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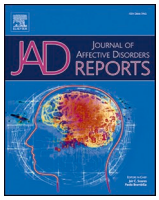

Research Paper

Real-world evidence from a European cohort study of patients with treatment resistant depression: Country-specific data for Portugal

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ABSTRACT

Background: Treatment resistant depression (TRD; failure to respond to ≥2 treatments in the same major depressive episode) affects 10–30 % of patients with major depressive disorder. In Portugal, the disease burden is estimated to exceed that of heart failure, highlighting the critical unmet needs of these patients.
Methods: A non-interventional cohort study of patients with TRD collected real-world data from several European countries. All patients started a new antidepressant treatment at baseline. We present a sub-analysis of baseline characteristics and Month 6 treatment outcomes in Portuguese patients.
Results: Among 411 patients enrolled, 37 were Portuguese. At baseline, 45.9 % of Portuguese patients had severe depression versus 32.6 % of the total study population. Portuguese patients had numerically greater impairments in work and productivity, measured by the Work Productivity and Activity Impairment questionnaire and the Sheehan Disability Scale. There was considerable heterogeneity in treatments used in the Portuguese subgroup, with 31 different treatment strategies reported. At Month 6, a greater proportion of Portuguese patients ($n = 27$) achieved either response or remission (40.7 %) compared with the total study population ($n = 306$; 26.5 %).
Limitation: Small patient numbers in the Portuguese subgroup.
Conclusions: The higher baseline disease severity and productivity impairment in the Portuguese subgroup relative to the total study population suggests notable societal disease burden, whilst the heterogeneity of treatments used indicates a lack of clinical consensus. Despite Portuguese patients reporting higher rates of response and remission than the overall study population, most patients failed to respond to treatment, highlighting an unmet need for TRD in Portugal.

1. Introduction

Major depressive disorder (MDD) is a common mood disorder, with a prevalence of around 6 % in Europe (Arias-de la Torre et al., 2021). Symptoms of MDD include low mood, low self-esteem, and lack of motivation. MDD is associated with significant morbidity and mortality (GBD, 2017; Disease and Injury Incidence and Prevalence Collaborators, 2018), and an increased risk of suicidal ideation and behaviour

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(Cavanagh et al., 2003). Currently, treatment options for patients with MDD include a range of medications, psychological therapies, and neurostimulation therapies, frequently used in variable combinations (National Institute for Health and Care, 2009; Cleare et al., 2015). While these treatments are effective for most patients with MDD, 10–30 % develop treatment resistant depression (TRD) (Al-Harbi, 2012; Jaffe et al., 2019; Rush et al., 2006; Voineskos et al., 2020). TRD is most commonly defined as a failure to respond to two or more different antidepressants, given at adequate dose and duration, in the same major depressive episode (MDE) (Souery et al., 1999; European Medicines Agency, 2009). While any medication approved for MDD can be used for patients with TRD, the majority of these medications have been shown to be insufficiently effective in these patients (Heerlein et al., 2021a), and there is currently only one treatment with European-wide market approval specifically for TRD (Mahase, 2019).

Portugal has been reported to have a high prevalence of MDD. The European Health Interview Survey conducted from 2013 to 2015 reported the prevalence of MDD in Portugal at 9.2 %, which is higher than the overall prevalence of 6.4 % across 27 European countries (Arias-de la Torre et al., 2021). Another study estimated the lifetime prevalence of adult onset-MDD in Portugal to be as high as 13.3 % (Oliveira et al., 2021).

TRD has been shown to cause a substantial disease burden in Portugal, with disability-adjusted life years (DALY) lost due to TRD estimated to be as high as 25,200 in 2017 (Sousa et al., 2022), which exceeded DALY estimates for heart failure (Gouveia et al., 2019). In addition, TRD also has a substantial impact on quality of life, functioning and productivity at an individual patient level (Heerlein et al., 2021b). Economic and societal consequences of TRD include increased healthcare resource utilisation, such as the need for outpatient care (primary and specialised) and cases of hospitalisation, as well as increased numbers of sick days and loss of productivity at work (Heerlein et al., 2022). To begin addressing the personal and societal burden of TRD, a better understanding of the characteristics, treatment profiles and clinical outcomes of patients with TRD in Portugal is needed.

The European Observational TRD Cohort (EOTC) study was a prospective, multi-centre, non-interventional, observational study of adult patients with TRD in seven European countries, including Portugal (Heerlein et al., 2021b). It aimed to describe the socio-demographic and disease-related characteristics, naturalistic treatment patterns and clinical outcomes in patients with TRD, as well as the healthcare resource utilisation, social and economic burden associated with TRD (K Heerlein et al., 2021; Heerlein et al., 2022). Here, we report baseline characteristics and 6-month treatment outcomes for patients with TRD who were recruited in Portugal, as compared to the total EOTC population.

