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Real-world evidence from a European cohort study of patients with treatment resistant depression: Treatment patterns and clinical outcomes

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A B S T R A C T

Background: Treatment resistant depression (TRD) characterizes a subgroup of 10–30% of patients with major depressive disorder, and is associated with considerable morbidity and mortality. A consensus treatment for TRD does not exist, which often leads to wide variations in treatment strategies. Real-world studies on treatment patterns and outcomes in TRD patients in Europe are lacking and could help elucidate current treatment strategies and their efficacy.

Methods: This non-interventional cohort study of patients with TRD (defined as treatment failure on ≥2 oral antidepressants given at adequate dose and duration) with moderate to severe depression collected real-world data on treatment patterns and outcomes in several European countries. Patients were started on a new treatment for depression according to routine clinical practice.

Results: Among 411 patients enrolled, after 6 months, only 16.7% achieved remission and 73.5% showed no response. At Month 12, while 19.2% achieved remission and 69.2% showed no response, 33.3% of those in remission at Month 6 were no longer in remission. Pharmacological treatments employed were heterogenous; 54 different drugs were recorded at baseline, and the top 5 treatment types according to drug classes accounted for 40.0% of patients. Even though remission rates were very low, at Month 12, 60.0% of patients had not changed treatment since enrolment.

Conclusions: The heterogeneity of treatments highlights a lack of consensus. Moreover, despite low response rates, patients often remained on treatments for substantial periods of time. These data further support existence of an unmet treatment need for TRD patients in Europe.

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Author Interview, Animated Summary and Plain Language Summary

To view an interview with one of the authors, Professor Giulio Perugi, summarizing this publication, please see the video below, or visit the manuscript on line at doi:10.1016/j.jad.2021.03.073.

PLAIN LANGUAGE SUMMARY

What is Treatment Resistant Depression?

Major depressive disorder (MDD) is a debilitating condition that affects up to 10% of the general population during their lifetime. A diagnosis of MDD requires five or more symptoms of depression, including depressed mood, loss of interest or pleasure in most or all activities, fatigue, sleeping excessively or insomnia, inability to concentrate or make decisions, over eating or loss of appetite, and feelings of worthlessness, when those symptoms cause significant distress and last at least two weeks. In addition to making patients feel extremely unwell, MDD reduces people's ability to function in everyday activities at work and at home and is also associated with suicide. Once, within the same episode of depression, two different antidepressive treatments have not led to improvement, patients are diagnosed with 'treatment resistant depression', or TRD, which affects between 10 and 30% of patients with MDD. Among the many treatments approved for MDD, there is very little information about which are used to treat TRD patients across Europe and how effective the different treatments are. As a result, it is difficult to understand how TRD is best treated, and patients often have to try many different treatments to find one that works.

What was this study investigating?

Our study looked at the treatments currently prescribed to patients with TRD in several European countries, and whether the treatments are effective. We identified 411 patients with TRD who were starting a new treatment, and followed them for at least 6 months, to record if their symptoms improved. Data were collected from medical records, with assessments completed by specialist clinicians. Patients also completed questionnaires rating the severity of their symptoms and how they affected their quality of life and ability to do tasks at work and at home.

What did the results of the study show?

The study found many different treatments were prescribed to the patients, including combinations of medications as well as single drugs. In a small number of patients, psychological treatments (ie 'talking' therapies) and brain stimulation therapies were also used. Most often, an antidepressant (eg selective serotonin reuptake inhibitor [SSRI] or serotonin and norepinephrine reuptake inhibitor [SNRI]) was prescribed with a non-antidepressant 'add-on' treatment (including antipsychotics, or mood stabilizers), but it was also common for patients to be prescribed two antidepressants together. After 6 months, 73.5% of patients had not responded to treatment, and at 12 months, 69.2% of patients had still not responded. Of the patients who had responded at 6 months and were re-assessed at 12 months, symptoms had returned in more than half. Despite such low levels of response, after 12 months of treatment only 40.0% of patients had changed treatment strategy and 60.0% were still on the same drug strategy that was prescribed when they enrolled in the study.

What are the key findings from the study?

Despite the many different treatments prescribed, most patients had not improved after 12 months. Many who had initially shown improvement with treatment found their symptoms returned later, so the beneficial effects of the treatment did not last long. Surprisingly, most patients stayed on their initial drug combination, even though many were not improving and treatment could be changed at any time.

