4 mg/d		
vilazodona		40mg/d		
vortioxetina		10 mg/d		

Seção II. Medicamentos Aprovados pela FDA para Aumentar / Potencializar Efeito Antidepressivo

Instruções:

1. Por favor **assinale** (√) os nomes de qualquer medicamento que o participante fez uso para aumentar ou potencializar efeito antidepressivo durante o **EPISÓDIO ATUAL** de depressão.
2. Por favor **assinale** (√) se o participante tomou no mínimo esta dose por pelo menos 6 semanas em combinação com um **tratamento com antidepressivo da Seção I.**
3. Por favor indique o nome do antidepressivo da Seção I com o qual essa droga foi usada para aumentar ou potencializar seu efeito antidepressivo.
4. Por favor indique o valor (%) de melhora na depressão que o participante relatou, quando essa combinação estava funcionando melhor.

Nome genérico	Administrado durante o episódio ATUAL de depressão (√)	Tomou no mínimo essa dose *por pelo menos* 6 semanas em combinação com um antidepressivo da Seção I**? (√)		Nome do Antidepressivo da Seção I (ver acima) com o qual essa droga foi tomada	Apenas para os que utilizaram a dose terapêutica mínima por pelo menos 6 semanas: Baseado no feedback do participante, indique o percentual (%) de melhora no quadro depressivo relatado por ele quando o tratamento funcionou melhor. A. De 75% a 100% B. De 50% a <75% C. De 26% a <50% D. ≤ 25%
aripiprazol		5 mg/d			
quetiapina		150 mg/d			
brexpiprazol		1 mg/d			

**O antidepressivo da Seção I também deve ter sido tomado na dose terapêutica mínima durante as 6 semanas que o medicamento foi tomado para aumentar/potencializar o efeito.

APÊNDICE C

INSTRUMENTO DE COLETA DE DADOS DOS PARTICIPANTES DA PESQUISA

Adaptação transcultural e validação da versão brasileira do Massachusetts General Hospital Antidepressant Treatment History Questionnaire (MGHATRQ)

Você está sendo convidado a participar da pesquisa: Adaptação transcultural e validação da versão brasileira do Massachusetts General Hospital Antidepressant Treatment History Questionnaire (MGHATRQ) e características clínicas associadas a depressão refratária coordenada pela doutoranda Juliana Brum Moraes e sua orientadora Professora Dra. Sandra Odebrecht Vargas Nunes na Clinica Heber Vargas. O objetivo da pesquisa é adaptar e validar o MGHATRQ, uma escala de autoavaliação usada para determinar a resistência ao tratamento em Transtorno Depressivo Maior, para uma população brasileira. Agradecemos sua participação.

*** Indica uma pergunta obrigatória**

1. E-mail *

2. Nome completo *

3. Telefone com DDD *

4. Data de nascimento *

Exemplo: 7 de janeiro de 2019

5. Idade em anos *

6. Naturalidade *

Marcar apenas uma oval.

Brasileira Outro:

7. Situação conjugal *

Marcar apenas uma oval.

0- Solteiro(a)

1- União estável/Casado(a)

2- Separado/divorciado(a)

3- Viúvo(a)

8. Cor da pele *

Marcar apenas uma oval.

0- Branca

1- Preta

2- Pardo

3- Amarela

4- Indígena

9. Sexo *

Marcar apenas uma oval.

Feminino

Masculino

10. Anos de Estudo (responda em números) *

11. Reside *

Marcar apenas uma oval.

Sozinho (a)

Familiares Outro:

12. Renda familiar *

Marcar apenas uma oval.

0 - Menor que um salário mínimo

1 - Entre 1 e 2 salários mínimos inclusive

2 - Entre 2 e 3 salários mínimos inclusive

3 - Entre 3 e 4 salários mínimos inclusive

Entre 4 e 5 salários mínimos inclusive

Maior que 5 salários mínimos

13. Quantas pessoas vivem desta renda? (responda em números) *

14. Situação laboral *

Marcar apenas uma oval.

0 - Trabalha

1 - Desempregado (a)

2 - Auxílio-doença

3 - Aposentado (a)

4 - Trabalho não-remunerado

5 - Estudante

Diagnóstico de Transtorno Depressivo Maior

Critérios SCID para DSM-5 e critérios para CID-11

SCID - EPISÓDIO DEPRESSIVO MAIOR ATUAL

Agora irei fazer mais algumas perguntas sobre o seu humor.

15. A1. No último mês, desde (UM MÊS ATRÁS), houve algum período de tempo em que você se sentiu deprimido ou abatido na maior parte do dia, quase todos os dias? (Alguém disse que você parece triste, abatido ou deprimido?)

SE A RESPOSTA FOR NÃO: E quanto a se sentir triste, vazio ou sem esperança na maior parte do dia, quase todos os dias?

SE A RESPOSTA FOR SIM PARA UMA DAS PERGUNTAS ACIMA: Como foi isso? Quanto tempo durou? (Cerca de suas semanas?)

Marcar apenas uma oval.

–

+

16. A2. SE O ITEM ANTERIOR FOI CLASSIFICADO COMO "+":

Durante esse período, você sentiu menos interesse ou prazer com coisas de que normalmente gosta? (Como foi isso?) SE O ITEM ANTERIOR FOI CLASSIFICADO COMO "-" :

E houve algum período desde (UM MÊS ATRÁS) em que você perdeu o interesse ou o prazer por coisas de que normalmente gosta? (Como foi isso?)

SE A RESPOSTA FOR SIM PARA CADA UMA DAS PERGUNTAS ACIMA: Isso aconteceu quase todos os dias? Quanto tempo durou? (Cerca de duas semanas?) Marcar apenas uma oval.

-

+

SE PELO MENOS A1 OU A2 FOREM + , PROSSIGA PARA A3.

PARA AS PERGUNTAS A SEGUIR, CONCENTRE-SE NO PIOR PERÍODO DE DUAS SEMANAS

DO MÊS ANTERIOR:

Durante (PERÍODO DE DUAS SEMANAS)...

17. A3. ...como estava o seu apetite? (Como foi em comparação ao seu apetite habitual? Você teve que se forçar a comer? Comeu

[menos/mais] do que o habitual? Isso aconteceu quase todos os dias? Você perdeu ou ganhou peso?)

SE A RESPOSA FOR SIM: Quanto? (Você estava tentando [perder/ganhar] peso?

Marcar apenas uma oval.

-

+

18. A4. ...como você tem dormido? (Problema para adormecer, acordando frequentemente, problema para permanecer dormindo, acordando cedo demais OU dormindo em excesso?)

Quantas horas (incluindo cochilos) você tem dormindo? Quantas horas você costuma dormir antes de ficar (deprimido/TERMOS PRÓPRIOS DO PACIENTE)? Isso aconteceu quase todas as noites?

Marcar apenas uma oval.

-

+

19. A5. ...você tem se sentindo tão inquieto ou agitado que não consegue ficar sentado?

E quanto ao oposto: você tem falado mais lentamente, ou se movido mais lentamente do que o normal, como se estivesseatravessando um lamaçal?

(Em ambos os casos, chegou ao ponto de as outras pessoas notarem? O que elas notaram? Isso aconteceu quase todos os dias?)

Marcar apenas uma oval.

-

+

20. A6. ...como tem estado o seu nível de energia? (Sente-se cansado o tempo todo? Quase todos os dias?)

Marcar apenas uma oval.

-

+

21. A7. ...você tem tido sentimentos de inutilidade?

E tem se sentindo culpado em relação às coisas que você fez ou deixou de fazer?

SE A RESPOSTA FOR SIM: que tipo de coisas? (E isso é apenas porque você não consegue tomar conta das coisas, já que tem estado doente?)

SE A RESPOSA FOR SIM PARA UMA DAS PERGUNTAS ACIMA: Quase todos os dias?

Marcar apenas uma oval.

–

+

22. A8. ...tem tido problemas para pensar ou se concentrar? Tem sido difícil tomar decisões sobre coisas cotidianas? (Isso tem interferido em que tipo de coisas? Quase todos os dias?) Marcar apenas uma oval.

-

+

23. A9. ...as coisas tem estado tão ruins que você pensou bastante sobre a morte ou que seria melhor se estivesse morto? Você pensou em tirar a sua própria vida?

SE A RESPOSTA FOR SIM: Você fez alguma coisa a respeito?(O que você fez? Fez algum plano específico? Tomou alguma atitude para prepará-lo? Você chegou a tentar suicídio?) Marcar apenas uma oval.

-

+

24. A10. AO MENOS CINCO DOS SINTOMAS DO CRITÉRIO A ACIMA (A1-A9) SÃO CLASSIFICADOS COMO "+".

Marcar apenas uma oval.

NÃO Continue com A15 (Episódio Depressivo Maior Anterior)

SIM Continue com A11, a seguir.

25. A11. SE NÃO ESTIVER CLARO: Que efeito os (SINTOMAS DEPRESSIVOS) tiveram em sua vida?

FAÇA AS SEGUINTES PERGUNTAS APENAS QUANDO FOR NECESSÁRIO:

Como os (SINTOMAS DEPRESSIVOS) têm afetado seus relacionamentos ou suas iterações com outras pessoas? (Os [SINTOMAS DEPRESSIVOS] têm causado problemas em seus relacionamentos com familiares, parceiros românticos ou amigos?)

Como os (SINTOMAS DEPRESSIVOS) afetaram seu trabalho/seus estudos? (E quanto à sua assiduidade no trabalho/nos estudos? Os [SINTOMAS DEPRESSIVOS] têm tornado mais difícil a realização do seu trabalho/das suas tarefas escolares? Os [SINTOMAS

DEPRESSIVOS] têm afetado a qualidade de seu trabalho/das suas tarefas escolares?)

Como os (SINTOMAS DEPRESSIVOS) têm afetado sua capacidade de tomar conta das coisas em casa? E quanto a fazer coisas simples do dia a dia, como se vestir, tomar banho ou escovar os dentes? E quanto a fazer outras coisas que são importantes para você, como atividades religiosas, exercício físico ou passatempos? Você tem evitado de fazer algo porque sentiu não estava à altura da tarefa?

Os (SINTOMAS DEPRESSIVOS) afetaram outra parte importante da sua vida?

SE OS SINTOMAS DEPRESSIVOS NÃO INTERFEREM NA VIDA:

O quanto você se sente incomodado ou aborrecido por ter (SINTOMAS DEPRESSIVOS)?

Marcar apenas uma oval.

- Continue com A15 (Episódio Depressivo maior Anterior)

+ Continue Com A12, a seguir.