2. Methods

2.1. Patients

Patients aged 18 to 74 years with a diagnosis of MDD, according to either the Fifth Edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) or the Tenth Revision of the International Statistical Classification of Diseases and Related Health Problems (ICD-10), were eligible. Patients were also required to have a diagnosis of TRD (defined as failing to respond to two or more different oral antidepressants, given at an adequate dose and for a sufficiently long period during the current MDE, as determined using the Massachusetts General Hospital-Antidepressant Treatment Response Questionnaire [MGH-ATRQ]), and a Montgomery-Åsberg Depression Rating Scale (MADRS) total score of 20 or more (range: 0–60) (Montgomery and Asberg, 1979; Quilty et al., 2013). At enrolment, all patients were starting a new antidepressant treatment at the discretion of the prescribing clinician. A new antidepressant treatment was considered as any new pharmacological and/or non-pharmacological treatment, prescribed either to replace the existing antidepressive treatment or in addition to the previously established antidepressant treatment. Dose escalation of the previously established antidepressant treatment, or the addition of a drug intended to increase the plasma concentration of the previously established antidepressant was not considered a new treatment. Full inclusion and exclusion criteria for the EOTC study have been published previously (Heerlein et al., 2021b). All participants provided written informed consent and were considered capable of providing consent by their physician. This study was conducted in accordance with the Declaration of Helsinki, with approval from country-specific ethics review boards.

2.2. Study design

The EOTC (registry number 54135419DEP4001) was a prospective, non-interventional, multi-centre study in patients initiating a new, routine treatment for TRD in a real-world setting. The study was comprised of a baseline data collection period and a 6 to 12-month observational period (**Supplementary Figure 1**). Eligible patients were enrolled from Belgium, Germany, Italy, the Netherlands, Portugal, Spain, and the United Kingdom, recruited from inpatient and outpatient settings.

2.3. Study procedures and evaluations

Data were obtained from patient medical records, clinician-rated assessments, and questionnaires completed by patients, collected at baseline and Month 6. Baseline clinical assessments were performed within 14 days before and 7 days after the date that the new antidepressant treatment was started. At baseline, demographic data were collected, including age, sex, educational level, and employment status. Clinical characteristics and disease history data were also collected: age at diagnosis of MDD, date of MDD diagnosis, number of previous MDEs, duration of current MDE, MADRS score, current medication (including treatment type, medication, daily dose, and frequency), age at diagnosis, number of drugs failed in the current MDE, and depression severity (assessed by MADRS score and Clinical Global Impression-Severity Scale [CGI-S] score) (Busner and Targum, 2007).

Health-related quality of life (HRQoL) was assessed via the EuroQoL 5-dimension 5-level (EQ-5D-5L) patient-reported questionnaire, which includes the EuroQoL Visual Analogue Scale (EQ-VAS; range: 0–100) (Herdman et al., 2011). Functional impairment and associated productivity were measured via the Sheehan Disability Scale (SDS; range: 0–30) patient-reported questionnaire (Sheehan et al., 1996; Rating Scales and Safety Measurements in Bipolar Disorder and Schizophrenia - A Reference Guide, 2017), whilst impairment in work, productivity, and activity was assessed via the Work Productivity and Activity Impairment (WPAI) patient-reported questionnaire (Reilly et al., 1993).

During the study, any events indicating a clinically-relevant worsening or improvement triggered an assessment by the patient's treating physician. These events were defined as worsening or improvement of the current MDE (confirmed by Clinical Global Impression of Change [CGI-C] $\leq$3 or $\geq$5), relapse of depressive symptoms, admission to or discharge from inpatient care, remission of the current MDE (defined as MADRS score $\leq$10), any change in pharmacological treatment (such as adding an augmentation medication or switching therapy), or any change in non-pharmacological therapy. Event-triggered data collected included HRQoL, functional impairment and disability in work and other areas, depression symptoms spectrum and severity, and any changes to treatment.

The remission or response status of each patient was assessed 6 months after baseline. Remission was defined as a MADRS score of $\leq$10, while MADRS scores >10 but with $\geq$50 % improvement from baseline were defined as response without remission. Where the MADRS score was not available, a response/remission proxy was inferred based on CGI scores: if the final CGI-S score was 1 or 2 then the patient was said to be in remission; if the final CGI-S score was >2, yet the Clinician Global

Impression-Change (CGI-C) score was 1 or 2, then the patient was said to be in response. In all other cases, the outcome was considered to be no response. Visits occurring 150–216 days after enrolment were considered to be Month 6; data obtained outside this window were excluded from the Month 6 analysis.