Were there any limitations to the study?

Limitations of the study were the absence of a control group for comparison (so the results cannot be compared to what might have happened in patients not starting a new treatment), and the fact that a considerable number of patients did not have all the assessments completed during the study.

What are the wider implications of the study?

This study shows that treatment strategies prescribed across Europe lack effectiveness in most patients with TRD. So far, only one drug combination, an SSRI or SNRI plus esketamine nasal spray, has specific approval in Europe for treating TRD. However, research into other potential treatments is ongoing, providing future prospects for additional treatments for these patients.

1. Introduction

Major depressive disorder (MDD) is a debilitating condition that results in considerable morbidity and mortality, in part due to high suicide risk (Cavanagh et al., 2003). MDD is thought to affect 4–10% of the general population across their lifetime (National Institute for Health and Care Excellence, 2020) and depressive disorders are a leading cause of disability (James et al., 2018). Approximately 10–30% of patients with MDD have treatment resistant depression (TRD) (Rush et al., 2006b; Jaffe et al., 2019; Al-Harbi et al., 2012; Voinescos et al., 2020), defined as a major depressive episode (MDE) that fails to respond to two or more different antidepressants, given at adequate dose and duration (European Medicines Agency, 2013; Souery et al., 1999). Other definitions of TRD have also been used, precluding consensus on the prevalence of the condition (Wiles et al., 2014; Conway et al., 2017; Nemeroff et al., 2007).

Current treatments for MDD include medication, psychological and neurostimulation therapies (National Institute for Health and Care Excellence, 2020; European Medicines Agency, 2013; Cleare et al., 2015). Clinical management of TRD can include different combinations of these treatments, including antidepressant and non-antidepressant drugs, as well as non-pharmacological therapies (European Medicines Agency, 2013; Voineskos et al., 2020; Bennabi et al., 2019; Ionescu et al., 2015). All antidepressant drugs can be used in the treatment of TRD including selective serotonin reuptake inhibitors (SSRIs), dual serotonin and norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants (TCA), monoamine oxidase inhibitors (MAOIs), and 'other' antidepressants such as tianeptine, agomelatine and α2-antagonists (Ionescu et al., 2015; Kim et al., 2019; Tobe and Rybakowski, 2013). Medications without primary antidepressant properties can also be used in the treatment of TRD to potentiate the effects of an antidepressant drug. These include lithium, thyroid hormone and antipsychotics such as quetiapine (Bauer et al., 2013). Pharmacological treatment strategies for TRD can be categorized as switching (from one antidepressant to another); combination therapy (adding another antidepressant to the current one); and augmentation/add-on therapy (use of a non-antidepressant medication in addition to a current antidepressant) (Barowsky and Schwartz, 2006; Ionescu et al., 2015; Voineskos et al., 2020). Non-pharmacological (psychotherapeutic and neurostimulatory) therapies, have also been developed for TRD (Voineskos et al., 2020; van Bronswijk et al., 2019; Lefaucheur et al., 2020; Lisanby, 2007) but will not be discussed in detail here.

While treatment patterns and outcomes in patients with TRD in clinical practice have been studied in the US (Kubitz et al., 2013; Amos et al., 2018), recent research in Europe is limited. The US Sequenced Treatment Alternatives to Relieve Depression (STAR*D) trial is the largest multistep treatment study of patients with depression to date and provided key insights into treatment failure in the clinical setting (Rush et al., 2006b). STAR*D showed that most patients with TRD fail to achieve remission with current treatments. Remission rates of approximately 33%, 25–33%, 14% and 13% were achieved during the first, second, third and fourth treatment steps in the study, respectively, leading the authors to suggest that the likelihood of remission is reduced in patients with TRD (equating to those reaching steps three and four). In patients that achieved remission, loss of response was common; 60% of TRD patients that responded to treatment became unresponsive to treatment within 6 months. A prospective, 2-year observational study of

patients with TRD being treated in routine clinical practice, reported a 12-month remission rate of 3.6% . Loss of remission between Month 12 and 24 occurred in 75% of patients, highlighting that maintenance of therapeutic effect is poor (Dunner et al., 2006). Data from European patients, although limited, suggest similar outcomes. In a study in the UK, the 18-month remission rate for patients with TRD receiving treatment as usual, as directed by their primary care practitioner, was 6.5% and dropped to 4.4% at 42-month follow up (Fonagy et al., 2015).

