FACULTY OF MEDICINE, UNIVERSITY OF COIMBRA

INTEGRATED MASTER'S DEGREE IN MEDICINE – FINAL WORK

JOÃO ANDRÉ DE SILVEIRA DIAS GOUVEIA

Comorbidity, treatment, and service use utilization patterns in difficult-to-treat depression patients: a retrospective chart review study in a Portuguese community mental health team

ORIGINAL SCIENTIFIC ARTICLE

SCIENTIFIC AREA: PSYCHIATRY

Work developed under the orientation of:

PROF. ANTÓNIO JOÃO FERREIRA DE MACEDO E SANTOS

DR. VÍTOR MANUEL OLIVEIRA DOS SANTOS

April/2024

Comorbidity, treatment, and service use utilization patterns in difficult-to-treat depression patients: a retrospective chart review study in a Portuguese community mental health team

João Gouveia[1]; Vítor Santos[1,2], MD; António Macedo[1,2], MD, PhD

1. FMUC - FACULTY OF MEDICINE, UNIVERSITY OF COIMBRA, PORTUGAL
2. ULS - UNIDADE LOCAL DE SAÚDE DE COIMBRA, PORTUGAL

João Gouveia
joaoasdgouveia@outlook.com
Corresponding author at FMUC – Faculty of Medicine, University of Coimbra
Unidade Central - Azinhaga de Santa Comba, Celas. 3000-548 Coimbra
Portugal

TABLE OF CONTENTS

ABSTRACT

INTRODUCTION: Observational studies with data from real-world clinical practice with Difficult-to-treat Depression (DTD) patients are scarce and there is none in a Portuguese context. This study aims to gather observational data from real-world clinical practice of a Portuguese Community Mental Health Team (CMHT) about the prevalence of DTD, to explore the differences between the DTD and non-DTD groups in treatment resistance, comorbidity, pharmacological strategies, and service use patterns.

METHODS: We conducted a retrospective chart review study using data from Electronic Health Records (EHRs) of adult patients with psychiatric disorders followed by a single CMHT from the Department of Psychiatry of Coimbra University Hospital Centre: Cantanhede CMHT (between 01.12.2020 - 31.12.2022). Extracted data from EHRs comprised sociodemographic data, psychiatric diagnosis, relevant clinical and treatment history data, and service use data. Dutch Measure for quantification of Treatment Resistance in Depression (DM-TRD) was used to grade the level of treatment resistance, and the original version of the Charlson Comorbidity Index (CCI) to measure medical comorbidity.

RESULTS: 473 patients were referred to Cantanhede CMHT for a first assessment, 219 patients met the criteria for a primary diagnosis of any depressive disorder, assistant psychiatrists identified 57 patients with DTD, approximately 26%, during follow-up, using the definition of 'depression that continues to cause a significant burden despite normal treatment efforts'. The DTD group had higher rates of depressive episodes; depression severity; service use variables; DM-TRD scores; prevalence of comorbid anxiety symptoms; personality disorders; severe medical comorbidities; prescription of Serotonin and Norepinephrine Reuptake Inhibitors (SNRI) and Mirtazapine. We observed differences in the use of antidepressant augmenting strategies, in the prescription of anticoagulant/antiplatelet drugs and analgesics with higher prescription in the DTD group. We stated correlations between DM-TRD and CCI scores, and between DM-TRD score and all service use variables, and that both DM-TRD and CCI scores are predictors of psychiatric consultations.

DISCUSSION: The differences in DTD definition, operationalization, and context, may explain the differences of prevalence between our study (26%) and others. The differences between the DTD and non-DTD groups in treatment resistance, comorbidity, pharmacological strategies, and service use patterns found on our work are consistent

with the literature, which suggests that our operationalization of the DTD definition is compatible with a perspective of depression treatment refractoriness in a real-world clinical context.

CONCLUSION: Our results are in accordance with similar studies in other countries, which highlights the need of a different management of DTD patients, that continues to live with a significant burden despite usual pharmacological and non-pharmacological treatments.

Keywords: difficult-to-treat depression, Portuguese community mental health team, depression, treatment-resistant depression, real-world data.

RESUMO

INTRODUÇÃO: Os estudos observacionais com dados da prática clínica real com doentes com Depressão Difícil de Tratar (DTD) são escassos e não existem no contexto português. Este estudo tem como objetivo recolher dados observacionais da prática clínica do mundo real de uma Equipa de Saúde Mental Comunitária portuguesa sobre a prevalência de DTD, explorar as diferenças entre os grupos DTD e não DTD na resistência ao tratamento, comorbilidade, estratégias farmacológicas e padrões de uso de serviços de saúde.

MÉTODOS: Realizámos um estudo de revisão retrospetivo de dados de Registos Eletrónicos de Saúde de doentes adultos com doença psiquiátrica acompanhados por uma única Equipa de Saúde Mental Comunitária do Departamento de Psiquiatria do Centro Hospitalar Universitário de Coimbra em Cantanhede (entre 01.12.2020 - 31.12.2020). Os dados extraídos dos registos incluíram dados sociodemográficos, diagnósticos psiquiátricos, dados relevantes do histórico clínico e de tratamento e dados de utilização dos serviços de saúde. Para calcular o nível de resistência ao tratamento foi utilizada a *Escala Holandesa para quantificação da Resistência ao Tratamento na Depressão* (DM-TRD), e para medir a comorbilidade médica foi usada a versão original do *Índice de Comorbilidade de Charlson* (CCI).

RESULTADOS: 473 doentes foram encaminhados à Equipa de Saúde Mental Comunitária de Cantanhede para uma primeira avaliação, 219 doentes preencheram os critérios para um diagnóstico primário de uma qualquer doença depressiva, os psiquiatras identificaram 57 doentes com DTD, aproximadamente 26%, durante o seu acompanhamento, usando a definição de “depressão que continua a causar sofrimento significativo, apesar dos esforços de tratamento habituais”. O grupo DTD apresentou maiores índices de episódios depressivos; gravidade da depressão; utilização dos serviços de saúde; pontuações da DM-TRD; prevalência de sintomas de ansiedade como comorbilidade; transtornos de personalidade; comorbilidades médicas graves; prescrição de Inibidores de Recaptação de Serotonina e Noradrenalina (SNRI) e de Mirtazapina. Observámos diferenças no uso de estratégias potencializadoras de antidepressivos, na prescrição de anticoagulantes/antiagregantes plaquetários e analgésicos, com maior prescrição no grupo DTD. Afirmamos que existem correlações entre as pontuações da DM-TRD com o índice ICC, e entre a pontuação da DM-TRD com todas as variáveis de utilização de serviços de saúde, e que tanto as pontuações da DM-TRD como do índice ICC são preditores do número de consultas psiquiátricas.

DISCUSSÃO: As diferenças na definição, operacionalização e contexto podem explicar as diferenças de prevalência de DTD entre o nosso estudo (26%) e outros. As diferenças entre os grupos DTD e não DTD em relação à resistência ao tratamento, comorbilidade, estratégias farmacológicas e padrões de uso de serviços de saúde encontradas no nosso trabalho são coerentes com a literatura, o que sugere que a nossa operacionalização da definição de DTD é compatível com uma perspetiva de tratamento de depressão refratária num contexto clínico do mundo real.

CONCLUSÃO: Os nossos resultados estão de acordo com estudos semelhantes realizados em outros países, o que destaca a necessidade de uma gestão diferente dos doentes com DTD, que continuam a viver com sofrimento significativo, apesar dos tratamentos farmacológicos e não farmacológicos habituais.

Palavras-chave: depressão difícil de tratar, equipa de saúde mental comunitária portuguesa, depressão, depressão resistente ao tratamento, dados do mundo real.

ABBREVIATIONS

AD – Antidepressants

CCI – Charlson Comorbidity Index

CMHT – Community Mental Health Team

DALYs – Disability-Adjusted Life Years

DTD – Difficult-to-Treat Depression

DM-TRD – Dutch Measure for quantification of Treatment Resistance in Depression

EMA – European Medicines Agency

FDA – Food and Drug Administration

FMUC – Faculty of Medicine of the University of Coimbra, Portugal

HERs – Electronic Health Records

ICD-11 – International Classification of Diseases, Eleventh Revision

MSM – Maudsley Staging Model

NHS – National Health Service

NSAID – Nonsteroidal anti-inflammatory drug

SNRI – Serotonin and Norepinephrine Reuptake Inhibitors

SSRI – Selective Serotonin Reuptake Inhibitors

t – independent sample *t-tests*

TRD – Treatment-Resistant Depression

UK – United Kingdom

ULS – *Unidade Local de Saúde*

χ^2 – chi-square

1. INTRODUCTION

Depressive disorders are one of the leading causes of global burden of disease, affecting millions of people worldwide. It causes considerable suffering to patients and their families, impairs social functioning and economic productivity, and is associated with premature mortality from suicide and medical comorbidities, leading to a substantial demand for mental health services.[1] Treatment of depressive disorders commonly involves pharmacological therapy with antidepressant medications, psychotherapy, or a combination of both.[2] Lifestyle interventions (e.g.: exercise)[3] and neuromodulation techniques (e.g.: electroconvulsive therapy, transcranial magnetic stimulation)[4] are also therapeutic options with robust evidence of effectiveness in depression.

Despite the availability of various treatment modalities, a significant proportion of patients with depression fail to achieve remission or even a significant symptom improvement. Almost a third of patients with a depressive episode will not achieve sustained remission, even with several well-delivered treatments prescribed by their doctor. These patients experience prolonged suffering, and are heavy consumers of mental health care services, resulting in high costs for health resources for years.[5] Furthermore, relapse and recurrence of depression are common, adding to the overall burden of depression.[6] These phenomena have spurred the delineation of two distinct but related concepts within the realm of depression treatment refractoriness: Treatment-Resistant Depression (TRD) and Difficult-to-Treat Depression (DTD).