2.4. Statistical analysis

Continuous variables were summarised using descriptive statistics (N, mean, standard deviation [SD], median, minimum and maximum). Categorical variables were summarised by frequency distribution (number and percentage of patients in each category). Baseline patient data and treatment outcomes are presented for Portuguese patients enrolled in the study, compared with the entire EOTC cohort.

3. Results

3.1. Baseline patient socio-demographics

Across the seven countries represented in the final analysis set, 411 patients with TRD were included, of which 37 were from Portugal. The mean (SD) age of patients at baseline was 50.0 (13.1) years in the Portuguese cohort, and 51.0 (10.8) years across the total study population (Table 1). Similar rates of unemployment were seen in Portugal (32.4 %) and the total study population (30.2 %). In the Portuguese cohort, the proportions of patients educated to either a university level (32.4 %) or primary school level (29.7 %) were greater than in the total study population (17.0 % and 15.8 %, respectively).

3.2. Baseline psychiatric and medical history

The mean (SD) number of years since MDD diagnosis for Portuguese patients was greater than that of the total study population (15.6 [11.5] years versus 13.7 [11.2] years, respectively; Table 1). The mean (SD) duration of current MDE in the Portuguese cohort was 126.0 (139.9) weeks, compared with 136.3 (203.8) in the total study population. However, the median (range) duration was 104.3 (13–626) weeks in the Portuguese cohort, compared with 69.6 (10–2242) weeks in the total study population (Table 1). The number of previous MDEs experienced (Table 1) and number of drugs failed in the current MDE (Fig. 1) were similar across the Portuguese and total study cohorts.

3.3. Baseline patient clinical characteristics

A greater proportion of Portuguese patients were severely depressed, according to MADRS score category, with 45.9 % classified as having severe depression, compared with 32.6 % in the overall study population (Table 1). CGI-S scores were also greater in Portuguese patients; 81.1 % of Portuguese patients were categorised as at least markedly ill, compared with 65.6 % of the total study population (Fig. 2).

HRQoL impairment (measured via the EQ-5D-5L and EQ-VAS) and functional impairment measured via SDS score were similar across Portuguese patients and the total study population. However, Portuguese patients reported greater impairments in work productivity and activity across all individual components of the WPAI questionnaire versus the total study population (Table 1).

3.4. Baseline treatment strategy

A wide range of treatments strategies were reported in the Portuguese and total population at baseline, with substantial variation in the proportion of patients receiving each type of treatment. The classes of oral antidepressants prescribed at baseline were broadly similar (Fig. 3**A**), although mood stabilisers were prescribed less frequently in the Portuguese cohort compared with the total study population (2.7 % and 15.8 %, respectively). Neurostimulation treatments (including transcranial magnetic stimulation [TMS], electroconvulsive therapy [ECT] and other) were more frequently used in the Portuguese cohort (Fig. 3**B**). Psychosocial therapies (including cognitive behavioural therapy, interpersonal therapy and other) were less commonly used by Portuguese patients compared with the total cohort. Overall, 31 different treatment lines were prescribed at baseline across the 37 Portuguese patients (Fig. 4).

Table 1
Baseline socio-demographics and clinical characteristics.

Mean (SD), unless otherwise stated	Portuguese patients (n = 37)	All patients (N = 411)
Socio-demographics		
Age, years	50.0 (13.1)	51.0 (10.8)
Female patients, % (n)	75.7 (28)	62.3 (256)
Unemployed (seeking work), % (n)	8.1 (3)	7.1 (29)
Unemployed (not seeking work), % (n)	24.3 (9)	23.1 (95)
Long-term sick leave, % (n)	18.9 (7)	19.0 (78)
Highest education level, % (n)		
University	32.4 (12)	17.0 (70)
High school	8.1 (3)	27.0 (111)
Secondary school	27.0 (10)	36.0 (148)
Primary school	29.7 (11)	15.8 (65)
No formal education	0	0.5 (2)
Psychiatric and medical history		
Age at diagnosis of MDD, years	34.4 (12.2)	37.2 (13.1)
Years since MDD diagnosis	15.6 (11.5)	13.7 (11.2)
Number of previous MDEs	2.4 (2.0)	3.4 (5.6; n = 403)
Duration of current MDE, weeks		
Mean (SD)	126.0 (139.9)	136.3 (203.8)
Median (range)	104.3 (13–626)	69.6 (10–2242)
Clinical characteristics		
MADRS total score	33.2 (5.6)	31.8 (6.0)
Depression severity: MADRS score category, % (n)		
Severe	45.9 (17)	32.6 (134)
Moderate	54.1 (20)	67.4 (277)
Health-related quality of life		
EQ-5D-5L (UK utility values)	0.39 (0.22)	0.41 (0.25; n = 397)
EQ-VAS	38.8 (21.5)	41.1 (18.7; n = 403)
Functional impairment		
SDS total score	23.8 (4.7; n = 29)	22.4 (5.5; n = 341)
WPAI		
"Percent work time missed due to problem"	81.1 (36.8; n = 13)	57.0 (44.9; n = 132)
"Percent impairment while working due to problem"	66.0 (29.7; n = 5)	54.7 (29.5; n = 86)
"Percent overall work impairment due to problem"	78.9 (15.5; n = 4)	60.5 (29.9; n = 76)
"Percent activity impairment due to problem"	77.1 (17.4; n = 35)	73.3 (19.9; n = 390)