26. A12. SE FOR DESCONHECIDO: Quando os (EPISÓDIOS DE DEPRESSÃO) começaram?

Você estava fisicamente doente logo antes deste período de depressão ter começado?

SE A RESPOSTA FOR SIM: O que o médico disse?

Você estava tomando medicamentos logo antes de isso ter começado?

SE A RESPOSTA FOR SIM: Houve alguma mudança na quantidade do que você estava tomando?

Você estava bebendo ou usando drogas vendidas nas ruas logo antes disso começar?

Marcar apenas uma oval.

NÃO

SIM

27. RESPOSTA NÃO: Diagnóstico: Transtorno Depressivo devido a OCM ou Transtorno Depressivo Induzido por Substância Continue com A15 (Episódio Depressivo Maior Anterior)

RESPOSTA SIM: PRIMÁRIO; EPISÓDIO DEPRESSIVO MAIOR ATUAL Continue com A13, a seguir.

28. A13. SE FOR DESCONHECIDO: Quando este período de (depressão/TERMOS

PRÓPRIOS DO PACIENTE) começou?

29. A14. Em quantos períodos separados na sua vida você esteve (deprimido/TERMOS PRÓPRIOS DO PACIENTE) quase todos os dias por pelo menos 2 semanas e teve diversos dos sintomas que você descreveu , como (SINTOMAS DO EPISÓDIO DEPRESSIVO MAIOR ATUAL)?

SCID- EPISÓDIO DEPRESSIVO MAIOR ANTERIOR

30. A15. Você já teve um período de tempo em que se sentiu deprimido ou abatido pela maior parte do dia, quase todos os dias?

(Como foi isso?)

SE A RESPOSTA FOR NÃO: E quanto a se sentir triste, vazio ou sem esperança na maior parte do dia, quase todos os dias?

SE A RESPOSTA FOR SIM PARA UMA DAS PERGUNTAS ACIMA: Quanto tempo isso durou? (Cerca de duas semanas?) Marcar apenas uma oval.

-

+

31. A16. SE O ITEM ANTERIOR FOI CLASSIFICADO COMO "+":

Durante esse período, você perdeu o interesse ou prazer com coisas que normalmente gosta? (Como foi isso?)

SE O ITEM ANTERIOR FOI CLASSIFICADO COMO "-":

Você já teve um período de tempo em que perdeu o interesse ou prazer com coisas que normalmente gostava? (Como foi isso?)

SE A RESPOSTA FOI SIM PARA UMA DAS PERGUNTAS ACIMA: Quando isso aconteceu? Isso aconteceu quase todos os dias? Quanto tempo durou? (Cerca de duas semanas?)

Marcar apenas uma oval.

-

+

Você teve mais de um período como esse? (Que período foi o pior?)

SE NÃO ESTIVER CLARO: Você já teve períodos como esse (DE UM ANO PARA CÁ)?

NOTA: Se houver a possibilidade de mais de um episódio anterior, selecione o pior para sua

investigação de Episódio Depressivo Maior. Contudo, se houver um episódio no anterior, pergunte sobre esse episódio, mesmo que ele não tenha sido o pior.

PARA AS PERGUNTAS A SEGUIR, CONCENTRE-SE NAS PIORES DUAS SEMANAS DO EPISÓDIO DEPRESSIVO MAIOR ANTERIOR SOBRE O QUAL VOCÊ ESTÁ INQUIRINDO.

SE NÃO ESTIVER CLARO: Durante o (EPISÓDIO DEPRESSIVO MAIOR), quando você ficou mais (deprimido/TERMOS PRÓPRIOS DO PACIENTE)?

32. A17. Durante o (PIO PERÍODO DE DUAS SEMANAS)...

...como estava o seu apetite? (Como foi em comparação ao seu apetite habitual Você teve que se forçar a comer? Comeu [menos/mais] do que o habitual? Isso aconteceu quase todos os dias? Você perdeu ou ganhou peso? (Quanto? Você estava tentando perder ou ganhar peso?) Marcar apenas uma oval.

-

+

33. A18. ...como estava a qualidade do seu sono? (Problema para adormecer, acordando frequentemente, problema para permanecer dormindo, acordando cedo demais OU dormindo em excesso?)

Quantas horas (incluindo cochilos) você dormia?

Quantas horas você costuma dormir antes de ficar (deprimido/TERMOS PRÓPRIOS DO PACIENTE)? Isso aconteceu quase todas as noites?

Marcar apenas uma oval.

-

+

34. A19. ...você estava se sentindo tão inquieto ou agitado que não conseguia ficar sentado?

E quanto ao oposto: você falava mais lentamente, ou se mexia mais lentamente do que o normal, como se estivesse atravessando um lamaçal?

(Em ambos os casos, chegou ao ponto de as outras pessoas notarem? O que elas notaram? Isso aconteceu todos os dias?) Marcar apenas uma oval.

-

+

35. A20. ...como era o seu nível de energia? (Sentia-se cansado o tempo todo? Quase todos os dias?)

Marcar apenas uma oval.

-

+

36. A21. ...teve sentimentos de inutilidade?

Sentia-se culpado em relação às coisas que você fez ou deixou de fazer?

SE A RESPOSTA FOR SIM: Que tipo de coisas?(E isso foi apenas porque você no conseguiu tomar conta das coisas, já que ficou doente?)

SE A RESPOSTA FOR SIM PARA UMA DAS PERGUNTAS ACIMA: Quase todos os dias?

Marcar apenas uma oval.

–

+

37. A22. ... teve problemas de pensar ou se concentrar? Tem sido difícil tomar decisões sobre coisas cotidianas? (Isso tem interferido em que tipo de coisas? Quase todos os dias?) Marcar apenas uma oval.

-

+

38. A23. ...As coisas estavam tão ruins que você pensou bastante sobre a morte ou que seria melhor se estivesse morto? Você já pensou em tirar a própria vida?

SE A RESPOSTA FOR SIM: Você fez alguma coisa a respeito? (O que você fez? Fez algum plano específico? Tomou alguma atitude para prepará-lo? Você chegou a tentar suicídio?) Marcar apenas uma oval.

-

+

39. A24. AO MENOS CINCO DOS SINTOMAS DO CRITÉRIO A ACIMA (A15-A23) SÃO CLASSIFICADOS COMO "+".

Marcar apenas uma oval.

NÃO

SIM Continue com A25 (Critério B).

40. A25. SE NÃO ESTIVER CLARO: Que efeito os (SINTOMAS DEPRESSIVOS) tiveram em sua vida?

FAÇA AS SEGUINTES PERGUNTAS APENAS QUANDO FOR NECESSÁRIO:

Como os (SINTOMAS DEPRESSIVOS) afetaram seu relacionamento com outras pessoas? (Os [SINTOMAS

DEPRESSIVOS] causaram problemas em seu relacionamento com familiares, parceiros

românticos ou amigos?)

Como os (SINTOMAS DEPRESSIVOS) afetaram seu trabalho/seus estudos? (E quanto à sua assiduidade no trabalho/seus estudos? Os [SINTOMAS DEPRESSIVOS] tornaram mais difícil a realização do seu trabalho/das suas tarefas escolares? Os [SINTOMAS DEPRESSIVOS] afetam a qualidade do seu trabalho/das suas tarefas escolares?)

Como os [SINTOMAS DEPRESSIVOS] afetaram sua capacidade de tomar conta as coisas de casa? E quanto a fazer coisas simples do dia a dia, como se vestir, tomar banho ou escovar os dentes? E quanto a fazer outras coisas que eram importantes para você, como atividades religiosas, exercício físico ou passatempos?

Você evitou de fazer algo porque sentiu que não estava à altura da tarefa?

Os (SINTOMAS DEPRESSIVOS) afetaram outra parte importante de sua vida?

SE OS SINTOMAS DEPRESSIVOS NÃO INTERFERIRAM NA VIDA:

O quanto você se sentiu incomodado ou aborrecido por ter (SINTOMAS DEPRESSIVOS)?

Marcar apenas uma oval.

-

+ Continue com A26 (Critério C), a seguir.

41. A26. SE FOR DESCONHECIDO: Quando os (EPISÓDIOS DE DEPRESSÃO) começaram?

Você estava fisicamente doente logo antes de isso ter começado?

SE A RESPOSTA FOR SIM: O que o médico disse?

Você estava tomando medicamentos logo antes de isso ter começado?

SE A RESPOSTA FOR SIM: Houve alguma mudança na quantidade que você estava tomando?

Você estava bebendo ou usando drogas vendidas nas ruas logo antes de isso ter começado?

Marcar apenas uma oval.

-

+

RESPOSTA NÃO: Diagnóstico: Transtorno Depressivo devido a OCM ou Transtorno Depressivo Induzido por Substância RESPOSTA SIM: PRIMÁRIO; EPISÓDIO DEPRESSIVO MAIOR ATUAL Continue com A27, a seguir.

42. A27. SE FOR DESCONHECIDO: Quando este período de (depressão/TERMOS PRÓPRIOS DO PACIENTE) começou?

43. A28. Em quantos períodos separados na sua vida você esteve (deprimido/TERMOS

PRÓPRIOS DO PACIENTE) quase todos os dias por pelo menos duas semanas e teve diversos dos sintomas que descreveu, como (SINTOMAS DO PIOR EPISÓDIO)?

RESPOSTA "-" : Diagnóstico: Transtorno Depressivo devido a OCM ou Transtorno Depressivo Induzido por Substância RESPOSTA "+": PRIMÁRIO; Continue com A90, a seguir.

CID-11

Depressive disorders

(BlockL2-6A7)

Depressive disorders are characterized by depressive mood (e.g., sad, irritable, empty) or loss of pleasure accompanied by other cognitive, behavioural, or neurovegetative symptoms that significantly affect the individual's ability to function. A depressive disorder should not be diagnosed in individuals who have ever experienced a manic, mixed or hypomanic episode, which would indicate the presence of a bipolar disorder.

Coded Elsewhere: Premenstrual dysphoric disorder (GA34.41)

6A70 Single episode depressive disorder

Single episode depressive disorder is characterized by the presence or history of one depressive episode when there is no history of prior depressive episodes. A depressive episode is characterized by a period of almost daily depressed mood or diminished interest in activities lasting at least two weeks accompanied by other symptoms such as difficulty concentrating, feelings of worthlessness or excessive or inappropriate guilt, hopelessness, recurrent thoughts of death or suicide, changes in appetite or sleep, psychomotor agitation or retardation, and reduced energy or fatigue. There have never been any prior manic, hypomanic, or mixed episodes, which would indicate the presence of a bipolar disorder.