Various definitions of TRD have been proposed, associated with different conceptual frameworks.[7,8] The definition of TRD adopted by regulatory agencies such as the US Food and Drug Administration (FDA)[9] and the European Medicines Agency (EMA)[10] is failure to respond to two or more antidepressant regimens despite adequate dose and duration and adherence to treatment. Other authors proposed a staging model that operationalizes TRD in a dimensional continuum of failed antidepressant trials.[11] However, these definitions had some limitations, such as the operationalization of 'failure' of treatment, the definition of clinical characteristics of the depression (e.g.: severity, duration), and the failure to include other treatment modalities besides pharmacological ones.[8] To address some of these limitations the Maudsley Staging Model (MSM) was developed.[12] It defines treatment resistance as failure to attain a significant level of improvement from an accurately diagnosed depressive episode following treatment with an antidepressant given at an adequate dose for a minimum of six weeks. Three dimensions of resistance are included in this model: treatment failure, duration of the depressive episode, and severity of depression. The Dutch Measure for quantification of Treatment-Resistant Depression Model (DM-TRD) is the most comprehensive in terms of variables included and was developed to improve the MSM.

Items for functional impairment, comorbid anxiety, personality disorders, psychosocial stressors, failed psychotherapy, and intensified treatment were added. It was proved that it reveals better predictive validity for clinical outcomes than previous models used in quantification of TRD, resulting in a treatment improvement of TRD patients.[13]

The DTD construct represents a broader and more inclusive approach to the outcome of depression treatment, encompassing psychological, biological, and interactive aspects for an integrative model of therapeutic management of resistance in depression.[14] An international consensus, comprising 15 clinical researchers from across Europe, the United States, Canada, and Australia, with expertise in mood disorders, was established in 2020 and defined DTD as depression that continues to cause a significant burden despite normal treatment efforts.[15] This expert panel conceptualized DTD as a dimensional construct, without explicitly specifying criteria to distinguish patients who did and did not have DTD. However, this clinical phenomenon lies in a spectrum that includes partial response, nonresponse, and frequent relapses, shifting the treatment focus from an acute objective of remission to a disease management model that emphasizes symptom control, better functioning and quality of life, and minimization of therapy side effects.[15,16] The consensus statement identified multiple variables that are associated with DTD and emphasized the importance of conducting a comprehensive evaluation to identify possible contributors to inadequate treatment response. Some of the patient and disorder characteristics that predict poorer outcomes in the treatment of depression include prior nonresponse to treatment, symptom chronicity, personality pathology, comorbid disorders, childhood trauma, suicidality, substance misuse, psychosocial stress, social isolation, and early age of onset.[15] Recently, a self-report scale that can be incorporated into clinical practice that identifies patient, clinical, and treatment risk factors for DTD was developed.[17]

There are few studies about TRD in Portugal. One epidemiological study estimated the prevalence of TRD and quantified the disease burden (Disability-Adjusted Life Year - DALY) due to the disability generated by TRD in Portugal in 2017, based on data from the National Epidemiological Study of Mental Health. The estimated prevalence of TRD was 90.7 thousand persons and the estimated disease burden due to the disability generated by TRD was 25.7 thousand DALYs. The authors also concluded that although TRD represents relatively small direct costs for the health system, it had a relevant disease burden and substantial productivity costs for the Portuguese economy and society due to reduced employment, absenteeism, presenteeism, and premature death.[18] Another article focused on the perspective of a panel of seven Portuguese psychiatry experts, to characterize and discuss TRD epidemiology, diagnosis, patient care pathways, treatment options, and unmet clinical needs. They reached consensual

statements that TRD diagnosis and treatment are mostly decided by psychiatrists at public hospitals; treatment type and duration must be adapted to characteristics of the patient and the depressive episode; antidepressant switch interventions occur more frequently with non-response, while optimization, combination, and augmentation strategies are considered for patients with a partial response; psychotherapy should be considered in parallel to pharmacological treatment; neuromodulation techniques are underused; lifelong treatment is required for recurrent or more chronic TRD episodes and TRD management is limited by lack of access to specialist care and to many treatment options.[19]

Observational studies with data from real-world clinical practice with patients identified with DTD are even more scarce. One study analyzed the electronic health records (EHRs) of five specialist mental health National Health Service (NHS) Trusts in the United Kingdom (UK), using a natural language processing model. Data on disease characteristics, comorbidities, and treatment histories were extracted. In a sample of 28,184 patients with major depressive disorder, 19% met criteria for DTD. Compared to the non-DTD group, patients with DTD were more likely to have severe depression, suicidal ideation, and psychiatric and medical comorbidities, as well as higher rates of hospitalization. They were also more likely to receive unemployment and sickness/disability benefits. More intensive treatment strategies were used in the DTD group, including higher rates of combination therapy, augmentation, psychotherapy, and electroconvulsive therapy.[20] To our knowledge, there are no DTD observational studies with data from real-world clinical practice in a Portuguese context.

The objective of the present study is to gather observational data from real-world clinical practice of a Portuguese community mental health team (CMHT) about:

1) The prevalence of DTD in a cohort of patients with depressive disorders treated by a CMHT;
2) Differences between the DTD and non-DTD groups in depression treatment resistance; psychiatric and medical comorbidity; use of different antidepressant pharmacological strategies; use of other treatment modalities and service use patterns. We hypothesize that the DTD group, compared with the non-DTD group, will have higher scores in TRD multidimensional measures, higher rates of psychiatric and medical comorbidities, more frequent use of antidepressant combination and augmentation strategies, more frequent use of psychotherapeutic and neuromodulatory interventions, more psychiatric consultations, more psychiatric hospitalization days, and more emergency room visits during the follow-up;

3) Associations and relations between TRD multidimensional scores, medical comorbidity scores, and service use variables.

2. METHODS

2.1 Design and sample

This retrospective chart review study was conducted using data from EHRs from patients followed by a single CMHT from the Department of Psychiatry of Coimbra University Hospital Centre: Cantanhede CMHT. Cantanhede CMHT is a multidisciplinary mental health team that is responsible for the specialized care of adult (18 years or more) persons with psychiatric disorders referred from primary care centers of Cantanhede and Mira (circa 47,000 habitants), in articulation with other psychiatric department units (inpatient units, day care hospital, psychiatric emergency services, specialized ambulatory teams).

The study population comprised those with a first consultation by one of the Cantanhede CMHT psychiatrists between 01 January 2020 and 31 December 2022, with a primary diagnosis of depressive disorder, defined as International Classification of Diseases, Eleventh Revision (ICD-11), codes 6A7x. Patients with a primary diagnosis of a neurodevelopmental, neurocognitive, primary psychotic, or bipolar disorder were excluded.

The patients with DTD were identified by one of the two practicing psychiatrists of the CMHT, based on the broad definition of the international consensus panel ('depression that continues to cause a significant burden despite normal treatment efforts')[15] and taking into account factors that include the chronicity of the current episode, the frequency of recurrences and a history of multiple antidepressant treatments from different modalities (psychopharmacologic, psychotherapeutic or neuromodulation interventions).

The relevant study data were extracted from the EHRs of all eligible patients and were pseudo-anonymized, through the assignment of a numeric code to each patient who was paired with their respective data. The data obtained was stored in a computerized database, protected by a password.

2.2 Data and measures

Extracted data from EHRs comprised sociodemographic data (age, gender), psychiatric diagnosis formulated by the CMHT psychiatrist based on International Classification of Diseases, Eleventh Revision (ICD-11), relevant clinical, treatment history data, and medical history to compute scores of depression treatment resistance and medical comorbidity measures, data from treatment options during the follow-up and service use data (psychiatric consultations, emergency room visits, psychiatric hospitalization days).

DM-TRD[13] was used to grade the level of treatment resistance, assigning a score that varies between 2 and 27. This scale includes the following items: 1) Duration (acute; subacute; chronic); 2) Symptom severity (subsyndromal; mild; moderate; severe without psychosis; severe with psychosis); 3) Functional impairment (no impairment; mild impairment; moderate impairment; severe impairment); 4) Comorbid anxiety symptoms (not present; present, but not fulfilling DSM-IV criteria; fulfilling one or more DSM-IV anxiety disorder); 5) Comorbid personality disorder (not present; present, not based on formal interview; present, based on formal interview); 6) Psychosocial stressors (no psychosocial stressor; one or more psychosocial stressors); 7) Treatment failures – Antidepressants (Level 0: not used; Level 1: 1-2 medications; Level 2: 3-4 medications; Level 3: 5-6 medications; Level 4: 7-10 medications; Level 5: more than 10 medications; 8) Treatment failures – Augmentation/combination: Level 0: not used; Level 1: 1-2 medications; Level 2: 3-4 medications; Level 3: 5-6 medications); 9) Treatment failures – Electroconvulsive therapy (Not used; Used); 10) Treatment failures – Psychotherapy (Not used; Supportive therapy; one empirically supported psychotherapy; two or more supported psychotherapies); 11) Treatment failures – Intensified treatment (Not used; Day patient treatment; Inpatient treatment).