For Portuguese patients and all patients, n = 37 and 411, respectively, unless otherwise stated. Severe depression was defined as a MADRS score >34; moderate depression was defined as a MADRS score of 20–34. The ranges for the MADRS, EQ-VAS and SDS are 0–60, 0–100 and 0–30, respectively (Quilty et al., 2013; Herdman et al., 2011; Rating Scales and Safety Measurements in Bipolar Disorder and Schizophrenia - A Reference Guide, 2017). EQ-5D-5L: EuroQoL 5-dimension 5-level questionnaire; EQ-VAS: EuroQoL Visual Analogue Scale; MADRS: Montgomery-Åsberg Depression Rating Scale; MDD: major depressive disorder; MDE: major depressive episode; SD: standard deviation; SDS: Sheehan Disability Scale; UK: United Kingdom; WPAI: Work Productivity and Activity Impairment.

3.5. Treatment outcomes at month 6

The proportion of Portuguese patients achieving remission was higher than that of the total study population (29.6 % versus 16.7 %,

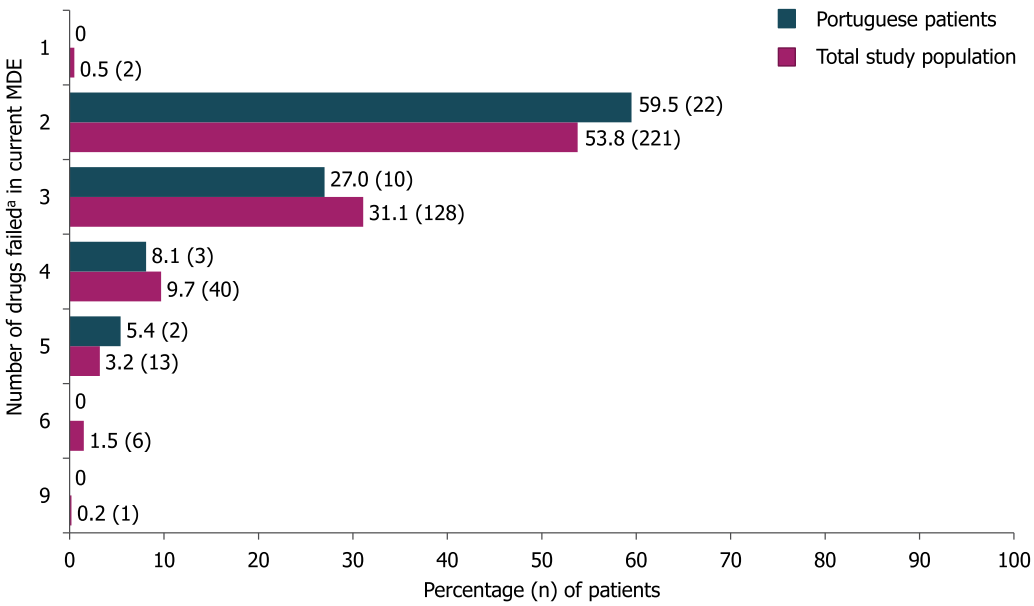

Fig. 1. Number of individual drugs failed[a] in the current MDE. [a] Number of individual drugs failed according to those listed in the MGH-ATRQ. MDE: major depressive episode; MGH-ATRQ: Massachusetts General Hospital-Antidepressant Treatment Response Questionnaire.