Exclusions: recurrent depressive disorder (6A71)

Adjustment disorder (6B43)

Bipolar or related disorders (BlockL2-6A6)

6A70.0 Single episode depressive disorder, mild

Single episode depressive disorder, mild, is diagnosed when the definitional requirements of a Depressive episode are met and the episode is of mild severity. None of the symptoms of the Depressive episode should be present to an intense degree. An individual with a Mild depressive episode typically has some, but not considerable, difficulty in continuing with ordinary work, social, or domestic activities and there are

no delusions or hallucinations.

6A70.1 Single episode depressive disorder, moderate, without psychotic symptoms

Single episode depressive disorder, moderate, without psychotic symptoms is diagnosed when the definitional requirements of a depressive episode have been met, there is no history of prior depressive episodes, the episode is of moderate severity, and there are no delusions or hallucinations during the episode. A depressive episode is characterized by a period of almost daily depressed mood or diminished interest in activities lasting at least two weeks accompanied by other symptoms such as difficulty concentrating, feelings of worthlessness or excessive or inappropriate guilt, hopelessness, recurrent thoughts of death or suicide, changes in appetite or sleep, psychomotor agitation or retardation, and reduced energy or fatigue. In a moderate depressive episode, several symptoms of a depressive episode are present to a marked degree, or a large number of depressive symptoms of lesser severity are present overall. An individual with a moderate depressive episode typically has considerable difficulty in continuing with work, social, or domestic activities, but is still able to function in at least some areas.

6A70.2 Single episode depressive disorder, moderate, with psychotic symptoms

Single episode depressive disorder, moderate, with psychotic symptoms is diagnosed when the definitional requirements of a depressive episode have been met, there is no history of prior depressive episodes, the episode is of moderate severity, and there are delusions or hallucinations during the episode. A depressive episode is characterized by a period of almost daily depressed mood or diminished interest in activities lasting at least two weeks accompanied by other symptoms such as difficulty concentrating, feelings of worthlessness or excessive or inappropriate guilt, hopelessness, recurrent thoughts of death or suicide, changes in appetite or sleep, psychomotor agitation or retardation, and reduced energy or fatigue. In a moderate depressive episode, several symptoms of a depressive episode are present to a marked degree, or a large number of depressive symptoms of lesser severity are present overall. An individual with a moderate depressive episode typically has considerable difficulty in continuing with work, social, or domestic activities, but is still able to function in at least some areas.

6A70.3 Single episode depressive disorder, severe, without psychotic symptoms

Single episode depressive disorder, severe, without psychotic symptoms is diagnosed when the definitional requirements for Single episode depressive disorder are met and the current episode is severe and there are no delusions or hallucinations during the episode. A depressive episode is characterized by a period of almost daily depressed

mood or diminished interest in activities lasting at least two weeks accompanied by other symptoms such as difficulty concentrating, feelings of worthlessness or excessive or inappropriate guilt, hopelessness, recurrent thoughts of death or suicide, changes in appetite or sleep, psychomotor agitation or retardation, and reduced energy or fatigue. In a severe depressive episode, many or most symptoms of a depressive episode are present to a marked degree, or a smaller number of symptoms are present and manifest to an intense degree, and the individual is unable to function in personal, family, social, educational, occupational, or other important domains, except to a very limited degree.

Inclusions: Agitated depression single episode without psychotic symptoms

Major depression single episode without psychotic symptoms

Vital depression single episode without psychotic symptoms

6A70.4 Single episode depressive disorder, severe, with psychotic symptoms

Single episode depressive disorder, severe, with psychotic symptoms is diagnosed when the definitional requirements for Single episode depressive disorder are met and the current episode is severe and there are delusions or hallucinations during the episode. A depressive episode is characterized by a period of almost daily depressed mood or diminished interest in activities lasting at least two weeks accompanied by other symptoms such as difficulty concentrating, feelings of worthlessness or excessive or inappropriate guilt, hopelessness, recurrent thoughts of death or suicide, changes in appetite or sleep, psychomotor agitation or retardation, and reduced energy or fatigue. In a severe depressive episode, many or most symptoms of a depressive episode are present to a marked degree, or a smaller number of symptoms are present and manifest to an intense degree and the individual is unable to function in personal, family, social, educational, occupational, or other important domains, except to a very limited degree.

6A70.5 Single episode depressive disorder, unspecified severity

Single episode depressive disorder, unspecified severity is diagnosed when the definitional requirements of a depressive episode have been met, there is no history of prior depressive episodes, and there is insufficient information to determine the severity of the current depressive episode. A depressive episode is characterized by a period of almost daily depressed mood or diminished interest in activities lasting at least two weeks accompanied by other symptoms such as difficulty concentrating, feelings of worthlessness or excessive or inappropriate guilt, hopelessness, recurrent thoughts of death or suicide, changes in appetite or sleep, psychomotor agitation or retardation,

and reduced energy or fatigue. The symptoms are associated with at least some difficulty in continuing with ordinary work, social, or domestic activities.

6A70.6 Single episode depressive disorder, currently in partial remission

Single episode depressive disorder, currently in partial remission, is diagnosed when the full definitional requirements for a depressive episode have been met and there is no history of prior depressive episodes. The full definitional requirements for a depressive episode are no longer met but some significant mood symptoms remain.

6A70.7 Single episode depressive disorder, currently in full remission

Single episode depressive disorder, currently in full remission is diagnosed when the full definitional requirements for one depressive episode have been met in the past and there are no longer any significant mood symptoms. There is no history of depressive episodes preceding the episode under consideration.

6A70.Y Other specified single episode depressive disorder

6A70.Z Single episode depressive disorder, unspecified

6A71 Recurrent depressive disorder

Recurrent depressive disorder is characterized by a history or at least two depressive episodes separated by at least several months without significant mood disturbance. A depressive episode is characterized by a period of almost daily depressed mood or diminished interest in activities lasting at least two weeks accompanied by other symptoms such as difficulty concentrating, feelings of worthlessness or excessive or inappropriate guilt, hopelessness, recurrent thoughts of death or suicide, changes in appetite or sleep, psychomotor agitation or retardation, and reduced energy or fatigue. There have never been any prior manic, hypomanic, or mixed episodes, which would indicate the presence of a Bipolar disorder.

Inclusions: seasonal depressive disorder

Exclusions: Adjustment disorder (6B43)

Bipolar or related disorders (BlockL2-6A6)

Single episode depressive disorder (6A70)

6A71.0 Recurrent depressive disorder, current episode mild

Recurrent depressive disorder, current episode mild is diagnosed when the definitional requirements for Recurrent depressive disorder have been met and there is currently a depressive episode of mild severity. A depressive episode is characterized by a period of almost daily depressed mood or diminished interest in activities lasting at least two weeks accompanied by other symptoms such as difficulty concentrating,

feelings of worthlessness or excessive or inappropriate guilt, hopelessness, recurrent thoughts of death or suicide, changes in appetite or sleep, psychomotor agitation or retardation, and reduced energy or fatigue. In a mild depressive episode, none of the symptoms are present to an intense degree. An individual with a mild depressive episode typically has some, but not considerable, difficulty in continuing with ordinary work, social, or domestic activities and there are no delusions or hallucinations.

6A71.1 Recurrent depressive disorder, current episode moderate, without psychotic symptoms

Recurrent depressive disorder, current episode moderate, without psychotic symptoms is diagnosed when the definitional requirements for recurrent depressive disorder have been met and there is currently a depressive episode of moderate severity, and there are no delusions or hallucinations during the episode. A depressive episode is characterized by a period of almost daily depressed mood or diminished interest in activities lasting at least two weeks accompanied by other symptoms such as difficulty concentrating, feelings of worthlessness or excessive or inappropriate guilt, hopelessness, recurrent thoughts of death or suicide, changes in appetite or sleep, psychomotor agitation or retardation, and reduced energy or fatigue. In a moderate depressive episode, several symptoms of a depressive episode are present to a marked degree, or a large number of depressive

symptoms of lesser severity are present overall. An individual with a moderate depressive episode typically has considerable difficulty in continuing with work, social, or domestic activities, but is still able to function in at least some areas.

6A71.2 Recurrent depressive disorder, current episode moderate, with psychotic symptoms

Recurrent depressive disorder, current episode moderate, with psychotic symptoms is diagnosed when the definitional requirements for Recurrent depressive disorder have been met and there is currently a depressive episode of moderate severity, and there are delusions or hallucinations during the episode. A depressive episode is characterized by a period of almost daily depressed mood or diminished interest in activities lasting at least two weeks accompanied by other symptoms such as difficulty concentrating, feelings of worthlessness or excessive or inappropriate guilt, hopelessness, recurrent thoughts of death or suicide, changes in appetite or sleep, psychomotor agitation or retardation, and reduced energy or fatigue. In a moderate depressive episode, several symptoms of a depressive episode are present to a marked degree, or a large number of depressive symptoms of lesser severity are present overall. An individual with a moderate depressive episode typically has

considerable difficulty in continuing with work, social, or domestic activities, but is still able to function in at least some areas.

6A71.3 Recurrent depressive disorder, current episode severe, without psychotic symptoms

Recurrent depressive disorder, current episode severe, without psychotic symptoms is diagnosed when the definitional requirements for Recurrent depressive disorder are met and the current episode is severe and there are no delusions or hallucinations during the episode. A depressive episode is characterized by a period of almost daily depressed mood or diminished interest in activities lasting at least two weeks accompanied by other symptoms such as difficulty concentrating, feelings of worthlessness or excessive or inappropriate guilt, hopelessness, recurrent thoughts of death or suicide, changes in appetite or sleep, psychomotor agitation or retardation, and reduced energy or fatigue. In a severe depressive episode, many or most symptoms of a depressive episode are present to a marked degree, or a smaller number of symptoms are present and manifest to an intense degree, and the individual is unable to function in personal, family, social, educational, occupational, or other important domains, except to a very limited degree.

Inclusions: Endogenous depression without psychotic symptoms

Major depression, recurrent without psychotic symptoms
Manic-depressive psychosis, depressed type without psychotic symptoms

Vital depression, recurrent without psychotic symptoms

6A71.4 Recurrent depressive disorder, current episode severe, with psychotic symptoms

Recurrent depressive disorder, current episode severe, with psychotic symptoms is diagnosed when the definitional requirements for Recurrent depressive disorder are met and the current episode is severe and there are delusions or hallucinations during the episode. A depressive episode is characterized by a period of almost daily depressed mood or diminished interest in activities lasting at least two weeks accompanied by other symptoms such as difficulty concentrating, feelings of worthlessness or excessive or inappropriate guilt, hopelessness, recurrent thoughts of death or suicide, changes in appetite or sleep, psychomotor agitation or retardation, and reduced energy or fatigue. In a severe depressive episode, many or most symptoms of a depressive episode are present to a marked degree, or a smaller number of symptoms are present and manifest to an intense degree and the individual is unable to function in personal, family, social, educational, occupational, or other important

domains, except to a very limited degree.