Regarding European-wide market approval, a single pharmacological treatment, esketamine nasal spray (in combination with an SSRI or SNRI) was the first treatment approved for TRD specifically (European Medicines Agency, 2013; Mahase, 2019; European Medicines Agency, 2019). Importantly, however, it was not approved until after this study ended (European Medicines Agency, 2013; Mahase, 2019; European Medicines Agency, 2019). Additionally, there is no consensus on treatment pathways for TRD, and evidence suggests wide variation between and within European countries (MacQueen et al., 2017). The current cohort study was established to collect data from TRD patients with moderate to severe depression being treated in routine clinical practice in a sample of European countries. The aim of the study was to describe real-world clinical features and, as such, did not include a specific hypothesis. Treatment patterns and outcomes were followed for up to 21 months in patients starting a new therapy, having already experienced at least two treatment failures in the current MDE. The objectives of the study were to describe the disease-related and socio-demographic characteristics and disease burden of TRD patients in Europe; treatment patterns used to manage TRD in European clinical practice, and the resulting clinical outcomes; and healthcare resource utilisation associated with TRD. The baseline characteristics of the patient cohort have been published recently, demonstrating that patients had low health-related quality of life (HRQoL) and reduced function (Heerlein et al., 2021). This paper reports data supporting the second objective, focusing on treatment patterns and clinical outcomes among patients from this cohort.

2. Methods

2.1. Patients

Patients aged 18 to 74 years fulfilling the criteria for TRD were eligible. A diagnosis of MDD (fulfilling the Diagnostic and Statistical Manual of Mental Disorders Fifth Edition [DSM-5] or the International Statistical Classification of Diseases and Related Health Problems, Tenth Revision [ICD-10] criteria for MDD or Depressive disorder) was required for inclusion (European Medicines Agency, 2013), as well as a Montgomery-Åsberg Depression Rating Scale (MADRS; Montgomery and Asberg, 1979) score ≥20, indicating moderate to severe depression. TRD was defined by treatment failure (≤25% improvement on best day) on ≥2 different oral antidepressants, taken for ≥6 weeks, at adequate dose in the same MDE, as determined using the Massachusetts General Hospital-Antidepressant Treatment Response Questionnaire (MGH-ATRQ; Chandler et al, 2010).

For inclusion, patients needed to be starting a new antidepressant treatment, as an inpatient or outpatient. Treatment was according to routine clinical practice in that setting; choice of treatment, dose and method of administration was at the discretion of the treating physician. In the context of the study, any pharmacological or non-pharmacological treatment, including neurostimulation and psychotherapeutic interventions, prescribed to replace, or in addition to, the previous treatment, was considered a new antidepressant treatment. Switches to a generic drug or changes in dose did not count as a new treatment.

The following were exclusion criteria: current or prior diagnosis of psychotic disorders, MDD with psychotic features, bipolar disorders or intellectual disability according to DSM-5 or ICD-10; history of suicidal behavior within one year prior to enrolment; homicidal ideation or intent, or suicidal ideation or intent, within one month prior to entering the study; moderate to severe substance misuse (including alcohol) within six months before enrolment. Written informed consent was provided by all participants, and their capability for doing so was judged by the treating physician. Local ethics review boards provided approval for the study, which adhered to the Declaration of Helsinki.

2.2. Study design

A prospective, multicenter, observational cohort study of patients with TRD in Europe was conducted. The study has been described in detail elsewhere (Heerlein et al., 2021). Briefly, the study was comprised of baseline data collection, a 12-month observational period with a minimum follow-up of approximately 6 months for each enrolled patient, and an extended observation period up to 6 months from recruitment of the last patient, resulting in a maximum of 21 months of follow-up. Analysis was conducted only on data collected at 6 and 12 months after baseline (**Supplementary Fig. 1**). Patients were enrolled from Belgium, Germany, Italy, the Netherlands, Portugal, Spain and the United Kingdom.

2.3. Treatments

Antidepressant treatments (pharmacological, psychotherapeutic and neurostimulatory) prescribed on enrolment and during the observational period were documented in medical records. Pharmacological treatment strategies were categorized as monotherapy, combination therapy or augmentation therapy. Treatment could be changed at any time during the study, at the discretion of the treating physician.