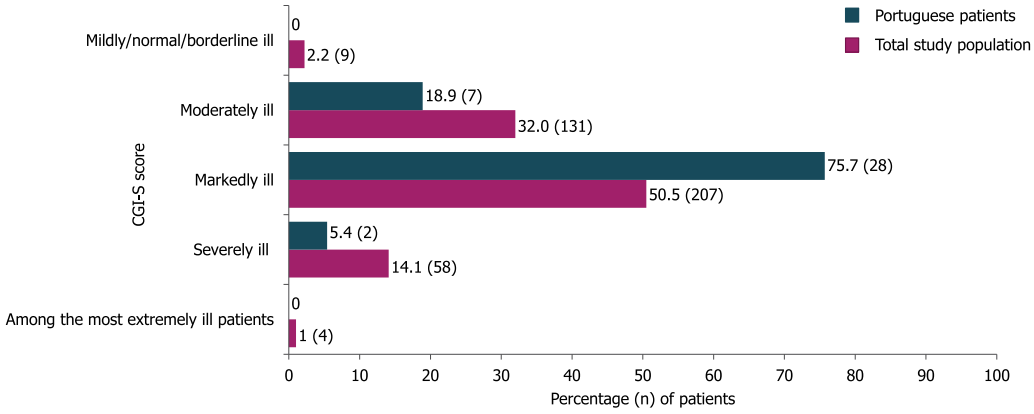

Fig. 2. Depression severity at baseline. CGI-S: Clinical Global Impression-Severity scale.

respectively; Fig. 5). 11.1 % of Portuguese patients and 9.8 % of the total study population achieved response without remission, whilst 59.3 % of Portuguese patients and 73.5 % of the total study population failed to achieve either response or remission.

4. Discussion

Here, in the context of the EOTC, we compared baseline socio-demographics, clinical characteristics, and functional impairments of Portuguese patients with TRD with those of the total study population, which spanned seven European countries. Baseline characteristics of the Portuguese cohort were largely similar to those of the total study population, although there were some notable differences. Highest obtained education level in the Portuguese subgroup was inconsistent with the total study population, where double the proportion of patients reported either primary school or university level education, when compared with the total group. This may be attributed to the recruitment of patients from both private and public healthcare settings. Previous data have indicated that qualification level and income are correlated in Portugal, therefore it follows that private healthcare may be more accessible to highly qualified, high-earning patients (Peralta et al., 2020). As such, less qualified individuals with lower incomes are more likely to utilise public healthcare resources, which may contribute to the large range of education levels observed in the Portuguese cohort.

Portuguese patients were found to have higher disease severity relative to the total study population, as shown by both MADRS and CGI-S scores, indicating a greater personal disease burden than the total study population. Although these scores only provide a single time-point measure of disease burden, the Portuguese cohort also displayed a notably higher median current MDE duration, and greater impairments in work productivity and activity. In combination, these findings suggest that there is a high unmet need in the Portuguese cohort, and a potentially greater disease burden over time. Despite the limited sample size of this analysis, these findings were in agreement with a previous study reporting a substantial disease burden of TRD in Portugal in the form of high numbers of life years lost, and notable associated economic costs (Sousa et al., 2022).

Previous studies have described an association between lower educational attainment and both risk and severity of MDD (Bień and Bień-Barkowska, 2016; Chlapecka et al., 2020; Cohen et al., 2020). In this study, there was an approximately two-fold greater proportion of patients with primary school-level education in the Portuguese cohort compared with the total population. However, contrary to this, there was also a higher rate of university-educated patients in the Portuguese