Inclusions: Endogenous depression with psychotic symptoms Manic-depressive psychosis, depressed type with psychotic symptoms

6A71.5 Recurrent depressive disorder, current episode, unspecified severity

Recurrent depressive disorder current episode, unspecified severity is diagnosed when the definitional requirements of a depressive episode have been met and there is a history of prior depressive episodes, but there is insufficient information to determine the severity of the current depressive episode. A depressive episode is characterized by a period of almost daily depressed mood or diminished interest in activities lasting at least two weeks accompanied by other symptoms such as difficulty concentrating, feelings of worthlessness or excessive or inappropriate guilt, hopelessness, recurrent thoughts of death or suicide, changes in appetite or sleep, psychomotor agitation or retardation, and reduced energy or fatigue. The symptoms are associated with at least some difficulty in continuing with ordinary work, social, or domestic activities.

6A71.6 Recurrent depressive disorder, currently in partial remission

Recurrent depressive disorder, currently in partial remission, is diagnosed when the definitional requirements for Recurrent depressive disorder have been met; the full definitional requirements for a depressive episode are no longer met but some significant mood symptoms remain.

6A71.7 Recurrent depressive disorder, currently in full remission

Recurrent depressive disorder, currently in full remission is diagnosed when the definitional requirements for recurrent depressive disorder have been met but currently there are no significant mood symptoms.

6A71.Y Other specified recurrent depressive disorder

6A71.Z Recurrent depressive disorder, unspecified

44. CID-11 6A70 Single episode depressive disorder

Marque todas que se aplicam.

6A70.0 Single episode depressive disorder, mild

6A70.1 Single episode depressive disorder, moderate, without psychotic symptoms

6A70.2 Single episode depressive disorder, moderate, with psychotic symptoms

6A70.3 Single episode depressive disorder, severe, without psychotic symptoms

6A70.4 Single episode depressive disorder, severe, with psychotic symptoms

6A70.5 Single episode depressive disorder, unspecified severity

6A70.6 Single episode depressive disorder, currently in partial remission

6A70.7 Single episode depressive disorder, currently in full remission

6A70.Y Other specified single episode depressive disorder 6A70.Z Single episode depressive disorder, unspecified

45. CID-11 6A71 Recurrent depressive disorder

Marque todas que se aplicam.

6A71.0 Recurrent depressive disorder, current episode mild

6A71.1 Recurrent depressive disorder, current episode moderate, without psychotic symptoms

6.A71.2 Recurrent depressive disorder, current epiosde moderate, with psychotic symptoms

6A71.3 Recurrent depressive disorder,current episode severe, without psychotic symptoms

6A71.4 Recurrent depressive disorder, current episode severe, with psychotic symptoms

6A71.5 Recurrent depressive disorder, current episode, unspecified severity

6A71.6 Recurrent depressive disorder, currently in partial remission

6A71.7 Recurrent depressive disorder, currently in full remission

6A71.Y Other specified recurrent depressive disorder

6A71.Z Recurrent depressive disorder, unspecified

Conhecendo mais o Transtorno Depressivo

46. Idade ao primeiro episódio depressivo *

47. Idade quando iniciou tratamento da depressão pela primeira vez *

48. Quantos episódios depressivos já apresentou ao longo da vida? Se não se lembra o número exato, especifique se for 4 ou mais. *

49. Alguma vez apresentou tentativa de suicídio? Se sim, quantas vezes? *

Marcar apenas uma oval.

Não

Sim, uma vez.

Sim, duas vezes.

Sim, três ou mais vezes.

50. Possui familiar de primeiro grau (pai, mãe, irmãos e filhos) com diagnóstico de depressão? *

Marcar apenas uma oval.

0 - não

1 - sim

51. Possui familiar de segundo grau (tios, sobrinhos e avós) com diagnóstico de depressão? *

Marcar apenas uma oval.

0 - não

1 - sim

52. Possui diagnóstico de alguma das seguintes comorbidades psiquiátricas? *

Marque todas que se aplicam.

Transtorno de Ansiedade Generalizada

Transtorno de Pânico

Transtorno Obsessivo-Compulsivo Transtorno Alimentar

Transtorno do Uso do Tabaco

Transtorno do Uso do Álcool Nenhuma

Escala de Depressão de Hamilton

Gostaria de lhe fazer algumas perguntas sobre a última semana. Como você tem se sentido desde a última (dia da semana)? Se paciente ambulatorial: Você tem trabalhado? Se não: Especifique por que não?

53. 1.HUMOR DEPRESSIVO (tristeza, desesperança, desamparo, inutilidade) *

Como tem estado seu humor na última semana?

Você tem se sentido para baixo ou deprimido?

Triste? Sem esperança?

Na última semana, com que frequência você se sentiu (utilize a palavra referida pelo paciente)? Todos os dias? O dia inteiro?

Você tem chorado?

Marcar apenas uma oval.

0 – ausente

1 – sentimentos relatados somente se perguntados

2 – sentimentos relatados espontaneamente, com palavras

3- comunica os sentimentos não com palavras, mas com expressão facial, postura, voz e tendência ao choro

4- o paciente comunica quase que exclusivamente esses sentimentos, tanto em seu relato verbal como na comunicação não-verbal.

54. 2.SENTIMENTOS DE CULPA *

Você tem se sentido especialmente autocrítico nesta última semana, sentindo que fez coisas erradas ou decepcionou outras pessoas?

SE SIM: quais foram esses pensamentos?

Você tem se sentido culpado em relação a coisas que fez ou não fez?

Você tem pensado que, de alguma forma, você é responsável pela sua depressão?

Você sente que está sendo punido ficando doente?

Marcar apenas uma oval.

0- ausente

1- auto-recriminação, acha que decepcionou outras pessoas

2- idéias de culpa ou ruminações de erros ou ações pecaminosas (más) no passado.

3- paciente acha que a doença atual é uma punição (castigo). Delírio de culpa.

4- ouve vozes que o acusam ou denunciam e/ou tem alucinações visuais ameaçadoras.

55. 3.SUICÍDIO *

Nessa última semana, você teve pensamentos de que não vale a pena viver ou que você estaria melhor morto? ou pensamentos de se machucar ou até de se matar?

SE SIM: o que você tem pensado sobre isso? Você já se machucou?

Marcar apenas uma oval.

0 – ausente

1- acha que não vale a pena viver

2- deseja estar morto ou pensa em uma possível morte para si

3- ideias ou atitudes suicidas

4- tentativas de suicídio

56. 4. INSÔNIA INICIAL *

Como tem sido seu sono na última semana?

Você teve alguma dificuldade em iniciar o sono? Após se deitar, quanto tempo leva para conseguir dormir?

Em quantas noites nesta última semana você teve problemas para iniciar o sono?

Marcar apenas uma oval.

0- sem dificuldades para iniciar o sono

1- queixa de dificuldade ocasional para iniciar o sono, ou seja, mais que meia hora

2- queixa de dificuldade para iniciar o sono todas as noites

57. 5. INSÔNIA INTERMEDIÁRIA *

Durante essa última semana, você tem acordado no meio da noite?

SE SIM: você sai da cama? o que você faz? (somente vai ao banheiro?) Quando volta para a cama, você volta a dormir logo?

Você sente que seu sono é agitado ou perturbado em algumas noites?

Marcar apenas uma oval.

0- sem dificuldade

1- queixa de agitação e perturbação durante a noite

2- acorda durante a noite – qualquer saída da cama (exceto por motivos de necessidade fisiológica)

58. 6. INSÔNIA TARDIA *

A que horas você tem acordado pela manhã na última semana?

Se cedo: acorda com despertador ou sozinho? A que horas você normalmente acordava (ou seja, antes de ficar deprimido)?

Marcar apenas uma oval.

0- sem dificuldade

1- acorda durante a madrugada, mas volta a dormir

2- não consegue voltar a dormir se levantar da cama durante a noite

59. 7. TRABALHO E ATIVIDADES *

Como você tem passado seu tempo na última semana (quando não está no trabalho)?

Você se sente interessado em fazer (essas atividades) ou você tem de se forçar?

Você parou de fazer atividades que costumava fazer? SE SIM: Por quê?

Há alguma coisa que você aguarda ansiosamente?

(no seguimento): Seu interesse voltou ao normal?

Marcar apenas uma oval.

0- sem dificuldades

1- pensamentos e sentimentos de incapacidade, fadiga ou fraqueza, relacionados a atividades, trabalho ou passatempos.

2- perda de interesse em atividades, passatempos ou trabalho, quer relatado diretamente pelo paciente, quer indiretamente por desatenção,indecisão ou vacilação (sente que precisa se esforçar para o trabalho ou outras atividades)

3- diminuição no tempo gasto em atividades ou queda de produtividade. No hospital, o paciente ocupa-se por menos de três horas por dia ematividades (trabalho hospitalar ou passatempos) com exceção das tarefas rotineiras da enfermaria

4- parou de trabalhar devido à doença atual. No hospital, sem atividades, com exceção das tarefas rotineiras da enfermaria, ou se nãoconsegue realizá-las sem ajuda.

60. 8. RETARDO *

Avaliação baseada na observação durante a entrevista:(lentificação do pensamento e da fala, dificuldade de concentração, diminuição da atividade motora) Marcar apenas uma oval.

0 - pensamentos e fala normais

1 - lentificação discreta à entrevista

2 - lentificação óbvia durante à entrevista

3 - entrevista difícil

4 - estupor completo

61. 9. AGITAÇÃO *

Avaliação baseada na observação durante a entrevista:

Marcar apenas uma oval.

0 - nenhuma

1 – inquietação

2 - mexe as mãos, cabelos etc.;

3 - movimenta-se bastante, não consegue permanecer sentado durante a entrevista

4 - retorce as mãos, rói as unhas, puxa os cabelos, morde os lábios

62. 10. ANSIEDADE PSÍQUICA *

Você tem se sentido especialmente tenso ou irritado nesta última semana?

Você tem estado preocupado com coisas pouco importantes com as quais normalmente não se preocuparia? SE SIM: Como com o quê, por exemplo?

Marcar apenas uma oval.

0 - sem dificuldade

1 - tensão e irritabilidade subjetivas

2 - preocupa-se com trivialidades

3 - atitude apreensiva aparente no rosto ou na fala

4 - paciente expressa medo sem ser perguntado

63. 11. ANSIEDADE – SOMÁTICA *

Na última semana, você sofreu de alguns dos seguintes sintomas físicos?