2.4. Study procedures and evaluations

Data were collected at baseline, on scheduled visits every 6 months and at the end of the study, which was planned to run until 6 months after enrolment of the last patient. The data collection planned for the end of the study was also performed in the event of a patient leaving the study before the end of the observational period and, for patients who withdrew consent, were lost to follow-up or died before the end of the study, as many data were collected as possible. Additional data collection was encouraged in case of clinically relevant events, namely: admission to, or discharge from, inpatient settings; relapse of symptoms (including suicidal ideation/intent/behavior); remission of the current MDE (as confirmed by MADRS ≤10); visit/consultation with treating physician due to worsening or improvement of the current MDE (confirmed by Clinical Global Impression of Change [CGI-C; Busner and Targum, 2007] ≤3 or ≥5); change in pharmacological treatment (medication switch; dose changes except those relating to titration during switching; start of augmentation therapy); change in non-pharmacological treatment.

Baseline data were collected on patient socio-demographics, disease history and current clinical characteristics as well as details of all antidepressant treatments used in the current MDE prior to study entry. Assessment at any visit could include documentation of: spectrum and severity of depression symptoms (MADRS; Clinical Global Impression of Severity [CGI-S] score); change in depression severity since initiating last treatment (CGI-C score); suicidality (Columbia Suicide Severity Rating Scale; Posner et al., 2011); HRQoL (EuroQoL 5-dimension 5-level [EQ-5D-5L] patient-reported questionnaire, including the EuroQoL Visual Analog Scale [EQ-VAS]; Herdman et al., 2011); functional impairment or disability in and outside of work (Work Productivity and Activity Impairment [WPAI; Reilly et al., 1993] and the Sheehan Disability Scale [SDS; Sheehan et al., 1996] patient-reported questionnaires).

2.5. Data processing and statistical analysis

The remission or response status of each patient (irrespective of treatment strategy) was assessed at 6 and 12 months after baseline,