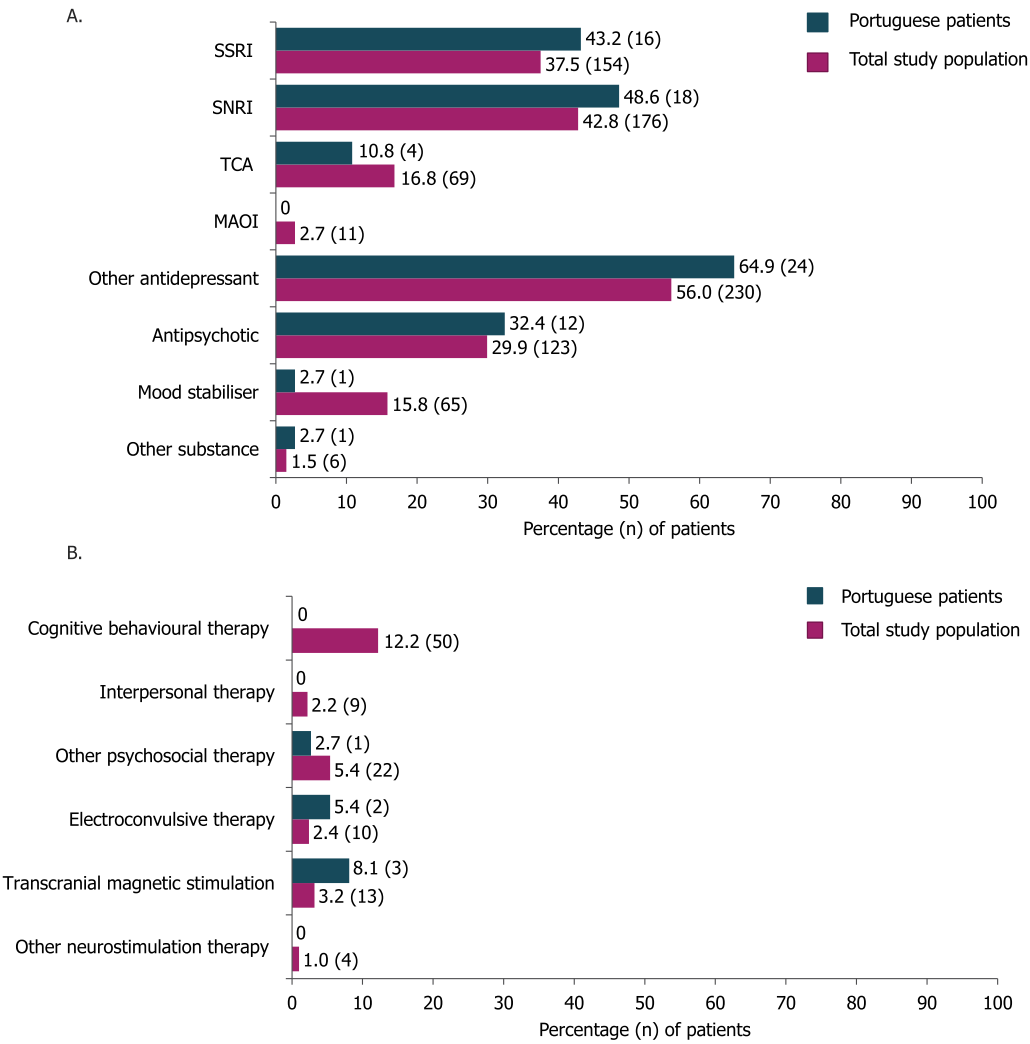

Fig. 3. Baseline treatment strategy. A. Frequency of different drug classes prescribed at baseline. **B.** Frequency of psychosocial and neurostimulation therapies prescribed at baseline. 'Other antidepressant' includes agomelatine, bupropion, esketamine, ketamine, ludiomil, mianserine, mirtazapine, nefazodone, opipramol, reboxetine, tianeptine, trazodone and vortioxetine. Other substance includes levothyroxine, liothyronine methylphenidate and modafinil. MAOI: monoamine oxidase inhibitor; SNRI: serotonin-norepinephrine reuptake inhibitor; SSRI: selective serotonin reuptake inhibitor; TCA: tricyclic antidepressants.

cohort versus all patients. Thus, it is unclear how educational attainment may contribute to the clinical characteristics of the Portuguese subgroup, as the small sample size limits any possible conclusions.

In the present study, TRD was defined as the failure to respond to two or more different antidepressants given at adequate dose and duration in the same MDE. This is a commonly used definition, though there is no universal consensus regarding the required length of the trial, drug dose or outcome measure to assess response. Due to this, alternative definitions of TRD have been suggested, including the recently suggested definition of difficult-to-treat depression (DTD) (Nuñez et al., 2022; Bartova et al., 2019; McAllister-Williams et al., 2020). DTD is considered depression that continues to cause significant burden despite usual treatment efforts; in a study based in the United Kingdom, 19 % of patients with MDD met the criteria for DTD (Costa et al., 2022).

When treating TRD, there was substantial heterogeneity in the treatment options prescribed to Portuguese patients at baseline, indicating a lack of clinical consensus. This is consistent with the opinion panel of Portuguese experts in TRD, who stated that TRD treatment should depend on the individual characteristics of each patient, including treatment history (Bessa et al., 2022). Additionally, it is in line with data published previously from the EOTC study, in which 54 different drugs were prescribed to patients at baseline (Heerlein et al., 2021b), demonstrating a lack of consensus in treating TRD that extends beyond Portugal. More frequent use of neurostimulation treatments and less frequent use of psychosocial therapies were seen in the Portuguese cohort compared with the total study population. ECT, one example of a neurostimulation therapy, is recommended in several European countries, either when other treatments have failed or for severe cases of TRD or emergencies, such as imminent risk of suicide (National Institute for Health and Care, 2009; European Medicines Agency, 2009). For other non-invasive neurostimulation treatments, such as TMS, this difference could be due to differing opinions or available options between clinicians in Portugal and those in other European countries participating in this study.