Leia a lista, parando após cada sintoma para resposta.

O quanto esses sintomas o incomodaram na última semana? Quão intensos foram? Quanto tempo ou com que freqüência os teve? Nota: não considerar se claramente relacionados à medicação (por exemplo, boca seca e imipramina)

Concomitantes fisiológicos da ansiedade, como:

GI: boca seca, flatulência, indigestão, diarréias, cólicas, eructações

CV: palpitação, cefaléias

Respiratórios: hiperventilação, suspiros

Ter de urinar freqüentemente Sudorese

Marcar apenas uma oval.

0 - ausente

1 - duvidoso ou trivial: sintomas menores, relatados quando questionados

2 - leve: paciente descreve espontaneamente os sintomas, que não são acentuados ou incapacitantes

3 - moderado: mais do que 2 sintomas e com maior freqüência. São acompanhados de estresse subjetivo e prejudicam o funcionamento

4 - grave: numerosos sintomas, persistentes e incapacitantes na maior parte do tempo, ou ataques de pânico quase diariamente

64. 12. SINTOMAS SOMÁTICOS – GASTRINTESTINAIS *

Como tem estado seu apetite nesta última semana? (Como se compara ao seu apetite habitual?)

Você tem tido que se forçar a comer?

As outras pessoas têm que insistir para você comer?

Marcar apenas uma oval.

0 – nenhum

1 - perda de apetite, mas come sem necessidade de insistência

2 - dificuldade para comer se não insistirem

65. 13. SINTOMAS SOMÁTICOS – GERAIS *

Como tem estado sua "energia" nesta última semana?

Você se sente cansado o tempo todo?

Nesta última semana, você teve dor nas costas, dor de cabeça ou dor muscular?

Nesta última semana, você tem sentido um peso nos membros, nas costas ou na cabeça?

Marcar apenas uma oval.

0 - nenhum

1 - peso em membros, costas ou cabeça; dor nas costas, na cabeça ou nos músculos. Perda de energia e fadiga

2 - qualquer sintoma bem caracterizado e nítido.

66. 14. SINTOMAS GENITAIS *

Como tem estado seu interesse por sexo nesta semana? (não estou lhe perguntando sobre seu desempenho, mas sobre seu interesse por sexo- o quanto você tem pensado nisso?

Houve alguma mudança em seu interesse por sexo (em relação à época em que você não estava deprimido)?

Isso é algo em que você tem pensado muito? Se não: isso é pouco habitual para você?

Marcar apenas uma oval.

0 - ausentes

1 - leves ou infreqüentes: perda de libido, desempenho sexual prejudicado

2 - óbvio e graves: perda completa do interesse sexual

67. 15. HIPOCONDRIA *

Na última semana, o quanto seus pensamentos têm focalizado na sua saúde física ou no funcionamento de seu corpo (comparado ao seu pensamento habitual)

Você se queixa muito de sintomas físicos?

Você tem-se deparado com situações em que você pede ajuda para fazer coisas que poderia fazer sozinho?

SE SIM: Como o quê, por exemplo? Com que frequência isso tem ocorrido?

Marcar apenas uma oval.

0 - ausente

1 - auto-observação aumentada (com relação ao corpo)

2 - preocupação com a saúde

3 - queixas frequentes, pedidos de ajuda etc.

4 - delírios hipocondríacos

68. 16. PERDA DE PESO*

Você perdeu algum peso desde que essa (DEPRESSÃO) começou? SE SIM: Quanto?

SE INCERTO: Você acha que suas roupas estão mais folgadas?

No Seguimento: Você voltou a ganhar peso?

Marcar apenas uma oval.

0 - sem perda de peso ou perda de peso NÃO causada pela doença atual

1 - perda de peso provavelmente causada pela doença atual. Perda de menos de meio quilo

2 - perda de peso definitivamente causada pela doença atual. Perda de meio quilo ou mais

69. 17. CRÍTICA (CONSCIÊNCIA DA DOENÇA) *

Avaliação baseada na observação Marcar apenas uma oval.

0 - reconhece estar deprimido e doente OU não estar deprimido no momento

1 - reconhece estar, mas atribui a causa à má alimentação, ao clima, ao excesso de trabalho, a um vírus, à necessidade de descanso etc.2 - nega estar doente

70. Soma tota de HDRS-17 *

QUESTIONÁRIO DE RESPOSTA AO TRATAMENTO COM ANTIDEPRESSIVOS DO MASSACHUSETTS GENERAL HOSPITAL (MGHATRQ)

(População Não-Geriátrica: 18 a 64 anos de idade)

Nota: A dose terapêutica mínima para cada antidepressivo na Seção I é baseada em informações de bula, literatura relevante e consulta com médicos especialistas.

Seção I. Fármacos antidepressivos Instruções:

1. **Por favor assinale (√) o nome de qualquer medicamento que o participante fez uso desde o início do EPISÓDIO ATUAL de depressão.**
2. **Por favor assinale (√) se a dosagem diária do medicamento foi igual ou maior que a dose terapêutica mínima por no mínimo 6 semanas.**
3. **Apenas para os que utilizaram a dose terapêutica mínima por pelo menos 6 semanas, indique o percentual (%) de melhora no quadro depressivo relatado pelo participante quando ele (ela) sentiu que o tratamento funcionou melhor.**
4. **Se o (a) participante inicialmente sentiu uma melhora ≥50% e então perdeu esta resposta (tolerância/taquifilaxia), este medicamento não será contabilizado como uma tentativa falha de tratamento antidepressivo.**

71. Antidepressivos tricíclicos

Marcar apenas uma oval por linha.

150mg/d

72. Antidepressivos tricíclicos

Apenas para os que utilizaram a dose terapêutica mínima por pelo menos 6 semanas:

Baseado (a) no feedback do participante, indique o percentual (%) de melhora no quadro depressivo relatado por ele (ela) quando o tratamento funcionou melhor.

Marcar apenas uma oval.

A. De 75% a 100%

B. De 50% a <75%

C. De 26% a <50%

D. ≤ 25%

73. Inibidores da Monoaminoxidase (IMAOs)

Marcar apenas uma oval por linha.

dose por pelo menos 6

semanas?

(Obs: Se a dose estiver

Administrado abaixo do durante o mínimo episódio necessário, ATUAL de níveis depressão sanguíneos

dentro do índice

terapêutico do antidepressivo também são aceitáveis). pirlindol 200 mg/dpirlindol 200 mg/d

74. Inibidores da Monoaminoxidase (IMAOs)

Apenas para os que utilizaram a dose terapêutica mínima por pelo menos 6 semanas:

Baseado (a) no feedback do participante, indique o percentual (%) de melhora no quadro depressivo relatado por ele (ela) quando o tratamento funcionou melhor.

Marcar apenas uma oval.

A. De 75% a 100%

B. De 50% a <75%

C. De 26% a <50%

D. ≤ 25%

75. Inibidores Seletivos da Recaptação da Serotonina (ISRSs)

76. Inibidores Seletivos da Recaptação da Serotonina (ISRSs)

Apenas para os que utilizaram a dose terapêutica mínima por pelo menos 6 semanas:

Baseado (a) no feedback do participante, indique o percentual (%) de melhora no quadro depressivo relatado por ele (ela) quando o tratamento funcionou melhor.

Marcar apenas uma oval.

A. De 75% a 100%

B. De 50% a <75%

C. De 26% a <50%

D. ≤ 25%

77. Inibidores da Recaptação de Serotonina e Noradrenalina (IRSNs)

78. Inibidores da Recaptação de Serotonina e Noradrenalina (IRSNs)

Apenas para os que utilizaram a dose terapêutica mínima por pelo menos 6 semanas:

Baseado no feedback do participante, indique o percentual (%) de melhora no quadro depressivo relatado por ele quando o tratamento funcionou melhor.

Marcar apenas uma oval.

A. De 75% a 100%

B. De 50% a <75%

C. De 26% a <50%

D. ≤ 25%

79. Outros antidepressivos

Marcar apenas uma oval por linha.

vortioxetina

10mg/d

80. Outros antidepressivos

Apenas para os que utilizaram a dose terapêutica mínima por pelo menos 6 semanas:

Baseado no feedback do participante, indique o percentual (%) de melhora no quadro depressivo relatado por ele quando o tratamento funcionou melhor.

Marcar apenas uma oval.

A. De 75% a 100%

B. De 50% a <75%

C. De 26% a <50%

D. ≤ 25%

Medicamentos Aprovados pela FDA para Aumentar/Potencializar Efeito Antidepressivo Instruções:

1. Por favor assinale (√) os nomes de qualquer medicamento que o participante fez uso para aumentar ou potencializar efeito antidepressivo durante o EPISÓDIO ATUAL de depressão.

2. Por favor assinale

(√) se o participante tomou no mínimo esta dose por pelo menos 6 semanas em combinação com um tratamento com antidepressivo da Seção I.

3. Por favor indique o nome do antidepressivoda Seção I com o qual essa droga foi usada para aumentar ou potencializar seu efeito antidepressivo.

4. Por favor indique o valor (%) de melhora nadepressão que o participante relatou, quando essa combinação estava funcionando melhor.

81. Medicamentos Aprovados pela FDA para Aumentar/Potencializar Efeito Antidepressivo

82. Nome do Antidepressivo da Seção I - antidepressivos - (ver acima) com o qual essa droga foi tomada.

83. Medicamentos Aprovados pela FDA para Aumentar/Potencializar Efeito Antidepressivo Apenas para os que utilizaram a dose terapêutica mínima por pelo menos 6 semanas:

Baseado no feedback do participante, indique o percentual (%) de melhora no quadro depressivo relatado por ele quando o tratamento funcionou melhor.

Marcar apenas uma oval.

A. De 75% a 100%

B. De 50% a <75%

C. De 26% a <50%

D. ≤ 25%

Definição padronizada de Depressão Resistente ao Tratamento

84. Assinale os critérios de acordo com registros médicos. *

Marcar apenas uma oval por linha.

Falha em alcançar remissão após dois cursos de tratamento antidepressivo

bem
estabelecidos em dose e duração
aceitáveis
com base em evidências.

Score de HRSD 17> 16 após 8-12 semanas de tratamento

Escala de adesão ao tratamento - MARS

Escala deve ser respondida em relação ao uso de antidepressivos listados no MGHATRQ

85. 1. Alguma vez se esqueceu de tomar a sua medicação? *

Marcar apenas uma oval.

0 - não

1 - sim

86. 2. Por vezes é descuidado ao tomar a sua medicação? *

Marcar apenas uma oval.