The original version of the Charlson Comorbidity Index (CCI) was used to measure medical comorbidity. This measure contains 19 items corresponding to different medical comorbid conditions with different clinical weights based on the adjusted risk of 1-year mortality.[21] The conditions with an assigned weight of 1 are: myocardial infarction, congestive heart failure, peripheral vascular disease, cerebrovascular disease, dementia, chronic pulmonary disease, connective tissue disease, ulcer disease, mild liver disease, and diabetes. The conditions with an assigned weight of 2 are: hemiplegia, moderate or severe renal disease, diabetes with end organ damage, any tumor without metastasis, leukemia, and lymphoma. Moderate or severe liver disease has an assigned weight of 3 and metastatic solid tumor and Acquired Immune Deficiency Syndrome have an assigned weight of 6. The total score of the CCI consists in a simple sum of the weights, with higher scores indicating a greater mortality risk and a more severe comorbid condition.[22]

Extracted treatment history data included: the use of different groups of antidepressant medications; the use of antidepressant combination and augmentation strategies; the use of benzodiazepine and zolpidem; the prescription of drugs for treatment of comorbid medical diseases (statins; antihypertensive agents; antidiabetic agents; anticoagulants or antiplatelets; bronchodilators; opioid analgesics; non-steroidal anti-inflammatory drugs); the use of psychotherapy and neuromodulatory treatment interventions.

2.3 Statistical analysis

Descriptive statistics were performed for all variables. Univariate inferential statistic tests were used to compare the DTD and non-DTD groups. For continuous outcome variables (age, DM-TRD scores, CCI scores, psychiatric consultations, emergency room visits, and psychiatric hospitalization days), the groups were compared using independent samples *t-tests*. Effect sizes were estimated based on Cohen's *d* values, with *d* values >0.5 considered to represent potentially meaningful differences. All other outcome variables were categorical; groups were compared using chi-square tests (χ^2). Effect sizes for differences in the use of therapeutic interventions were estimated using Cramer's *V* statistic, with values around 0.1, 0.3, and 0.5 indicating small, medium, and large effect sizes.

A DM-TRD score raincloud plot was built to explore the differences between DTD and non-DTD groups.

Correlation analysis and linear regression were used to explore the associations and analyze the relations between DM-TRD scores, CCI scores, number of psychiatric consultations, emergency room visits, and psychiatric hospitalization days. The statistical analysis was performed in JASP version 0.18.3.[23]

2.4 Ethics

The study was approved by the Ethics Committee of the FMUC - Faculty of Medicine, University of Coimbra, Portugal (Appendix).

3. RESULTS

3.1 Patient selection

Figure 1 summarizes the patient selection flow diagram. Between 01 January 2020 and 31 December 2022, 473 patients were referred to Cantanhede CMHT for a first assessment consultation, and 219 patients met ICD-11 criteria for a primary diagnosis of any depressive disorder (codes 6A7x). During follow-up, assistant psychiatrists identified 57 patients with presumed DTD (26%), based on the international consensus statement definition of DTD as 'depression that continues to cause significant burden despite usual treatment efforts'.[15]

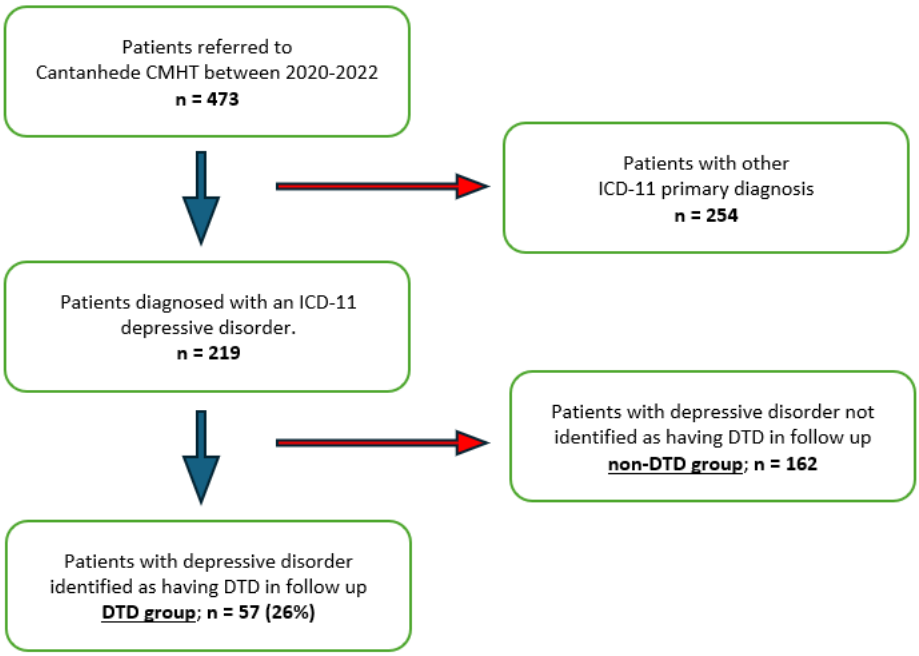

Figure 1: Patient selection flow diagram.

3.2 Sociodemographic, clinical, and service use variables

Table 1 provides a summary of sociodemographic, clinical, and service utilization variables. There were no statistically significant differences between DTD and non-DTD groups in age and gender. There were no statistically significant differences between DTD and non-DTD groups in the frequency of psychosocial stressors associated with the depressive illness. The DTD group had statistically significant higher rates of chronic depressive episodes (47,4% vs 5,6%; $p < 0.001$; $V = 0.539$) and significant differences in depression severity ($p = 0.005$; $V = 0.420$). There were significant statistically differences between DTD and non-DTD groups in service use variables, with more psychiatric consultations (10,26 consultations vs 6,00 consultations; $p < 0.001$; d =

1.068), emergency room visits (3,68 vs 0,76; p = 0.006; *d* = 0.766) and psychiatric hospitalization days (1,95 vs 0,09; p < 0.001; *d* = 0.516) in the DTD group.

3.3 Treatment resistance variables

The differences between DTD and non-DTD groups in DM-TRD are displayed in Figure 2 and summarized in Table 1. The DM-TRD scores are statistically significant higher in DTD group than non-DTD group, with an effect size that suggests a meaningful difference (12,63 vs 7,88; p < 0.001; *d* = 2.330).

Table 1: Comparison of sociodemographic, clinical, and service use variables between DTD and Non-DTD groups.

Variables		DTD group (n = 57)	Non-DTD group (n = 162)	Statistic	*p-value*	Effect size
Sociodemographic variables						
Age (years; mean, s.d.)		58.7(15.1)	57.7(14.2)	t = -0.278	0.782	*d*=0.267[a]
Gender (women)		84.2%	74.1%	χ^2=0.808	0.369	*V*=0.105[b]
Clinical variables						
Chronic depressive episodes		47.4%	5.6%	χ^2=21.178	**<0.001**	*V*=0.539[b]
Depression severity	Subsyndromal	0.0%	27.8%	χ^2=12.867	**0.005**	*V*=0.420[b]
	Mild	26.3%	37.0%			
	Moderate	57.9%	33.3%			
	Severe	15.8%	1.9%			
Psychosocial stressors		57.9%	57.4%	χ^2=0.808	0.971	*V*=0.004[b]
DM-TRD Score		12.63(1.77)	7.88(2.12)	t = -3.412	**<0.001**	*d*=2.330[a]
Service use variables						
Psychiatric consultations (mean, s.d.)		10.26 (4.99)	6.00(3.64)	t = -3.968	**<0.001**	*d*=1.068[a]
Emergency room visits (mean, s.d.)		3.68 (7.36)	0.76(1.21)	t = -2.846	**0.006**	*d*=0.766[a]
Psychiatric hospitalization days (mean, s.d.)		1.95 (6.85)	0.09(1.10)	t = -3.968	**<0.001**	*d*=0.516[a]

s.d.: standard deviation.
DM-TRD: Dutch measure for quantification of Treatment Resistance in Depression.
t: independent sample *t-tests* were used to compare groups and [a] Cohen's *d* values were used to estimate effect size for continuous outcome variables.
χ^2: chi-square tests were used to compare groups and [b] Cramer *V* statistic was used to estimate effect sizes for categorical outcome variables.

Figure 2 - DM-TRD score raincloud plot (DTD group vs. non-DTD group).

3.4 Psychiatric and medical comorbidity

The differences between DTD and non-DTD groups in psychiatric and medical comorbidities are summarized in Table 2. There were statistically significant differences in the prevalence of comorbid anxiety symptoms (89.5% vs 57.4%; p = 0.011; *V* = 0.297) and personality disorders and related traits (31.6% vs 3.8%; p < 0.001; *V* = 0.392), with higher rates in the DTD group. No statistically significant differences between DTD and non-DTD groups in rates of bodily distress disorder and substance use disorders were found. The DTD group had more severe medical comorbidities, as indicated by statistically significant higher scores in CCI than the non-DTD group, with an effect size that suggests a meaningful difference (1,89 vs 0.81; p < 0.001; *d* = 0.910).

Table 2: Comparison of psychiatric and medical comorbidity between DTD and Non-DTD groups.

Variables	**DTD group (n = 57)**	**Non-DTD group (n = 162)**	**Statistic**	***p-value***	**Effect size**
Psychiatric comorbidity					
Comorbid anxiety symptoms	89.5%	57.4%	χ^2=6.418	**0.011**	*V*=0.297[b]
Bodily distress disorder	10.5%	3.7%	χ^2=1.263	0.261	*V*=0.132[b]
Disorders due to substance use	15.8%	9.3%	χ^2=0.614	0.433	*V*=0.092[b]
Personality disorders and related traits	31.6%	3.8%	χ^2=11.192	**<0.001**	*V*=0.392[b]
Medical comorbidity					
CCI score (mean, s.d.)	1.89 (1.66)	0.81 (0.97)	t = -3.412	**<0.001**	*d*=0.910[a]

s.d.: standard deviation.
CCI: Charlson Comorbidity Index.
t: independent sample *t-tests* were used to compare groups and [a] Cohen's *d* values were used to estimate effect size for continuous outcome variables.
χ^2: chi-square tests were used to compare groups and [b] Cramer *V* statistic was used to estimate effect sizes for categorical outcome variables.