The proportion of Portuguese patients achieving response or remission at Month 6 was greater than that of the overall study population, with 40.7 % achieving response or remission in the Portuguese subgroup, versus 26.5 % in the total study population, seemingly occurring mostly due to higher remission rates. This is despite the higher baseline disease severity seen in the subgroup. A previous prediction model generated for TRD outcomes found that baseline MADRS score was one of the most informative predictors of treatment outcome with high scores associated with lower remission rates, further highlighting the high performance of Portuguese patients in this study (Kautzky et al., 2018). A previous meta-analysis concluded that a range of non-invasive brain stimulation treatments were efficacious across different outcome

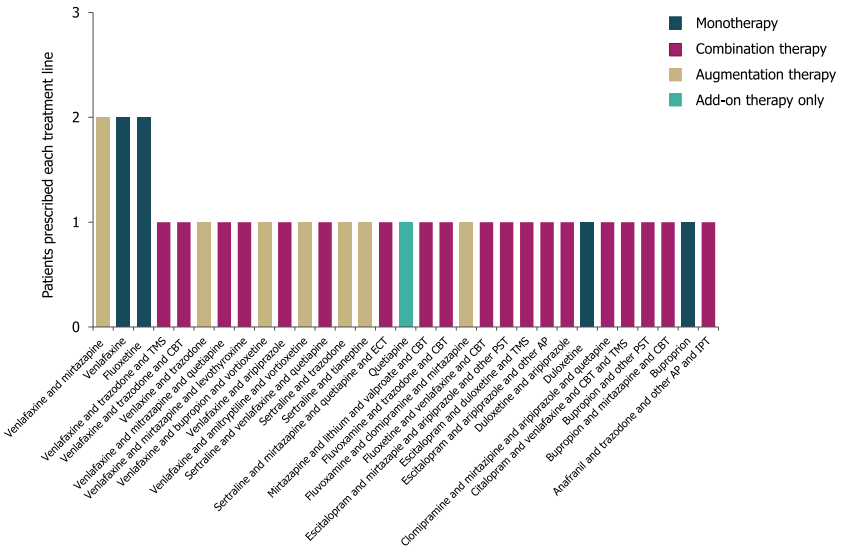

Fig. 4. Treatment strategies at baseline in the Portuguese cohort. Data missing for three patients; due to the non-interventional nature of this study, data were missing as they did not initiate a new treatment within the treatment window at baseline (between 7 days before and 14 days after baseline). AP: anti-psychotic; CBT: cognitive behaviour therapy; ECT: electroconvulsive therapy; IPT: interpersonal therapy; PST: psychosocial therapy; TMS: transcranial magnetic stimulation.

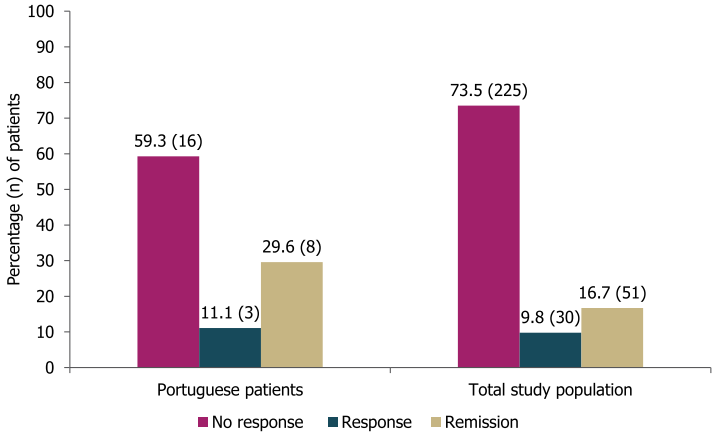

Fig. 5. Treatment outcomes at Month 6. Data missing for 10 Portuguese patients ($n = 27$) and 105 patients in the overall cohort ($n = 306$). Remission was defined as a MADRS score ≤10; response without remission was defined as MADRS improvement from baseline of ≥50 % and MADRS score >10. MADRS: Montgomery-Åsberg Depression Rating Scale.

metrics, when comparing brain stimulation in combination with an antidepressant versus sham stimulation and an antidepressant (Mutz et al., 2018). As such, it is possible that the greater utilisation of neurostimulation treatment strategies in the Portuguese cohort, as discussed above, may have partially contributed to the higher rates of response and remission at Month 6 versus the overall study population. However, causality cannot be inferred due to the study design and small cohort size.