0 não

1 sim

87. 3. Quando se sente melhor, deixa, por vezes, de tomar a sua medicação? *

Marcar apenas uma oval.

0 não

1 sim

88. 4. Por vezes, se sente pior quando toma a medicação, deixa de tomá-la? *

Marcar apenas uma oval.

0 - não

1 - sim

89. 5. Só tomo a medicação quando me sinto doente? *

Marcar apenas uma oval.

0 - não

1 - sim

90. 6. Não é natural para minha mente e meu corpo ser controlado pela medicação? *

Marcar apenas uma oval.

0 - não

1 - sim

91. 7. Os meus pensamentos são mais claros com a medicação? *

Marcar apenas uma oval.

0 - não

1 - sim

92. 8. Por eu estar usando a medicação posso prevenir que eu fique doente? *

Marcar apenas uma oval.

0 - não

1 - sim

93. 9. Sinto-me estranho ou como um zumbi com a medicação? *

Marcar apenas uma oval.

0 - não

1 - sim

94. 10. A medicação faz com que eu me sinta cansado e lento? *

Marcar apenas uma oval.

0 - não

1 - sim

Dados clínicos

95. Qual doença clínica você possui? (Pode assinalar mais de uma resposta) *

Marque todas que se aplicam.

0 Não possuo nenhuma doença clínica

1 - Hipertensão arterial

2 Diabetes

3 Dislipidemia (colesterol ou trigligerideos altos, HDL baixo)

4 Obesidade5- Hipotireoidismo

Outro:

96. Altura em centímetros *

97. Peso em quilogramas *

98. Circunferência abdominal em centímetros *

99. Gene MTHFR *

Marque todas que se aplicam.

677C>T homozigoto selvagem (negativo)

677C>T heterozigoto

677C>T homozigoto mutante

1298A>C homozigoto selvagem (negativo)

1298A>C heterozigoto

1298A>C homozigotomutante Teste não realizado

100. Está em uso atual de Metilfolato? *

Marcar apenas uma oval.

Não

Sim, porém uso irregular (menos que 4x/semana)

Sim, dose diária de 7,5 mg

Sim, dose diária de 15 mg

Escala de Incapacidade de Sheehan

Responda como você tem se desempenhado na ÚLTIMA SEMANA

Marque ZERO se não houver alteração e DEZ se estiver extremamente difícil realizar alguma tarefa.

101. Os sintomas têm interrompido suas atividades no trabalho/escola: *

Marcar apenas uma oval.

0 1 2 3 4 5 6 7 8 9 10

102. Os sintomas têm interrompido sua vida social: *

Marcar apenas uma oval.

0 1 2 3 4 5 6 7 8 9 10

103. Os sintomas têm interrompido sua vida familiar/responsabilidades do lar: *

Marcar apenas uma oval.

0 1 2 3 4 5 6 7 8 9 10

104. Dias perdidos - Teve faltas no trabalho (considere home office como dia regular de trabalho) e/ou escola? (Contabilize os dias * perdidos/faltas no último mês)

105. Dias improdutivos - Mesmo que tenha ido ao trabalho e escola ou trabalho em casa, os sintomas têm diminuído sua * produtividade?

(Contabilize os dias improdutivos no último mês)

Experiências adversas na infância

Antes dos 18 anos, como foram suas experiências ?

106. 1. Algum dos pais ou outro adulto em casa frequentemente ou muito frequentemente: a(o) ofendia, a(o) insultava, a(o)menosprezava, a(o) humilhava? Ou agiam de tal forma que a(o) faziam temer ser fisicamente agredida(o)?

Marcar apenas uma oval.

0 - não

1 - sim

107. 2. Algum dos pais ou outro adulto em casa frequentemente ou muito frequentemente: a(o) empurrava, agarrava, esbofeteava ou * atirava objetos contra si? Ou alguma vez lhe bateu de tal forma que gerou marcas ou danos físicos?

Marcar apenas uma oval.

0 - não

1 - sim

108. 3. Algum adulto ou pessoa pelo menos 5 anos mais velha alguma vez: a(o) tocou ou acariciou ou a(o) levou a tocar o corpo deles de * forma sexual? Ou tentou ter ou teve relações sexuais orais, anais ou vaginais consigo?

Marcar apenas uma oval.

0 - não

1 - sim

109. 4. Sentia frequentemente ou muito frequentemente que: Ninguém na sua família a(o) amava ou não pensava que você eraimportante ou especial? Ou membros da sua família não se preocupavam pelo bem estar de cada um, não se sentiam próximos uns dos outros, ou não apoiavam uns aos outros?

Marcar apenas uma oval.

0 - não

1 - sim

110. 5. Sentia frequentemente ou muito frequentemente que: Não tinha o suficiente para comer, tinha de usar roupas sujas, e não tinha * ninguém que (a)o protegesse? Ou seus pais estavam demasiado embriagados ou sobre o efeito de drogas para cuidar de si ou leválo ao médico caso precisasse?

Marcar apenas uma oval.

0 - não

1 - sim

111. 6. Alguma vez os seus pais se separaram ou divorciaram? *

Marcar apenas uma oval.

0 - não

1 - sim

112. 7. A sua mãe ou madrasta: Era frequentemente ou muito frequentemente empurrada, agarrada, esbofeteada, ou lhe atiravamobjetos contra ela? Ou era algumas vezes, frequentemente ou muito frequentemente pontapeada, mordida, batida com murros, ou atingida com objetos pesados?

Marcar apenas uma oval.

0 - não

1 - sim

113. 8. Viveu com alguém que sofresse de problemas de bebida ou alcoolismo, ou que usasse drogas ilícitas? *

Marcar apenas uma oval.

0 - não

1 - sim

114. 9 - Você viveu com alguém que estivesse deprimido, que tivesse algum problema psiquiátrico ou que tentou suicídio? *

Marcar apenas uma oval.

0 - não

1 - sim

115. 10. Algum dos membros da família foi preso? *

Marcar apenas uma oval.

0 - não

1 - sim

ANEXO 1

Parecer do Comitê de Ética em Pesquisa Envolvendo Seres Humanos

PARECER CONSUBSTANCIADO DO CEP

DADOS DA EMENDA

Título da Pesquisa: Intervenções digitais psicoeducacionais para pacientes com Transtorno Depressivo Maior e Transtorno de Ansiedade Generalizada ensaio clínico randomizado

Pesquisador: Sandra Nunes **Área Temática:**

Versão: 7

CAAE: 30628120.9.0000.5231

Instituição Proponente:CCS - Programa de Pós-Graduação em Ciências da Saúde - Stricto sensu **Patrocinador Principal:** Financiamento Próprio

DADOS DO PARECER

Número do Parecer: 5.420.735

Apresentação do Projeto:

Este é um protocolo de emenda ao projeto.

Trechos extraídos do original da pesquisadora:

"O Estudo tem por finalidade avaliar a o uso de um aplicativo de celular e de e-book como ferramentas para uma intervenção educação em saúde na promoção da saúde , adesão ao tratamento, estilo de vida saudável. A população do estudo será constituída por portadores de transtornos mentais (Transtornos de humor, transtornos de ansiedade) em acompanhamento ambulatorial e, em condições cognitivas para o uso do aplicativo e do ebook e compreensão do estudo. Os participantes da pesquisa serão recrutados via home page da clínica que faz acompanhamento psiquiátrico. Haverá a oferta para participação do estudo e uso do aplicativo e do ebook . Os interessados em participar do estudo receberão informações sobre a pesquisa e o Termo de Consentimento Livre e Esclarecido (TCLE- online). Após concordar com os termos dispostos no TCLE, o

questionário será liberado e o participante poderá preenchê-lo. Os participantes do estudo serão aleatorizados ou randomizados por meio de sorteio, confeccionado por uma estatística. Alocando os indivíduos em um grupo experimental (uso de aplicativo para celular) e um grupo controle (uso de e-book). Na fase tempo 0, fase basal, os participantes serão

avaliados por meio de questionário sociodemográfico, escalas para avaliar: qualidade de vida (WHOQOLBREF), traumas na infância (CTQ), percepção de estresse , Hamilton, perda do controle alimentar , atividade física, avaliação de transtornos alimentares, severidade do tabagismo, triagem do envolvimento com álcool, tabaco e outras substâncias. Após o paciente terminar de responder o instrumento de coleta da fase basal , será disponibilizado o acesso ao uso do aplicativo e do link para baixar o ebook . O aplicativo será interativo e com orientações diárias ao paciente por 12 semanas. O ebook contará com o conteúdo similar ao aplicativo móvel. Após esse período de 12 semanas serão refeitas as escalas qualidade de vida (WHOQOL-BREF), percepção de estresse , Hamilton, perda do controle alimentar , atividade física, avaliação de transtornos alimentares, severidade do tabagismo, triagem do envolvimento com álcool, tabaco e outras substâncias e de adesão ao tratamento. Será ofertado o uso do aplicativo aos participantes do grupo controle e do ebook para os participantes do grupo experimental após as 12 semanas. Após a realização da pesquisa o aplicativo será disponibilizado para Secretaria de Saúde do Município de Londrina e para Ministério da saúde para ser disponibilizado nos serviços de saúde públicos. Na Emenda E2 - O Objetivo será avaliar intervenções digitais (aplicativo ou e-book) em educação em saúde para adolescentes e jovens. A metodologia, as escalas e questionários a serem utilizados serão os mesmos. Como resultados esperados: contribuir para os jovens adquirirem autocuidados e comportamentos saudáveis. Espera-se, avaliar qual das intervenções digitais (app para celulares ou e-book) possa melhor contribuir para melhorar a gravidade dos sintomas, a qualidade de vida, redução do peso e circunferência abdominal, bem como aumentar comportamentos

saudáveis, em jovens. Na Emenda E3 - a população recrutada será com idade entre 18-65 anos.”