3.5 Treatment interventions for depression

Table 3 summarizes the differences between DTD and non-DTD groups related to the implementation of different antidepressant psychopharmacological and psychotherapeutic treatment interventions. There were statistically significant differences in the use of some specific antidepressant drugs, with higher rates of prescription of Serotonin and Norepinephrine Reuptake Inhibitors (SNRI) (31.6% vs 9.3%; p = 0.019; *V* = 0.274) and Mirtazapine in the DTD group (52.6% vs 24.2%; p = 0.021; *V* = 0.270). There were no statistically significant differences between DTD and non-DTD groups in the use of antidepressant combination strategies. There were statistically significant differences in the use of antidepressant augmenting strategies, with higher rates in DTD group (47.4% vs 18.5%; p = 0.014; *V* = 0.288). There were no statistically significant differences between DTD and non-DTD groups in the use of benzodiazepines or zolpidem. There was a trend to a higher use of psychotherapy in the

DTD group, but without reaching statistical significance (26.3% vs 9.3%; p = 0.063; *V* = 0.218). Transcranial magnetic stimulation was used in only one patient from the DTD group, and eletroconvulsivotherapy wasn´t used in any patient.

Table 3: Comparison of antidepressant treatment (psychopharmacologic and psychotherapeutic interventions) between DTD and Non-DTD groups.

Variables	**DTD group (n = 57)**	**Non-DTD group (n = 162)**	**Statistic**	***p-value***	**Effect size[a]**
Psychopharmacologic intervention					
SSRI	94.7%	81.5%	χ^2=1.930	0.165	*V*=0.163
SNRI	31.6%	9.3%	χ^2=5.471	**0.019**	*V*=0.274
Bupropiom	21.1%	7.4%	χ^2=2.682	0.102	*V*=0.102
Mirtazapine	52.6%	24.1%	χ^2=5.311	**0.021**	*V*=0.270
Trazodone	36.8%	26.9%	χ^2=0.817	0.366	*V*=0.106
Agomelatine	21.0%	7.4%	χ^2=2.682	0.102	*V*=0.192
Vortioxetine	10.5%	7.4%	χ^2=0.181	0.670	*V*=0.050
Tricyclic antidepressants	21.0%	9.3%	χ^2=1.809	0.179	*V*=0.157
AD combination	68.4%	48.1%	χ^2=2.321	0.128	*V*=0.178
AD augmentation	47.4%	18.5%	χ^2=6.076	**0.014**	*V*=0.288
Benzodiazepines	94.7%	79.6%	χ^2=2.335	0.126	*V*=0.179
Zolpidem	15.8%	3.7%	χ^2=3.218	0.073	*V*=0.210
Psychotherapeutic intervention					
Psychotherapy	26.3%	9.3%	χ^2=3.459	0.063	*V*=0.218

SSRI: Selective Serotonin Reuptake Inhibitors; SNRI: Serotonin and Norepinephrine Reuptake Inhibitors; AD: Antidepressants.
χ^2: chi-square tests were used to compare groups and [a] Cramer *V* statistic was used to estimate effect sizes for categorical outcome variables.

3.6 Prescription of drugs for medical comorbid disorders

The differences between DTD and non-DTD groups in prescription of some class of drugs used in treatment of medical conditions are displayed in Table 4. There were statistically significant differences in the prescription of anticoagulant/antiplatelet drugs (21.0% vs 1.9%; p = 0.004; *V* = 0.334), opioid analgesics (31.6% vs 7.4%; p = 0.008; *V* = 0.308) and NSAIDs (42.1% vs 7.4%; p < 0.001; *V* = 0.411), with higher rates of prescription in the DTD group. There were no statistically significant differences between DTD and non-DTD groups in the use of statins, antihypertensive drugs, antidiabetic drugs, aspirin, and bronchodilators.

Table 4: Comparison of pharmacological treatments for comorbid medical disorders between DTD and Non-DTD groups.

Variables	DTD group (n = 57)	Non-DTD group (n = 162)	Statistic	*p-value*	Effect size[a]
Statins	26.3%	27.8%	χ^2=0.015	0.902	*V*=0.014
Antihypertensives	47.4%	37.0%	χ^2=0.627	0.429	*V*=0.093
Antidiabetic agents	10.5%	11.1%	χ^2=0.005	0.944	*V*=0.008
Anticoagulants	21.0%	1.9%	χ^2=8.121	**0.004**	*V*=0.334
Aspirin	15.8%	11.1%	χ^2=0.285	0.594	*V*=0.062
Bronchodilators	10.5%	1.9%	χ^2=2.684	0.101	*V*=0.192
Analgesics - Opioids	31.6%	7.4%	χ^2=6.946	**0.008**	*V*=0.308
Analgesics - NSAID	42.1%	7.4%	χ^2=12.319	**<0.001**	*V*=0.411

NSAID: Nonsteroidal anti-inflammatory drug.
χ^2: chi-square tests were used to compare groups and [a] Cramer *V* statistic was used to estimate effect sizes for categorical outcome variables.

3.7 Associations between treatment resistance, medical comorbidity, and service use

The heatmap of Figure 3 displayed the Pearson correlations between DM-TRD scores, CCI scores, and service use variables. There were statistically significant correlations between DM-TRD and CCI scores, between DM-TRD scores and all service use variables (psychiatric consultations, emergency room visits, and psychiatric hospitalization days), and between CCI scores and psychiatric consultations, and between CCI scores and emergency room visits. However, when we performed a partial correlation analysis between DM-TRD scores and service use variables, with CCI as a covariable, only the correlations between DM-TRD scores and psychiatric consultations and between DM-TRD scores and psychiatric hospitalizations remained statistically significant (Figure 4).

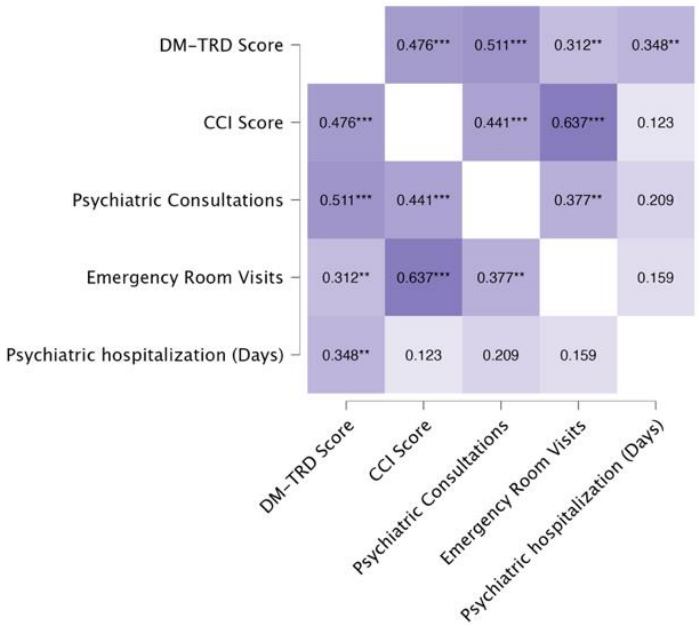

Figure 3: Pearson's heatmap – Correlations between DM-TRD score, CCI score, and service use variables. (*p<0.05; **p<0.01; ***p<0.001)

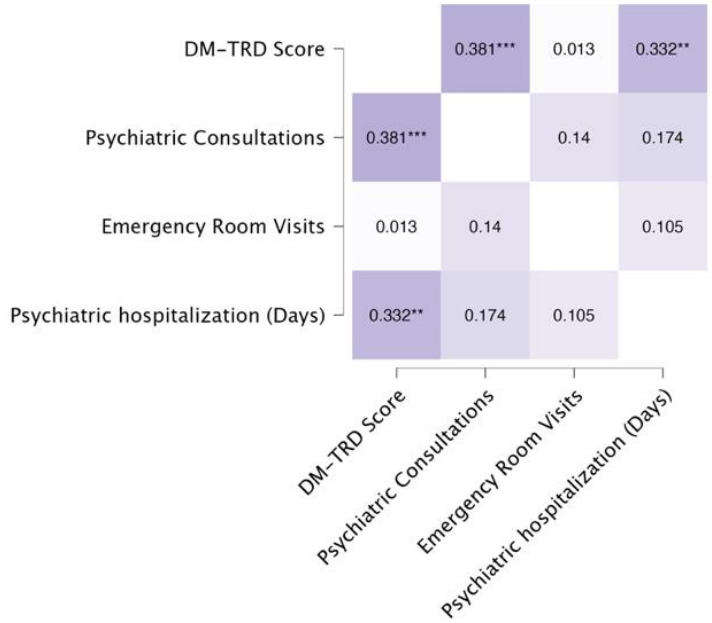

Figure 4: Partial Pearson's heatmap – Partial correlations between DM-TRD score and service use variables, adjusted for CCI scores. (*p<0.05; **p<0.01; ***p<0.001)

On the other hand, when we performed a partial correlation analysis between CCI scores and service use variables, with DM-TRD as a covariable, the correlations between CCI scores and psychiatric consultations and between CCI scores and emergency room visits remained statistically significant (Figure 5).