Despite the higher levels of remission seen in the Portuguese cohort, treatment did not result in a clinical response for most of this group: almost 60 % failed to achieve response or remission at Month 6. This highlights the unmet need for effective treatments for TRD, even in circumstances where country-specific data reveals better outcomes than observed in the overall study population. A lack of response to treatments can result in poor quality of life for patients, attributable to low mood, social withdrawal, and poorer functioning. This also carries an economic cost to individuals and society, resulting from increased healthcare resource utilisation, increased sick days, and loss of function and productivity for those who are employed. Indeed, previous data from the EOTC have shown that despite high levels of non-response, patients often continue with treatments for long periods of time (K Heerlein et al., 2021), which would result in further disease burden for a prolonged period.

4.1. Strengths and limitations

An advantage of this analysis was that the data were collected in a real-world setting. The stringent nature of randomised clinical trials can produce findings lacking external validity because of strict inclusion criteria and stringent monitoring (Rothwell, 2006), which may not reflect real-world clinical and demographic characteristics. The rigour of these trials do not allow for the influence of confounding factors such as clinicians' input and influence, and lower rates of medication adherence (Nieuwlaat et al., 2014), which are more representative of true clinical practice and can be captured in real-world evidence studies. A key limitation of this study is the small number of patients evaluated and the lack of control group, which is often the case with real-world studies. Due to these limitations, consideration should be taken when interpreting these findings, and further research is needed.

In this study, data were collected from patients in the instance of a clinically-relevant event, such as remission of the current MDE, change in pharmacological or non-pharmacological treatment, or relapse of

symptoms. These data were collected but were not included in this sub-analysis and therefore are not reported. Previously published data from the EOTC demonstrated that a higher proportion of responders and remitters in the overall study cohort utilised at least one consultation with a psychiatrist or neurologist outside of data collection versus non-responders/remitters (Heerlein et al., 2022). As such, the rates of remission and response reported here for all patients may be partially attributed to the additional contact with clinicians at data collection, and hence these data may not fully reflect real-world practice.

The methodologies used for sampling patients and selecting study sites to participate were inconsistent across the different countries participating in the study, limiting the validity of the comparisons made. With the Portuguese subgroup consisting of only 37 patients, drawing definitive conclusions from the data is not possible. Furthermore, some patients only attended the early visits and were lost to follow-up, and hence could not be included in some of these analyses. Given the loss of productivity and activity seen in those experiencing TRD, it is possible that this may have contributed to patients discontinuing the study. In addition, the comparisons of patient subgroups were descriptive and did not take confounding variables into account.

Differences between healthcare provision and funding across the participating countries may include the availability of state-funded care, as opposed to private insurance-funded care or a system combining elements of both. Germany, Belgium and the Netherlands depend on social security payments to fund their services, with varying proportions of the populations receiving health coverage financed by public funds (Ministerio de SanidadCyBS, 2019). In contrast, Portugal has a national health system, with 100 % of the population able to receive health coverage financed by public funds. However, there is an additional parallel private healthcare system available, from which patients within this study were also recruited (Ministerio de SanidadCyBS, 2019). The numbers of patients recruited from public versus private healthcare systems were not available for this study, although given the imbalance in the proportion of patients with a higher education compared to those without, more patients may have accessed care privately. Additionally, fewer Portuguese patients underwent psychosocial treatment, though the number of patients in the overall population receiving this treatment was also low. It is unclear as to whether this was a care access issue. The differing provision of care across the varied settings may have contributed to the differences in Month 6 outcomes in Portugal versus the overall study cohort. Varying access to specialist mental health and psychiatric clinics, and medication reimbursement as a result of the different healthcare systems, also had the potential to introduce further bias. Finally, the exclusion of patients with suicidal ideation, a well-established symptom of depression, as well as those with a history of alcohol and/or substance abuse, may further limit the generalisability of these results.

5. Conclusions

Baseline data for the TRD patient population assessed in this cohort study suggest that the burden of TRD is high in Portuguese patients, who have severe depression with substantial functional impairments and have often remained in their current MDE for a prolonged period. Furthermore, treatment strategies in Portugal are heterogenous, highlighting a lack of consensus in treating TRD. Despite Portuguese patients reporting higher rates of response and remission than the overall study population, nearly two-thirds of patients failed to achieve response or remission at Month 6, highlighting the poor outcomes for patients with TRD. Together, these data suggest an unmet need for more effective treatments for patients with TRD, in Portugal and across Europe.

Data sharing Statement

Janssen EMEA's Data Sharing Policy does not include non-interventional studies.

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Supplementary materials

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