“Segundo a Organização Mundial da Saúde (OMS) os problemas de saúde mental são responsáveis por uma morbidade significativa em todo o mundo, atingindo, aproximadamente, 700 milhões de pessoas (1). Cerca de 90% das pessoas com problemas de saúde mental apresentam manifestações de depressão e ansiedade, incluindo sintomas como insônia, fadiga, irritabilidade, dificuldade de memória e concentração e queixas somáticas (2) Os transtornos psiquiátricos apresentam comorbidades com transtornos relacionados ao uso de substâncias (3) , com a obesidade e outros distúrbios metabólicos. (4).Indivíduos que sofreram maus-tratos na infância possuem um risco maior de desenvolver transtornos do humor e doenças crônicas na a vida adulta (5). Os maus-tratos na infância estão associados ao desenvolvimento de problemas cognitivos e de aprendizado durante a infância e adolescência e, na vida adulta, ao abuso de substâncias, distúrbios metabólicos (6) . Os Maus tratos na infância aumenta o risco de doenças

cardiometabólicas , por meio de estilo de vida não saudável, fatores inflamatórios e comorbidades com depressão e ansiedade (5) A adesão a tratamentos para portadores de transtornos mentais é fundamental para que ações de reabilitação psicossocial sejam implementadas para reduzir a cronicidade (7) (8).Consideramos que as ações de reabilitação psicossocial efetivas devem comtemplar a promoção da saúde. A promoção da saúde é o processo que permite que as pessoas possam aumentar o controle e melhorar a sua saúde. Processo que possibilita as ações direcionadas ao fortalecimento das suas potencialidades e habilidades (9) (10).As estratégias de promoção enfatizam a transformação das condições de vida e de trabalho que conformam a estrutura subjacente aos problemas de saúde (11). Observamos que na promoção da saúde as ações não são determinadas a uma determinada doença ou desordem, mas sim para aumentar a saúde e o bem estar.Ações de promoção da saúde podem ser alcançadas por meio de educação em saúde, que inclui, em geral, o fornecimento de informações sobre a natureza da doença,

seus tratamentos e estratégias de enfrentamento de estressores para o paciente e a família.(12) A intervenção de psicoeducação para adesão ao tratamento pode reduzir os sintomas de fase aguda, prevenir as recaídas, restaurar a funcionalidade e a qualidade de vida. A intervenção por meio de educação em saúde realizada por meio de ferramentas digitais tem se mostrado uma estratégia efetiva e de alcance abrangente para esta população de adolescentes(13). Os adolescentes que sofreram maus-tratos na infância têm maior probabilidade de adquirir doenças cardiomtabólicas na adolescência e vida adulta (6) . A educação em saúde para doenças cardiometabólicos por meio de aplicativos digitais pode aprimorar o conhecimento relativo à estilo de vida saudável, melhorar o automonitoramento de peso, dieta, atividade física, prevenir o uso de cigarro e consumo alcoólico e promover uma participação ativa dos participantes em preservar a saúde(13). A educação em saúde por meio de intervenções digitais contribui melhorar a adesão ao tratamento, mesmo em pacientes com menor renda econômica e pouco nível educacional (14) . A Organização Mundial da Saúde reconhece a intervenção digital como meios em educação em saúde para mudanças comportamentais em doenças para a melhorar estilo de vida(15) .E2 - Fundamentação Teorica : Organização Mundial da Saúde (OMS) relata que a obesidade em crianças e adolescentes está sendo considerada uma doença crônica, com aumento progressivo, tendo triplicado em quatro décadas. A obesidade e sobrepeso na infância e adolescência pode ser prevenida (16). Os jovens que experimentam ansiedade e depressão. estão associados a obesidade a abuso de substâncias(17). Todavia, jovens, particularmente adolescentes mais jovens, não conseguem identificar os sintomas que experimentam, tais como "ansiedade" e‘depressão’, além de apresentarem dificuldade em falar sobre as emoções, portanto engajar os jovens em aplicativos

digitais poderia ser uma forma de educação em saúde para lidar com o emocional (18).Para enfrentar uma epidemia global de obesidade em adolescentes e jovens, será necessário buscar educação em saúde visando melhoria geral da promoção de saúde por meio de hábitos alimentares adequados e estímulo à atividades físicas (19). A intervenção por meio de educação em saúde realizada por meio de ferramentas digitais

tem se mostrado uma estratégia efetiva e de alcance abrangente para população de adolescentes e jovens 5.Os aplicativos móveis podem contribuir para a promoção de nutrição saudável, atividade física e

prevenção do excesso de peso em adolescentes (20). Assim, OMS autoriza uso de intervenções digitais por meio de programas de computador ou software, instalados em dispositivos eletrônicos móveis, para programas de educação em saúde (21).”

“Hipótese: 1. Os pacientes portadores de transtorno depressivo maior e ansiedade que experimentaram mais estresse de vida precoce poderão ter mais comorbidade com síndrome metabólica, estilo de vida não saudável (maior carga tabágica, maior consumo alcoólico, mais sedentarismo) e terão maior gravidade de sintomas de ansiedade e depressão. O uso de intervenções digitais para a educação em saúde pode estimular auto-cuidados e monitorização dos sintomas de ansiedade e depressão, com redução dos sintomas. 2. Os transtornos mentais são doenças progressivas que levam a resistência ao tratamento e à disfunção cognitiva a seguinte hipótese pode ser considerada: Os pacientes em uso de intervenções digitais para educação em saúde poderão ter mais adesão ao tratamento, automonitoramento dos sintomas, estilo de vida saudável e qualidade de vida. Emenda 2 - 1. Os pacientes na adolescência / juventude em uso de intervenções digitais para educação em saúde poderão ter maior adesão ao tratamento, redução de dados antropométricos e melhorar a qualidade de vida? 3. Que grupo de participantes: adolescentes ou jovens terão melhor perfil para o uso de intervenções digitais seja e-book ou app? Emenda 3: Os pacientes ambulatoriais ansiosos e com transtorno depressivo maior que estão em tratamento convencional e fizerem uso das intervenções digitais (e-book ou app) poderão ter maior redução de sintomas depressivos e ansiosos bem como melhor adesão ao tratamento e estilo de vida saudável comparados ao grupo controle que foi submetido apenas ao tratamento convencional.”

Tamanho da Amostra no Brasil: 300

Objetivo da Pesquisa:

Trechos extraídos do original da pesquisadora:

“Objetivo Primário: Avaliar se o uso de aplicativo de celular e de ebook para educação em saúde na promoção da saúde , adesão ao tratamento, estilo de vida saudável e nas ações de prevenção para a funcionalidade e síndrome metabólica em pacientes portadores de Transtornos Depressivos. Este estudo se propõe a oferecer as intervenções digitais para educação em saúde a pacientes portadores de transtornos mentais em acompanhamento psiquiátrico. Emenda 2 - Avaliar se a educação em saúde feita por meio digitais (app para celular ou e-book) em adolescentes / jovens podem contribuir para estilo de vida saudável, propiciar redução da gravidade dos sintomas, redução de transtornos aditivos e melhora de medidas antropométricas. Emenda 3: realizar ensaio clínico controlado com pacientes depressivos e ansiosos com uso de intervenções digitais (e-book ou app) além do tratamento convencional e compará-los com grupo controle de mesmo diagnóstico submetido apenas ao tratamento convencional.”

“Objetivo Secundário: a) Avaliar, por meio de escalas validadas no Brasil, para pacientes portadores de transtornos mentais : histórico de trauma infantil, escala de percepção de estresse , Hamilton, escala de perda do controle alimentar , qualidade de vida, avaliação de transtornos alimentares, severidade do tabagismo, triagem do envolvimento com álcool, tabaco e outras substâncias. b) Avaliar o perfil sociodemográfico dos pacientes estudados; c) Avaliar, por meio de escalas validadas no Brasil, se houve melhora da adesão ao tratamento;d) Avaliar se houve melhora nas medidas antropométricas e no perfil metabólico; e) Desenvolver um aplicativo de smartphone e de um ebook como ferramenta de educação em saúde para promoção da saúde , estilo de vida saudável ,monitoramento de sintomas e adesão ao tratamento para pacientes portadores de transtornos mentias. Emenda 2 - a) Descrever o perfil sociodemográfico dos jovens estudados; b) Avaliar, por meio de escalas validadas no Brasil, se houve melhora para promoção da saúde, estilo de vida saudável, e adesão ao tratamento para adolescentes / jovens.Emenda 3: Os pacientes depressivos e ansiosos que fizerem parte do grupo experimental terão redução dos sintomas depressivos e ansiosos e melhor adesão ao tratamento quando comparados ao grupo controle apenas com tratamento convencional.”

Avaliação dos Riscos e Benefícios:

Trechos extraídos do original da pesquisadora:

“Riscos: O estudo considera que os riscos são minimos, e que caso algum paciente durante o uso do aplicativo e ebook apresentar qualquer alteração emocional poderá procurar seu psiquiatra na

clinica sem nenhum tipo de gasto financeiro. Observamos que a população do estudo se encontra em acompanhamento ambulatorial, dessa forma iremos propiciar um monitoramento do uso do aplicativo para oferecer constantes feedback a estes para manutenção do seu bem estar e duvidas em relação ao seus sintomas e necessidades. E em qualquer necessidade emocional ou de sintomas o paciente será motivado a procurar o seu psiquiatra.Emenda 2 :RISCOS – O estudo considera que os riscos são mínimos, e que caso algum paciente adolescente durante o uso do aplicativo e ebook apresentar qualquer alteração emocional poderá procurar seu médico na clínica; Bem como garantir uma assistência psicológica sem nenhum tipo de gasto financeiro.”

“Benefícios: O uso de um aplicativo de smatphone e de ebook como ferramenta para uma intervenção em educação da saúde contribuirá para que o paciente possa fazer auto monitoramento de sintomas, pode ser considerado uma estratégia de tratamento adjuntivo para monitorar sintomas, adesão ao tratamento e promoção da saúde (alimentação, atividade física, sono, humor e lidar com estresse).Ementa 2 - Mesmos beneficios para a população de pacientes adolescentes.”

Comentários e Considerações sobre a Pesquisa:

Na justificativa da Emenda a pesquisadora afirma que é “Ensaio clínico randomizado com pacientes ansiosos e depressivos submetidos a intervenção digital de psicoeducação (app ou e-book) além de tratamento ambulatorial convencional e grupo controle de mesmo diagnóstico apenas com tratamento convencional de forma que possamos comparar ambas as intervenções digitais e controle.” Serão acrescentados participantes de pesquisa da Clínica Heber Vargas.

A pesquisa vem aumentando sua quantidade amostral a cada emenda,

iniciando com 100, passando para 200 e agora está em 300 participantes, aumentando também as instituições coparticipantes.

Considerações sobre os Termos de apresentação obrigatória:

Nesta emenda, os documentos apresentados que não constavam no protocolo anteriormente aprovado foram:

- Novo TCLE para participante de pesquisa;
- Declaração de Concordância da Clínica Heber Vargas.

Nas versões anteriores foram apresentados:

- TCLE ajustado para o uso do e-book.
- O próprio e-book confeccionado e publicado, já com ficha catalográfica. Importante salientar

que a pesquisadora afirma que "O ebook contará com o conteúdo similar ao aplicativo móvel". - Projeto na íntegra e informações básicas;

- TCLE;
- Anexo 3 corrigido.
- Os demais documentos forma entregues na primeira submissão.

Recomendações:

...