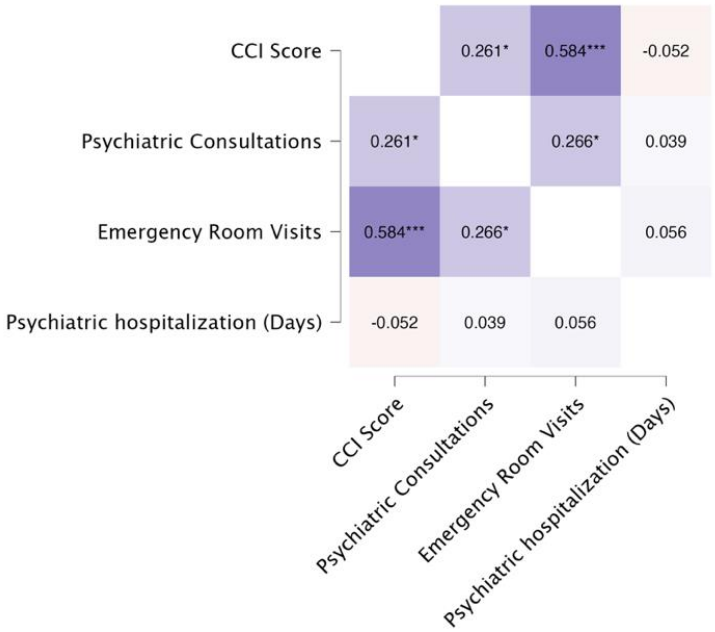

Figure 5: Partial Pearson's heatmap – Partial correlations between CCI score and service use variables, adjusted for DM-TRD score. (*p<0.05; **p<0.01; ***p<0.001)

We performed a linear regression to model the relationship between DM-TRD score, CCI score, and psychiatric consultations, using DM-TRD score and CCI score as predictors and psychiatric consultations as outcome. The overall regression was significant: $F(2, 216) = 48.753$, $p < 0.001$. The model explains about 30% of the variance in psychiatric consultations (Adjusted $R^2 = 0.305$). Table 5 gives information about regression coefficients for the predictors. Depression treatment resistance and medical comorbidities were significant predictors with a positive relationship with the number of psychiatric consultations.

Table 5: Regression coefficients – Regression analysis of the relationship between depression treatment resistance (DM-TRD score), medical comorbidity (CCI score) and number of psychiatric consultations.

Predictors	***B***	**Std. Error**	***β***	***t***	***p***
DM-TRD Score	0.589	0.097	0.389	6.055	< .001
CCI Score	0.888	0.223	0.255	3.974	< .001

4. DISCUSSION

The current study set out to investigate a cohort of patients with depressive disorders followed in the context of a Portuguese CMHT who met criteria for DTD and to study their clinical profile based on sociodemographic variables, treatment resistance in depression, psychiatric comorbidity, medical comorbidity, psychopharmacological treatment, pharmacological treatments for comorbid medical conditions and service utilization, when compared to non-DTD patients. In this work we used the definition proposed by the international consensus statement about the identification, assessment, and management of DTD: 'depression that continues to cause a significant burden despite normal treatment efforts'.[15]

The DTD prevalence in the group of patients studied in our work was approximately 26%. Given the conceptual flexibility in DTD definition, intended to be used in a clinical context reflecting the interactions between the patient and the health care practitioner and dependent on local treatment guidelines and practices, it is expected that DTD prevalence rates differ between empirical studies implemented at different health care settings. In an observational study in the UK, using a natural language processing model, to explore differences between DTD and non-DTD groups on disease characteristics, comorbidities, and treatment histories in a sample of 28,184 patients with depression, the prevalence rate of DTD was 19%.[20] In that study, DTD definition was pragmatically operationalized with the following criteria: the first episode of depression had been coded at least 3 years previously; the patient had a current chronic episode of depression (more than 2 years) or they had multiple recurrences (at least 3 episodes) and there were problems in finding a tolerable and effective treatment as indexed by having at least 4 antidepressant treatments, of which at least 2 were drugs for depression. [20] This pragmatic operationalization of the DTD definition was more restrictive than ours. In our study we asked the community team psychiatrist to identify the patients that they judge that meet the criteria of international consensus definition, with the objective to mimic the interactive nature of this formulation in a clinical context. The differences in DTD definition operationalization, study methodology and health care contexts between these studies may explain the differences of prevalence.

In terms of clinical variables, it was clear that the DTD group had statistically significant higher rates of chronic depressive episodes and depression severity when compared to the non-DTD group. There were also significant statistically differences between DTD and non-DTD groups in service use variables, with more psychiatric consultations, emergency room visits, and psychiatric hospitalization days in the DTD group. These results are in accordance with the studied literature.[20]

Compared to the non-DTD group, patients with DTD had significantly higher scores on a multidimensional scale that measures treatment resistance in depression (DM-TRD), which was also concluded by other studies.[13,20] This finding suggests that our operationalization of the DTD definition is compatible with a dimensional perspective of depression treatment refractoriness in a real-world clinical context. According to the literature, the DM-TRD has proven to demonstrate the ability to predict the clinical outcome of patients with depressive disorders. It was also reported that higher scores were associated with a more significant burden during follow-up of patients with depressive disorder, [13] which is compatible with our findings. Our results are also compatible with the view that DTD and TRD are related and somewhat overlapping concepts, but with key differences. DTD is a more open concept and the identification of DTD in real-world healthcare settings calls not only for subsequent therapeutic trials in an acute medical disease model but to more broad clinician and patient actions in a chronic disease management and recovery framework that include a search for treatable biomedical and psychosocial factors associated with suboptimal outcomes, a shift in treatment goals from remission to an optimization of symptom control, functioning and quality of life. [20]

Our study showed that DTD patients had higher rates of comorbid anxiety symptoms, comorbid personality disorders and traits, and medical comorbidity higher levels. These results are compatible with the findings of other observational real-world studies of DTD patients [20], where the rates of comorbid illness (both mental and physical) are higher in the DTD when compared to the non-DTD group. These higher levels of psychiatric and medical comorbidity can be a challenge when treating depressed patients in a real-world healthcare setting, contributing to lower rates of response and remission, higher probability of relapse and recurrence, more difficulty to achieve the premorbid level of functioning, lower quality of life and a higher frequency of treatment side effects and contraindications. All these outcomes can contribute for the clinician perception of the difficulties when treating depressed patients with comorbid conditions.[15] Our findings suggest that mental health service burden is related concurrently with depression treatment refractoriness and medical comorbidity. We found not only significant correlations between DM-TRD and medical comorbidity, as measured by CCI, but also associations between CCI and the frequency of psychiatric consultations and emergency room visits. Medical comorbidity is a variable that is not included in the different conceptualizations of TRD but is an important area to consider in the assessment of DTD. [20]

In terms of antidepressant prescription profile, when comparing DTD vs non-DTD patients, SNRIs and mirtazapine were more prescribed to the first group. These

prescription practices are compatible with depression guidelines recommendations about the use of specific antidepressants to address common residual depressive symptoms, like anxiety, sleep problems, cognitive difficulties, and somatic symptoms.[24] A recent meta-analysis also showed that the use of presynaptic alpha 2 autoreceptor antagonists like Mirtazapine in antidepressant combination strategies with SSRI or SNRI had a superior treatment outcome than other combinations, [25] suggesting that it can constitute a therapeutic option to consider in DTD patients. There was also a significantly higher proportion of antidepressant augmentation strategies in DTD patients as compared to non-DTD patients. In a similar UK study,[20] it was reported a greater proportion of antidepressant augmentation treatment in DTD patients and a consistent trend for higher dosages. One of the differences between our work and the secondary care UK patient's work previously reported is that we did not observe statistically significant differences in the use of antidepressant combination strategies between patients with DTD compared to non-DTD patients. In that study, it was clearly demonstrated that the use of intensive combination therapies, including non-pharmacological interventions, was more frequent in the DTD group.[20]

In terms of other non-psychiatric drugs, we studied the role of analgesics in DTD, and we concluded that, generally, they were more frequently prescribed to DTD patients than non-DTD patients. DTD patients constitute a heterogenous group, and chronic low-grade inflammation may play a role in the pathophysiology of treatment resistant depression, at least in a subset of patients.[25,26] The literature also reports a frequent comorbidity between depression and osteoarticular disorders[27], associations between treatment resistant disorder and risk of auto-immune disorders[26,28] and a positive correlation between both anxious and depressive symptomology and pain severity.[29] All these factors could provide a partial explanation for the more frequent use of analgesic drugs in DTD patients in our sample. The prescription of anticoagulants was also more frequent in DTD patients, despite the literature reporting that depression is an independent risk factor for major bleeding in anticoagulated individuals (particularly in patients with atrial fibrillation)[30,31], highlighting the importance of a comprehensive assessment of medical comorbidities in patients with depressive disorders.

Finally, when comparing the number of psychiatric consultations and emergency room visits, it was obvious that DTD patients had a statistically significant higher number when compared to non-DTD patients. These results were also expected since the definition of DTD includes patients that are heavier consumers of mental health care services[20], including consultations, emergency room visits, and psychiatric hospitalizations.

Our study has some important limitations. Compared with similar published observational real-world DTD studies,[20] our sample is smaller and restricted to a unique

community mental health team treated population, suggesting a special care about the generalization of our findings to other clinical settings. We are also aware that our operationalization of the definition of DTD rests solely on the team psychiatrist's clinical judgment informed by their knowledge of DTD literature and not in specified a priori criteria. This was an intentional choice with the objective of emulate the daily psychiatric practice but differs from the operationalization of DTD definition in similar studies[20] and didn't consider the patient perspective. Another important issue is that the metrics used to characterize the outcome of depression were suboptimal and consisted only in service use variables. To capture the longer-term clinical outcomes in DTD, we should consider the use of integrative metrics that aggregate information over time in symptomatic, functionality and quality of life domains.

Prospective research designs, with the use of self-report questionnaires to identify probable DTD patients[17], a more comprehensive assessment of psychiatric and medical comorbidities, treatment history and care pathways, and the use of integrative metrics to capture longer-term outcomes in symptomatic and quality of life domains is a possible avenue for future research projects.