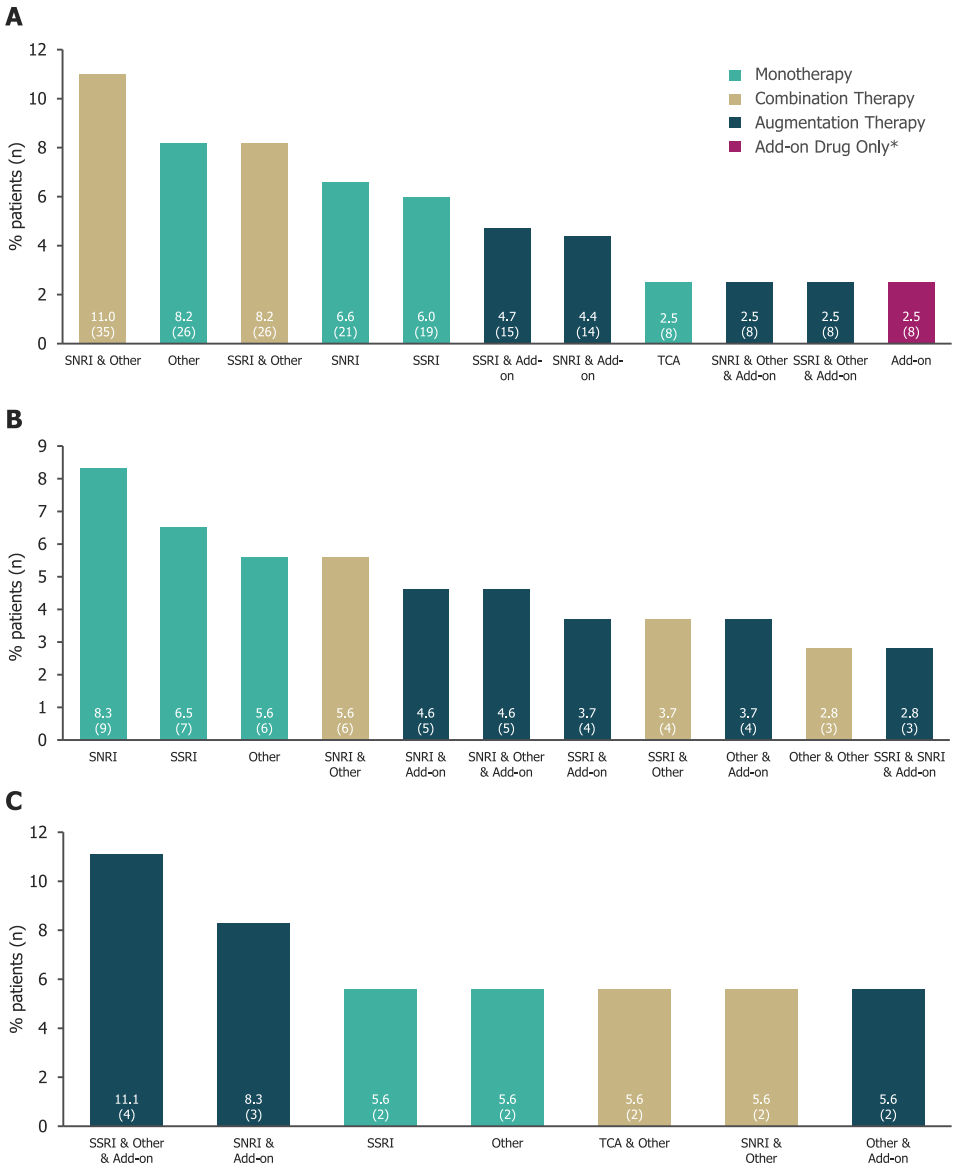

Fig. 1. MADRS responses at Month 6 and Month 12. **A.** Patient outcomes at Month 6 and 12 (total population). **B.** Patient outcomes at Month 12, by remission status at Month 6. **C.** Patient outcomes at Month 12, by response status at Month 6. Dataset includes all patients, irrespective of treatment strategy. Only patients with MADRS scores for both Month 6 and 12 were included in **B** and **C**. Remission: MADRS score ≤10; response: MADRS improvement from baseline ≥50%; response without remission: MADRS improvement from baseline ≥50% and MADRS score >10; no response: MADRS improvement from baseline <50% and MADRS score >10. MADRS: Montgomery-Åsberg Depression Rating Scale.

according to MADRS scores. Remission was defined as a score ≤10, while scores >10 but with improvement from baseline ≥50% defined response without remission. Visits were considered as occurring in Month 6 if they occurred 150–216 days after enrolment, while Month 12 visits were defined as those occurring 330–402 days after enrolment. Data obtained outside these windows were excluded from the relevant time point.

Treatment steps for each patient were reconstructed by matching MADRS scores to the start and end dates of each treatment strategy (dates and treatments obtained from medical records), with the end representing a change to a different treatment strategy. Only pharmacological treatment strategy changes were considered in the treatment strategy analysis, excluding any <30 days duration. The MADRS values at the start and end of each treatment strategy were used to determine whether the patient had experienced remission, response without remission, or no response. When the MADRS score was not available, a response/remission proxy was inferred based on CGI scores, to increase the number of treatment strategies for which a corresponding treatment outcome could be reported. If the end CGI-S score was 1 or 2 (out of 7, with higher scores indicating greater severity), the treatment strategy was considered to have resulted in remission (Turrina et al., 2015). When this was not the case, yet the CGI-C score was 1 or 2 (out of 7, where the lowest scores indicate substantial improvement and scores >4 indicate a worsening condition) then the treatment strategy was considered to have resulted in response without remission (Fava et al., 2017).

Continuous variables were summarized using descriptive statistics (N, mean, standard deviation [SD], median, minimum and maximum). Categorical variables were summarized by frequency distribution (number and percentage of patients in each category). Significance testing of data stratified by outcome (remission, response without remission, and non-response) was carried out first by using a Kruskal Wallis (KW) test to evaluate the null hypothesis that data from all three outcome groups were equal. If the KW test indicated a significant difference, it was followed by post-hoc Dunn's tests comparing the data between each of the three outcome groups. A p value <0.05 was considered significant. Treatment strategy duration by response status was compared using a repeated-measures model using SAS proc mixed procedure. The model statement included categorical variables for response status (two categories: response, no response) along with treatment strategy number at baseline (three categories: first step, second step, third step or higher). To account for within-subject correlation of treatment strategy duration, a repeated-measures statement with unstructured covariance matrix was included. The p value

Table 1
Patient outcomes at Month 6.