Conclusões ou Pendências e Lista de Inadequações:

As pendências foram providenciadas com clareza e precisão.

Considerações Finais a critério do CEP:

Este parecer foi elaborado baseado nos documentos abaixo relacionados:

Tipo Documento	Arquivo	Postagem	Autor	Situação
Informações Básicas do Projeto	PB_INFORMAÇÕES_BÁSICAS_1926965_E3.pdf	18/05/2022 14:47:05		Aceito

TCLE / Termos de Assentimento / Justificativa de Ausência	Termodeconsentimentocorrigido.pdf	18/05/2022 14:46:12	Sandra Nunes	Aceito
TCLE / Termos de Assentimento / Justificativa de Ausência	Termodeconsentimento.pdf	30/04/2022 09:58:26	Sandra Nunes	Aceito
Outros	projetoformgoogleemenda3.pdf	28/04/2022 19:16:03	Sandra Nunes	Aceito
Projeto Detalhado / Brochura Investigador	projetoemenda3.doc	28/04/2022 19:14:08	Sandra Nunes	Aceito
Outros	clinicahebervargas.pdf	28/04/2022 19:12:15	Sandra Nunes	Aceito
Solicitação Assinada pelo Pesquisador Responsável	termodeconfiabilidadeemenda2.pdf	12/04/2021 07:19:10	Sandra Nunes	Aceito
Outros	concordanciaemenda2.jpeg	12/04/2021 07:17:49	Sandra Nunes	Aceito
TCLE / Termos de Assentimento / Justificativa de	TERMODEASSENTIMENTOLIVREESCLARECIDOTALEnovo.doc	12/04/2021 07:04:11	Sandra Nunes	Aceito

Ausência	TERMODEASSENTIMENTOLIVREESCLARECIDOTALEnovo.doc	12/04/2021 07:04:11	Sandra Nunes	Aceito
TCLE / Termos de Assentimento / Justificativa de Ausência	TCLEajusteemendaparaadolesccentesnovo.doc	12/04/2021 07:03:45	Sandra Nunes	Aceito
Projeto Detalhado / Brochura Investigador	projetoemenda2.doc	12/04/2021 07:03:08	Sandra Nunes	Aceito
Outros	termocorcondanciaemenda.pdf	03/03/2021 07:08:09	Regina Celia Bueno Rezende	Aceito

			Machado	
TCLE / Termos de Assentimento / Justificativa de Ausência	TCLEajusteemenda.doc	14/08/2020 10:38:40	Sandra Nunes	Aceito
Outros	ebookeduprev.pdf	14/08/2020 10:31:41	Sandra Nunes	Aceito
Outros	anexo3ajuste.docx	05/05/2020 16:20:35	Sandra Nunes	Aceito
Projeto Detalhado / Brochura Investigador	projeto_educarparaprevenircomajuste.docx	05/05/2020 16:18:58	Sandra Nunes	Aceito
Outros	escalatraumainfancia.docx	25/03/2020 11:01:49	Sandra Nunes	Aceito
Outros	escalatabaco.docx	25/03/2020 11:01:31	Sandra Nunes	Aceito
Outros	escalaperdacontrolealimentar.docx	25/03/2020 11:00:54	Sandra Nunes	Aceito
Outros	escalahamilton.docx	25/03/2020 11:00:30	Sandra Nunes	Aceito
Outros	escaladadossociaiseclinicos.docx	25/03/2020 11:00:12	Sandra Nunes	Aceito
Declaração de concordância	declaracaoinstituicaocoparticiante.pdf	25/03/2020 10:59:48	Sandra Nunes	Aceito
Outros	ESCALAADESAO.docx	25/03/2020 10:59:27	Sandra Nunes	Aceito
Outros	escalaqualidadedevida.docx	25/03/2020 09:07:16	Sandra Nunes	Aceito
Outros	escalaatividadefisicaGPAQ.pdf	25/03/2020 08:59:31	Sandra Nunes	Aceito
Outros	escalaASSIST.pdf	25/03/2020 08:56:03	Sandra Nunes	Aceito
Outros	anexo2educarparaprevenirFINAL.docx	25/03/2020 07:19:41	Sandra Nunes	Aceito
Outros	anexo1NFe4091.pdf	25/03/2020 07:19:11	Sandra Nunes	Aceito
Folha de Rosto	folha_de_rosto.pdf	25/03/2020	Sandra Nunes	Aceito

Folha de Rosto	folha_de_rosto.pdf	07:13:14	Sandra Nunes	Aceito

Situação do Parecer:
Aprovado

Necessita Apreciação da CONEP:
Não

LONDRINA, 20 de Maio de 2022

Assinado por:
Adriana Lourenço Soares Russo
(Coordenador(a))

ANEXO 2

VERSÃO ORIGINAL DE MGH-ATRQ

MASSACHUSETTS GENERAL HOSPITAL (MGH) ANTIDEPRESSANT TREATMENT RESPONSE QUESTIONNAIRE (ATRQ)

(Non-Geriatric Population: 18 to 64 years of age)

Note: The minimum therapeutic dose for each antidepressant treatment in Section I is based on prescribing information, relevant literature, and consultation with expert clinicians.

Section I. Antidepressant Medications

Instructions:

5. Please **check (√)** the names of any medications that the participant has taken since the beginning of **THIS CURRENT EPISODE** of depression.
6. Please **check (√)** if the daily dosage of the medication was **equal to or greater than the minimum** therapeutic dose for at least 6 weeks.
7. Only for those taken at the minimum therapeutic dose for at least 6 weeks, indicate the amount (%) of improvement in depression that the participant reported when they felt it was working at its best.
8. If the participant initially experienced an improvement of ≥50% and then lost that response (tolerance/ tachyphylaxis), that medication will not be counted towards a failed antidepressant trial.

Tricyclic Antidepressants

Generic Name	Taken during THIS current episode of depression(√)	Took at least this dose* *for at least 6 weeks*? (√)		Only for those taken at minimum therapeutic dose for at least 6 weeks: Based on participant`s feedback, indicate the amount (%) of improvement in depression he/she reported when they feel it was working at its best. E. 75% to 100% F. 50% to <75% G. 26% to <50% H. ≤ 25%
doxepin		150mg/d		
clomipramine		150mg/d		
amoxapine		150mg/d		
amitriptyline		150mg/d		
maprotiline		150mg/d		
desipramine		150mg/d		
nortriptyline		75 mg/d		
trimipramine		150mg/d		
imipramine		150mg/d		
protriptyline		30mg/d		
pipofezine		150mg/d		
noxiptiline		100mg/d		

* If the dose is below the minimum dose required, a blood level that is within the therapeutic (antidepressant) range is also acceptable.

Monoamine Oxidase Inhibitors (MAOIs)

Generic Name	Taken during THIS current episode? (√)	Took at least this dose *for at least 6 weeks?* (√)		Only for those taken at minimum therapeutic dose for at least 6 weeks: Based on participant`s feedback, indicate the amount (%) of improvement in depression he/she reported when they feel it was working at its best. A. 75% to 100% B. 50% to <75% C. 26% to <50% D. ≤ 25%
isocarboxazid		30mg/d		
phenelzine		45mg/d		
tranylcypromine		30mg/d		
selegiline patch		6 mg/24 hrs		
moclobemide		300 mg/d		
pirlindole		200 mg/d		

Selective Serotonin Reuptake Inhibitors (SSRIs)

Generic Name	Taken during THIS current episode? (√)	Took at least this dose for *at least 6 weeks?* (√)		Only for those taken at minimum therapeutic dose for at least 6 weeks: Based on participant`s feedback, indicate the amount (%) of improvement in depression he/she reported when they feel it was working at its best. A. 75% to 100% B. 50% to <75% C. 26% to <50% D. ≤ 25%
fluvoxamine		50mg/d		
paroxetine		20/25mg/d		

fluoxetine		20 mg/d		
sertraline		50 mg/d		
citalopram		20mg/d		
escitalopram		10 mg/d		

Serotonin-Norepinephrine Reuptake Inhibitors (SNRIs)

Generic Name	Taken during THIS current episode? (√)	Took at least this dose for *at least 6 weeks?* (√)		Only for those taken at minimum therapeutic dose for at least 6 weeks: Based on participant`s feedback, indicate the amount (%) of improvement in depression he/she reported when they feel it was working at its best. A. 75% to 100% B. 50% to <75% C. 26% to <50% D. ≤ 25%
venlafaxine / venlafaxine XR		75 mg/d		
duloxetine		60mg/d		
desvenlafaxine		50mg/d		
milnacipran		100mg/d		
levomilnacipran		40mg/d		

Other Antidepressants

Generic Name	Taken during THIS current episode? (√)	Took at least this dose for at least 6 weeks? (√)		Only for those taken at minimum therapeutic dose for at least 6 weeks: Based on participant`s feedback, indicate the amount (%) of improvement in depression he/she reported when they feel it was working at its best. A. 75% to 100% B. 50% to <75% C. 26% to <50% D. ≤ 25%
trazodone		300mg/d		
bupropion		300mg/d		

mirtazapine		15 mg/d		
mianserin		30 mg/d		
opipramol		150 mg/d		
nefazodone		300 mg/d		
agomelatine		25 mg/d		
tianeptine		37.5 mg/d		
reboxetine		4 mg/d		
vilazodone		40mg/d		
vortioxetine		10 mg/d		

Section II. FDA-Approved Medications added to Augment /Boost Antidepressant Effect

Instructions:

1. Please **check** (√) the names of any medication the participant has taken to augment or boost the antidepressant effect during **THIS CURRENT EPISODE** of depression.
2. Please **check** (√) if the participant took at least this dose for at least 6 weeks in combination with an antidepressant treatment from Section I.
3. Please indicate the name of antidepressant treatment from Section I this drug was taken with to augment /boost its antidepressant effect.
4. Please indicate the amount (%) of improvement in depression that the patient reported when they felt this combination was working at its best.

Generic Name	Taken during THIS current episode? (√)	Took at least this dose for *at least* 6 weeks in combination with an antidepressant treatment from Section I**? (√)		Name of Antidepressant Treatment from Section I (see above) this drug was taken with	Only for those taken at minimum therapeutic dose for at least 6 weeks: Based on participant`s feedback, indicate the amount (%) of improvement in depression he/she reported when they feel the combination was working at its best. A. 75% to 100% B. 50% to <75% C. 26% to <50% D. ≤ 25%
aripiprazole		5 mg/d			
quetiapine		150 mg/d			
brexpiprazole		1 mg/d			

**The antidepressant treatment from Section I must also have been taken at the minimum therapeutic dose during the 6 weeks that the medication was taken to augment/boost antidepressant effect.