5. CONCLUSION

DTD is a recent conceptualization that extends TRD model, with important implications in the assessment and management of depressed patients with suboptimal outcomes in a clinical context. To our knowledge this is the first observational real-world evidence study about DTD in Portugal, and we find a prevalence of 26% of DTD in patients with depressive disorders treated by a Portuguese community mental health team in a 3-year period. Compared with non-DTD depressed patients, the DTD group had higher scores in a multidimensional measure of depression treatment resistance, higher rates of anxiety symptoms and personality disorders and traits, higher scores in a medical comorbidity index, higher proportion of use of antidepressant augmentation strategies and higher number of psychiatric consultations, emergency room visits and psychiatric hospitalizations days. Treatment resistance and medical comorbidity were independent predictors of the quantity of psychiatric consultations. These results are in accordance with findings from observational real world evidence studies implemented in other countries, highlighting the importance of adopting a different approach in the assessment and management of patients with depressive disorders that continues to cause a significant burden despite normal treatment efforts.

6. ACKNOWLEDGMENTS

To my advisor, Professor António Macedo, for all his orientation.

To my co-advisor, Dr. Vítor Santos, for all the incredible support, sympathy, and optimism.

To Drª. Ana Telma Pereira and Drª. Carolina Cabaços, for the help in writing the documents for the Ethics Committee of the Faculty of Medicine of the University of Coimbra.

7. REFERENCES

1. Herrman H, Patel V, Kieling C, Berk M, Buchweitz C, Cuijpers P, Furukawa TA, Kessler RC, Kohrt BA, Maj M, McGorry P. Time for united action on depression: a Lancet–World Psychiatric Association Commission. The Lancet. 2022 Mar 5;399(10328):957-1022.
2. Marx W, Penninx BW, Solmi M, Furukawa TA, Firth J, Carvalho AF, Berk M. Major depressive disorder. Nature Reviews Disease Primers. 2023 Aug 24;9(1):44.
3. Noetel M, Sanders T, Gallardo-Gómez D, Taylor P, del Pozo Cruz B, Van Den Hoek D, Smith JJ, Mahoney J, Spathis J, Moresi M, Pagano R. Effect of exercise for depression: systematic review and network meta-analysis of randomised controlled trials. bmj. 2024 Feb 14;384.
4. Conroy SK, Holtzheimer PE. Neuromodulation strategies for the treatment of depression. American Journal of Psychiatry. 2021 Dec;178(12):1082-8.
5. Voineskos D, Daskalakis ZJ, Blumberger DM. Management of treatment-resistant depression: challenges and strategies. Neuropsychiatric disease and treatment. 2020 Jan 21:221-34.
6. Moriarty AS, Meader N, Snell KI, Riley RD, Paton LW, Dawson S, Hendon J, Chew-Graham CA, Gilbody S, Churchill R, Phillips RS. Predicting relapse or recurrence of depression: systematic review of prognostic models. The British Journal of Psychiatry. 2022 Aug;221(2):448-58.
7. Gaynes BN, Lux L, Gartlehner G, Asher G, Forman-Hoffman V, Green J, Boland E, Weber RP, Randolph C, Bann C, Coker-Schwimmer E. Defining treatment-resistant depression. Depression and anxiety. 2020 Feb;37(2):134-45.
8. McIntyre RS, Alsuwaidan M, Baune BT, Berk M, Demyttenaere K, Goldberg JF, Gorwood P, Ho R, Kasper S, Kennedy SH, Ly-Uson J. Treatment-resistant depression: definition, prevalence, detection, management, and investigational interventions. World Psychiatry. 2023 Oct;22(3):394-412.
9. U.S. Food and Drug Administration. Center for Drug Evaluation and Research. Major depressive disorder: developing drugs for treatment. Silver Spring: U.S. Food and Drug Administration, 2018.
10. European Medicines Agency. Clinical investigation of medicinal products in the treatment of depression – Scientific guideline. Amsterdam: European Medicines Agency, 2018.
11. Ruhé HG, van Rooijen G, Spijker J, Peeters FP, Schene AH. Staging methods for treatment resistant depression. A systematic review. Journal of affective disorders. 2012 Mar 1;137(1-3):35-45.

12. Fekadu A, Wooderson SC, Markopoulou K, Cleare AJ. The Maudsley Staging Method for treatment-resistant depression: prediction of longer-term outcome and persistence of symptoms. Journal of Clinical Psychiatry. 2009 Jul 7;70(7):952.
13. Peeters FP, Ruhe HG, Wichers M, Abidi L, Kaub K, van der Lande HJ, Spijker J, Huibers MJ, Schene AH. The Dutch measure for quantification of treatment resistance in depression (DM-TRD): an extension of the Maudsley staging method. Journal of affective disorders. 2016 Nov 15;205:365-71.
14. Paganin W. Difficult-to-treat depression versus treatment-resistant depression: A new integrative perspective for managing depression. European Psychiatry. 2023 Jan;66(1):e73.
15. McAllister-Williams RH, Arango C, Blier P, Demyttenaere K, Falkai P, Gorwood P, Hopwood M, Javed A, Kasper S, Malhi GS, Soares JC. The identification, assessment and management of difficult-to-treat depression: an international consensus statement. Journal of Affective Disorders. 2020 Apr 15;267:264-82.
16. Paganin W, Signorini S, Sciarretta A. Difficult-to-treat depression. Scoping review. Clinical Neuropsychiatry. 2023 Jun;20(3):173.
17. Zimmerman M, Mackin DM. Reliability and validity of the difficult to treat depression questionnaire (DTDQ). Psychiatry Research. 2023 Jun 1;324:115225.
18. Sousa RD, Gouveia M, Rodrigues AM, Antunes AF, Canhao H. Treatment-resistant depression and major depression with suicide risk—The cost of illness and burden of disease. Frontiers in public health. 2022 Aug 11;10:898491.
19. Bessa JM, Carvalho S, Cunha IB, Fernandes M, Matos-Pires A, Neves R, Oliveira-Maia AJ, Santos S, Santos V. Treatment-resistant depression in Portugal: perspective from psychiatry experts. Frontiers in psychiatry. 2022 Mar 30;13:824919.
20. Costa T, Menzat B, Engelthaler T, Fell B, Franarin T, Roque G, Wei Y, Zhang X, McAllister-Williams RH. The burden associated with, and management of, difficult-to-treat depression in patients under specialist psychiatric care in the United Kingdom. Journal of Psychopharmacology. 2022;36(5):545-556.
21. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. Journal of chronic diseases. 1987 Jan 1;40(5):373-83.
22. Charlson ME, Carrozzino D, Guidi J, Patierno C. Charlson comorbidity index: a critical review of clinimetric properties. Psychotherapy and psychosomatics. 2022 Jan 6;91(1):8-35.
23. *JASP Team (2024). JASP (Version 0.18.3) [Computer software].*
24. Malhi GS, Bell E, Singh AB, Bassett D, Berk M, Boyce P, Bryant R, Gitlin M, Hamilton A, Hazell P, Hopwood M. The 2020 Royal Australian and New Zealand College of

Psychiatrists clinical practice guidelines for mood disorders: major depression summary. Bipolar disorders. 2020 Dec;22(8):788-804.

25. Suneson K, Grudt C, Ventorp F, Malm J, Asp M, Westrin A, Lindqvist D. An inflamed subtype of difficult-to-treat depression. Progress in Neuropsychopharmacology & Biological Psychiatry. 2023 Apr 6;110763.
26. Lauden A, Geishin A, Merzon E, Korobeinikov A, Green I, Golan-Cohen A, Vinker S, Manor I, Weizman A, Magen E. Higher rates of allergies, autoimmune diseases and low-grade inflammation markers in treatment-resistant major depression. Brain, Behavior, & Immunity-Health. 2021 Oct 1;16:100313.
27. Wang ST, Ni GX. Depression in Osteoarthritis: Current Understanding. Neuropsychiatric Disease and Treatment. 2022 Feb 22;18:375-389.
28. Chan VK, Luo H, Chan SS, Lau CS, Yeung WW, Peng K, Tong X, Lam MP, Wong IC, Li X. Treatment-resistant depression and risk of autoimmune diseases: evidence from a population-based cohort and nested case-control study. Translational Psychiatry. 2023 Mar 3;13(1):76.
29. Rodrigues DF, Rodrigues A, Martins T, Pinto J, Amorim D, Almeida A, Ribeiro FP. Correlation between pain severity and levels of anxiety and depression in osteoarthritis patients: a systematic review and meta-analysis. Rheumatology. 2021 Jun 21;61:53-75.
30. Teppo K, Jaakkola, Lehto M, Biancari F, Airaksinen KEJ. The impact of mental health conditions on oral anticoagulation therapy and outcomes in patients with atrial fibrillation: A systematic review and meta-analysis. American Journal of Preventive Cardiology. 2021 Jun 24;7:100221.
31. Michal M, Eggebrecht L, Göbel S, Panova-Noeva M, Nagler M, Arnold N, Lauterbach M, Bickel C, Wiltink J, Beutel ME, Münzel T. The relevance of depressive symptoms for the outcome of patients receiving vitamin K antagonists: results from the thrombEVAL cohort study. European Heart Journal-Cardiovascular Pharmacotherapy. 2021 Jul 1;7(4):271-9.
32. Aaronson ST, Sackeim HA, Jiang M, Badejo S, Greco T, Bunker MT, Conway CR, Demyttenaere K, Young AH, McAllister-Williams RH, Rush AJ. Alternative metrics for characterizing longer-term clinical outcomes in difficult-to-treat depression: II. Sensitivity to treatment effects. Australian & New Zealand Journal of Psychiatry. 2024 Mar;58(3):250-9.
33. Sackeim HA, Rush AJ, Greco T, Jiang M, Badejo S, Bunker MT, Aaronson ST, Conway CR, Demyttenaere K, Young AH, McAllister-Williams RH. Alternative metrics for characterizing longer-term clinical outcomes in difficult-to-treat depression: I.

Association with change in quality of life. Psychological Medicine. 2023 Oct;53(14):6511-23.

8. APPENDIX - APPROVAL FROM THE ETHICS COMMITTEE OF THE FACULTY OF MEDICINE OF THE UNIVERSITY OF COIMBRA

1 2 9 0 FACULDADE DE MEDICINA UNIVERSIDADE DE COIMBRA	**PROJETO DE INVESTIGAÇÃO**	Referência	Mod.CE_01/10
		Revisão	2.0
		Data	26-05-2022
Comissão de Ética da Faculdade de Medicina da Universidade de Coimbra			Página 1 de 7

Antes de preencher este formulário, leia atentamente as respetivas instruções de preenchimento
Todos os campos são de preenchimento obrigatório

1. IDENTIFICAÇÃO DA EQUIPA DE INVESTIGAÇÃO

1.1 IDENTIFICAÇÃO DO(A) INVESTIGADOR(A)

Nome (completo):	JOÃO ANDRÉ DE SILVEIRA DIAS GOUVEIA				
Morada:	Estrada Nacional N2 – Bairro das Aveleiras, N 9 – Carvoeira				
C. Postal:	3360 - 179	**Localidade:**	Penacova		
Telemóvel:	914310784	**Endereço de e-mail:**	Joaoasdgouveia@outlook.com		

1.2. IDENTIFICAÇÃO DO INVESTIGADOR COORDENADOR / ORIENTADOR *(se aplicável)*

Nome (completo):	PROF. DOUTOR ANTÓNIO JOÃO FERREIRA MACEDO SANTOS		
Telemóvel:	967010232	**Endereço de e-mail:**	amacedo@ci.uc.pt

1.3. IDENTIFICAÇÃO DO(S) CO-INVESTIGADOR(ES) /CO-ORIENTADOR (se aplicável)

Nome (completo):	DR. VÍTOR MANUEL OLIVEIRA RODRIGUES SANTOS		
Telemóvel:	926196179	**Endereço de e-mail:**	vitorsantos74@gmail.com
Nome (completo):	Não se aplica		
Telemóvel:	Não se aplica	**Endereço de e-mail:**	Não se aplica
Nome (completo):	Não se aplica		
Telemóvel:	Não se aplica	**Endereço de e-mail:**	Não se aplica
Nome (completo):	Não se aplica		
Telemóvel:	Não se aplica	**Endereço de e-mail:**	Não se aplica

1.4. IDENTIFICAÇÃO DO PROMOTOR

Faculdade de Medicina da Universidade de Coimbra (FMUC)

2. IDENTIFICAÇÃO DO PROJETO

Título do projeto:	CARACTERIZAÇÃO CLÍNICA DOS UTENTES DA UNIDADE DE SAÚDE COMUNITÁRIA DE CANTANHEDE QUE CUMPRAM CRITÉRIOS PARA DEPRESSÃO DIFÍCIL DE TRATAR
Tipo de estudo:	PROJETO DE INVESTIGAÇÃO OBSERVACIONAL, RETROSPETIVO, NÃO INTERVENCIONAL
Finalidade do estudo:	ESTUDO ACADÉMICO (OBTENÇÃO DE GRAU DE MESTRE EM MEDICINA)

Serviço(s) onde o projeto será executado:

UNIDADE DE SAÚDE COMUNITÁRIA DE CANTANHEDE

Existem outros centros, nacionais ou não, onde a mesma investigação será feita?

- ☐ Sim X Não

Em caso afirmativo indique qual/quais:

Não se aplica.

3. JUSTIFICAÇÃO CIENTÍFICA DA INVESTIGAÇÃO

A medicação com antidepressivos apenas atinge a remissão completa em cerca de 66% dos doentes com depressão major[1]. Os doentes com episódios de depressão major crónica têm menor probabilidade de recuperação e, frequentemente, sofrem de depressão resistente ao tratamento[2].
Existem diversas definições de depressão resistente ao tratamento na literatura. Esta pode ser definida como episódios de depressão major, com intensidade moderada a severa, sem melhoria clínica, depois do doente ser medicado com dois antidepressivos, perante uma boa adesão terapêutica, dose e duração adequadas de tratamento[3].
Há diversos desafios no estudo da depressão resistente ao tratamento. Um destes desafios é denominado de pseudo-resistência. A pseudo-resistência inclui doentes que foram prescritos com doses terapêuticas não otimizadas e/ou descontinuaram precocemente a terapêutica antidepressiva devido a efeitos secundários. A personalidade e o abuso de substâncias têm também consequências negativas na recuperação de episódios de depressão major[4].
A generalização a partir de vários estudos observacionais da literatura acerca da depressão resistente ao tratamento é, até ao momento, bastante limitada, bem como o impacto da depressão resistente ao tratamento a nível individual e na sociedade[5].

1 - Kennedy SH, Giacobbe P. Treatment resistant depression – advances in somatic therapies. Ann Clin Psychiatry. 2007;19(4):279–287

2 - Malhi GS, Parker GB, Crawford J, Wilhelm K, Mitchell PB. Treatment-resistant depression: resistant to definition? Acta Psychiatr Scand. 2005;112(4):302–309

3 - Bessa JM, Carvalho S, Cunha IB, Fernandes M, Matos-Pires A, Neves R, Oliveira-Maia AJ, Santos S, Santos V. Treatment-Resistant Depression in Portugal: Perspective From Psychiatry Experts. Front. Psychiatry. 2022; 13:824919

4 - Voineskos D, Daskalakis ZJ, Blumberger DM. Management of Treatment-Resistant Depression: Challenges and Strategies. Neuropsychiatric Disease and Treatment. Neuropsychiatric Disease and Treatment. 2020;(16):221–234

5 - Lundberg J, Cars T, Lööv SÅ, Söderling J, Sundström J, Tiihonen J, Leval A, Gannedahl A, Björkholm C, Själin M, Hellner C. Association of Treatment-Resistant Depression With Patient Outcomes and Health Care Resource Utilization in a Population-Wide Study. JAMA Psychiatry. 2023;80(2):167-175

4. PARTICIPANTES ABRANGIDOS NA INVESTIGAÇÃO

4.1. Grupo de estudo

Número: Estimativa de 100 (cem) doentes

Critérios de inclusão/exclusão utilizados:

Utentes seguidos em consulta de psiquiatria na unidade de saúde comunitária de Cantanhede que cumpram critérios de depressão difícil de tratar (doentes que apresentem episódios de depressão major sem melhoria clínica após serem medicados com dois antidepressivos, em dose, duração e adesão adequados). Estimamos uma amostra de cerca de 100 (cem) doentes, observados pela equipa comunitária entre janeiro de 2020 e setembro de 2023.

Indique como se processará o seu recrutamento:

ATRAVÉS DA CONSULTA DE PSIQUITRA DA UNIDADE DE SAÚDE COMUNITÁRIA DE CANTANHEDE

4.2 Grupo de controle

Número: NÃO SE APLICA

Critérios de inclusão/exclusão utilizados:

NÃO SE APLICA

Indique como se processará o seu recrutamento:

NÃO SE APLICA

4.3. Especifique se o estudo abrange grávidas, maiores incapazes e/ou menores de idade:

NÃO SERÃO RECRUTADAS MULHERES GRÁVIDAS, MAIORES INCAPAZES OU MENORES DE IDADE.

5. OUTROS DADOS SOBRE O PROJETO

a) A Investigação envolve a realização de exames complementares?

- ☐ Sim X Não

- Em caso afirmativo, por favor, indique:

Tipo:	NÃO SE APLICA
Frequência:	NÃO SE APLICA
Especifique se estes procedimentos são feitos especialmente para esta investigação ou são executados no âmbito dos cuidados médicos habituais a prestar aos doentes:	NÃO SE APLICA

b) A Investigação proposta envolve Questionários?

- ☐ Sim X Não

- Em caso afirmativo, por favor, indique:

A quem são feitos?	NÃO SE APLICA
Como são aplicados?	NÃO SE APLICA

(NOTA: Junte 1 exemplar do questionário que será utilizado).

c) A Investigação proposta envolve outros procedimentos?

- ☐ Sim X Não

- Em caso afirmativo, por favor, indique:

Tipo:	NÃO SE APLICA
Frequência:	NÃO SE APLICA
Especifique se estes procedimentos são feitos especialmente para esta investigação ou são executados no âmbito dos cuidados médicos habituais a prestar aos doentes:	NÃO SE APLICA

6. DESCRIÇÃO RESUMIDA DO PLANO E METODOLOGIA DE INVESTIGAÇÃO

O principal objetivo do nosso trabalho é selecionar doentes de uma unidade de saúde comunitária portuguesa (Cantanhede) que cumpram critérios para depressão resistente ao tratamento e estudar o seu perfil clínico baseado nas características da depressão, eventos traumáticos/stressantes anteriores, comorbilidades psiquiátricas e não-psiquiátricas e fatores

económicos. De entre dados disponíveis no processo clínico, iremos também explorar potenciais preditores de insucesso terapêutico na depressão resistente ao tratamento, tais como o número de recaídas, má adesão ao tratamento farmacológico e não farmacológico.
Será construída uma base de dados com as características anteriormente descritas de cada doente estudado.

7. AVALIAÇÃO DE RISCO/BENEFÍCIO

Que riscos ou incómodos podem ser causados aos participantes pelo estudo?

A PARTICIPAÇÃO NÃO ENVOLVE QUALQUER RISCO OU INCÓMODO PARA OS PARTICIPANTES.

Que benefícios imediatos poderão advir para os participantes pela sua anuência em participar no estudo?

ESTIMA-SE AUSÊNCIA DE BENEFÍCIOS IMEDIATOS PARA O PARTICIPANTE DECORRENTES DA PARTICIPAÇÃO NO ESTUDO.

8. PROTEÇÃO DE DADOS DOS PARTICIPANTES

Medidas tomadas para assegurar a proteção de dados.

8.1 Responsável pelo tratamento de dados

Nome (completo): DR. VÍTOR MANUEL OLIVEIRA RODRIGUES SANTOS

Telemóvel: 926196179 **Endereço de e-mail:** vitorsantos74@gmail.com

8.2. Categoria de Dados Pessoais

Identifique todos os dados pessoais e/ou especiais a que pretende ter acesso:

Dados sociodemográficos; dados médicos e de saúde, dados sobre utilização de serviços de saúde (internamentos, urgências, consultas psiquiátricas e médicas).

8.3 Colheita/Recolha de Dados Pessoais

- **Direta (ao próprio):**

☐ Presencial ☐ Por impresso ☐Telefone ☐ Inquérito on-line ☐ Outro (especificar):

- **Indireta:**

x Processo Clínico ☐ Registos de outras Instituições ☐ Familiares ☐ Outro (especificar):

8.4 Tratamento de Dados Pessoais

Indicar a forma como são armazenados ou gravados os dados recolhidos:

Os dados serão recolhidos do processo clínico dos doentes, para realização de estudo retrospetivo. Os dados serão pseudo-anonimizados, através da atribuição de um código numérico a cada participante que será emparelhado com os respetivos dados. Os dados obtidos serão armazenados numa base informatizada, que ficará na posse do investigador responsável, do orientador e do co-orientador. A base de dados só poderá ser acedida através de palavra-passe, apenas do conhecimento do investigador responsável, orientador e co-orientador.

8.5 Medidas de segurança

Indicar as medidas técnicas e organizativas adotadas para segurança dos dados pessoais:

8.5.1.O participante é identificado por código especificamente criado para este estudo?

x Sim ☐ Não

8.5.2. Em caso afirmativo, quem realiza a codificação dos dados?

X Investigador ☐ Promotor ☐ Outro (especifique)

8.5.2. Onde ficam os dados pessoais tratados?

X numa base de dados / ficheiro do Investigador

☐ numa base de dados / ficheiro do Hospital ou Instituição

☐ numa base de dados / ficheiro do Promotor

☐ numa base de dados / ficheiro fora da União Europeia

8.5.3. É criado um biobanco?

☐ Sim X Não

8.5.4. Existe Comunicação de Dados Pessoais a terceiros?

☐ Sim X Não

8.5.5. Existem Fluxos de Dados Pessoais transfronteiriços para fora da EU/EEE?

☐ Sim X Não

8.5.6. Indicar o Prazo Máximo de Conservação dos Dados

Os dados serão conservados até à publicação do estudo, sem ultrapassar, no máximo, 5 anos.

9. CONFLITO DE INTERESSES

Não existem conflitos de interesses.

10. CONSENTIMENTO

A expressão do consentimento informado terá forma escrita, conforme a Lei.
Nota: Deverá juntar um exemplar do Texto de Consentimento Informado a assinar pelo participante ou representante(s) legal(is).

Descreva resumidamente o conteúdo da informação a transmitir ao participante:

Uma vez que se trata de um estudo retrospetivo (com consulta de dados a partir do processo clínicos dos doentes), solicitamos a dispensa de consentimento informado – documento em anexo.

11. RELATIVAMENTE AO ESTUDO

a) **Data prevista de início: : 01/01/2020 Data prevista de conclusão: 31/09/2023**

b) **Existe reembolso e/ou ressarcimento aos participantes**

- Pelas deslocações: ☐ Sim x Não
- Pelas faltas ao serviço: ☐ Sim x Não
- Por danos resultantes da sua participação no estudo: ☐ Sim x Não

c) **Em caso afirmativo especifique a entidade que assume a responsabilidade pelo reembolso e/ou ressarcimento das despesas:**

Não se aplica.

d) **Existe um Seguro afeto a este Projeto de Investigação (especifique):**

Não.

e) **Do estudo resulta alguma espécie de benefício financeiro ou outro para o investigador e/ou instituição?**

☐ Sim x Não

Em caso afirmativo especifique: NÃO SE APLICA.

Os dados obtidos constituirão propriedade exclusiva de companhia farmacêutica ou de outra entidade?

☐ Sim x Não

Em caso afirmativo especifique a entidade: NÃO SE APLICA

TERMO DE RESPONSABILIDADE

Eu, abaixo assinado, declaro por minha honra, na qualidade de investigador, que as informações prestadas neste questionário são verdadeiras.
Comprometo-me a respeitar o direito à privacidade e à proteção dos dados pessoais dos participantes, vinculando-me ainda ao estrito cumprimento do dever de sigilo e de confidencialidade a que me encontro legalmente obrigado.
Declaro também que durante o estudo serão respeitadas todas as disposições legais em vigor e as recomendações constantes da Declaração de Helsínquia (1964 e subsequentes revisões) e da Organização Mundial de Saúde.

Data do pedido de aprovação: 03/10/2023

Assinado por: **João André da Silveira Dias Gouveia**
Num. de Identificação: 14308806
Data: 2023.10.02 15:36:12+01'00'

CHAVE MÓVEL *(assinatura)*

PEDIDO DE DISPENSA DE CONSENTIMENTO INFORMADO

À Comissão de Ética da Faculdade de Medicina da Universidade de Coimbra (FMUC),

Eu, João André de Silveira Dias Gouveia, aluno do sexto ano do Mestrado Integrado em Medicina da FMUC, investigador no projeto de investigação para obtenção do grau de mestre em medicina "CARACTERIZAÇÃO CLÍNICA DOS UTENTES DA UNIDADE DE SAÚDE COMUNITÁRIA DE CANTANHEDE QUE CUMPRAM CRITÉRIOS PARA DEPRESSÃO DIFÍCIL DE TRATAR" e restantes investigadores, orientadores do trabalho proposto, vimos por este meio pedir a dispensa de consentimento informado.

No nosso trabalho, pretendemos selecionar doentes de uma unidade de saúde comunitária portuguesa que cumpram critérios para depressão difícil de tratar e estudar o seu perfil clínico baseado nas características da depressão, eventos traumáticos/stressantes anteriores, comorbilidades psiquiátricas e não-psiquiátricas e variáveis económicas. De entre dados disponíveis no processo clínico, iremos também explorar potenciais preditores de insucesso terapêutico na depressão resistente ao tratamento, tais como o número de recaídas, a adesão ao tratamento farmacológico e não farmacológico e dados sobre utilização de serviços de saúde (internamentos, urgências, consultas psiquiátricas e médicas). Será construída uma base de dados com as variáveis anteriormente descritas de cada doente a incluir no estudo. Serão estudados, previsivelmente, 100 (cem) doentes. Os doentes foram recrutados através da consulta de psiquiatria da unidade de saúde comunitária de Cantanhede, entre janeiro de 2020 até setembro de 2023.

Os dados recolhidos serão pseudo-anonimizados, através da atribuição de um código numérico a cada doente que será emparelhado com os respetivos dados. Os dados obtidos serão armazenados numa base informatizada, protegida por palavra-passe, que ficará na posse apenas da equipa de investigação. Os dados serão conservados até à publicação do estudo, sem ultrapassar, no máximo, 5 anos.

Desta forma, tratando-se de um estudo observacional, retrospetivo e não intervencional, e sendo os dados dos doentes pseudo-anonimizados e apenas processados para fins deste projeto de investigação, solicitamos à Comissão de Ética da FMUC a dispensa de obtenção de consentimento informado.

Coimbra, 03/10/2023

Com os melhores cumprimentos em nome da equipa,

João André de Silveira Dias Gouveia (aluno)

Assinado por: **João André de Silveira Dias Gouveia**
Num. de Identificação: 14308806
Data: 2023.10.02 14:44:54+01'00'

CHAVE MÓVEL

Prof. Doutor António João Ferreira Macedo Santos (Orientador)

Assinado por: **ANTÓNIO JOÃO FERREIRA DE MACEDO E SANTOS**
Num. de Identificação: 04328057
Data: 2023.10.02 16:21:39+01'00'

Dr. Vítor Manuel Oliveira Rodrigues Santos (Co-orientador)

Assinado por: **VÍTOR MANUEL OLIVEIRA RODRIGUES DOS SANTOS**
Num. de Identificação: 10334480
Data: 2023.10.03 09:26:29 +0100

CHAVE MÓVEL

Comissão Ética - FMUC

Responder | Responder a todos | Encaminhar

Para: Joaoasdgouveia@outlook.com

Sex, 20/10/2023 17:45

Cc: amacedo@ci.uc.pt; vitorsantos74@gmail.com

Exmo. Senhor

Dr. João André de Silveira Dias Gouveia,

Cumpre-nos informar que o projeto de investigação apresentado por V. Exa. com o título "***Caracterização clínica dos utentes da unidade de saúde comunitária de Cantanhede que cumpram critérios para depressão difícil de tratar***", foi analisado na reunião da Comissão de Ética da FMUC de 12 de outubro, tendo merecido o parecer que a seguir se transcreve:

"A Comissão considera que se encontram respeitados os requisitos éticos adequados à realização do estudo, pelo que emite parecer favorável à sua realização, com dispensa de consentimento informado".

Cordiais cumprimentos.

Helena Craveiro
Universidade de Coimbra • Faculdade de Medicina • STAG – Secretariado Executivo
Pólo das Ciências da Saúde • Unidade Central Azinhaga de Santa Comba, Celas
3000-354 COIMBRA • PORTUGAL
Tel.: +351 239 857 708 (Ext. 542708) | Fax: +351 239 823 236
E-mail: comissaoetica@fmed.uc.pt | www.fmed.uc.pt