N Mean (SD)	**All** **(N=306)**	**No Response** **(n=225)**	**Response without Remission** **(n=30)**	**Remission** **(n=51)**
Total MADRS score	**306** 21.6 (10.2)	**225** 26.2 (7.5)	**30** 14.1 (2.7)	**51** 6.0 (2.6)
CGI-C score, n (%)				
Very much improved	28 (9.2)	2 (0.9)	2 (6.7)	24 (47.1)
Much improved	73 (23.9)	31 (13.8)	16 (53.3)	26 (51.0)
Minimally improved	92 (30.1)	82 (36.4)	9 (30.0)	1 (2.0)
No change	73 (23.9)	71 (31.6)	2 (6.7)	0
Minimally worse	25 (8.2)	24 (10.7)	1 (3.3)	0
Much worse	15 (4.9)	15 (6.7)	0	0
EQ-5D-5L (change from baseline)		**206** 0.11 (0.25)	**26** 0.26 (0.21)*	**46** 0.34 (0.28)***
EQ-VAS (change from baseline)		**210** 6.32 (21.20)	**26** 21.00 (19.21)**	**48** 32.35 (20.02)***
Total SDS (change from baseline)		**153** -2.67 (5.85)	**19** -7.58 (5.65)**	**38** -12.53 (6.88)***

Dataset includes all patients, irrespective of treatment strategy. *p<0.05; **p<0.01; ***p<0.001 when compared to no response (Kruskal Wallis test followed by post-hoc Dunn's test). Remission: MADRS score ≤10; response without remission: MADRS improvement from baseline ≥50% and MADRS score >10. CGI-C: Clinical Global Impression of Change scale; EQ-5D-5L: European Quality of Life (EuroQol)-5-dimension 5-level; EQ-VAS: EuroQol-visual analog scale; MADRS: Montgomery-Åsberg Depression Rating Scale; SD: standard deviation; SDS: Sheehan Disability Scale.

Table 2
Patient outcomes at Month 12.

N Mean (SD)	**All** **(N=146)**	**No Response** **(n=101)**	**Response without Remission** **(n=17)**	**Remission** **(n=28)**
Total MADRS score	**146** 20.0 (9.7)	**101** 25.1 (6.6)	**17** 13.6 (2.2)	**28** 5.7 (3.3)
CGI-C score, n (%)				
Very much improved	20 (13.7)	1 (1.0)	4 (23.5)	15 (53.6)
Much improved	29 (19.9)	13 (12.9)	7 (41.2)	9 (32.1)
Minimally improved	43 (29.5)	38 (37.6)	3 (17.6)	2 (7.1)
No change	34 (23.3)	31 (30.7)	2 (11.8)	1 (3.6)
Minimally worse	13 (8.9)	11 (10.9)	1 (5.9)	1 (3.6)
Much worse	6 (4.1)	6 (5.9)	0	0
EQ-5D-5L (change from baseline)		**94** 0.11 (0.26)	**16** 0.31 (0.26)*	**26** 0.35 (0.28)***
EQ-VAS (change from baseline)		**97** 9.73 (20.11)	**16** 23.13 (13.35)*	**27** 35.19 (24.40)***
Total SDS (change from baseline)		**67** -2.91 (6.73)	**9** -7.00 (6.34)	**18** -14.44 (7.76)***

Dataset includes all patients, irrespective of treatment strategy. *p<0.05; **p<0.01; ***p<0.001 when compared to no response (Kruskal Wallis test followed by post-hoc Dunn's test). Remission: MADRS score ≤10; response without remission: MADRS improvement from baseline ≥50% and MADRS score >10. CGI-C: Clinical Global Impression-Change scale; EQ-5D-5L: European Quality of Life (EuroQol)-5-dimension 5-level; EQ-VAS: EuroQol-visual analog scale; MADRS: Montgomery-Åsberg Depression Rating Scale; SD: standard deviation; SDS: Sheehan Disability Scale.

corresponding to the response status factor in the model statement was evaluated for significance. Time-to-treatment strategy change analysis was performed by Kaplan-Meier time-to-event analysis.

3. Results

3.1. Baseline characteristics and treatments

The final analysis set included 411 eligible patients (**Supplementary Table 1**). The mean (SD) age of patients was 51.0 (10.8) years and 62.3% were female. The mean (SD) MADRS score was 31.8 (6.0) and 67.4% of patients had moderate depression (MADRS 20–34); the remainder (32.6%) had severe depression (MADRS >34). In the current MDE, 53.8%, 31.1% and 14.6% of patients had experienced two, three or four or more treatment failures, respectively. At baseline, 343/411 (83.4%) patients were taking at least one pharmacological treatment. Psychotherapeutic treatment and neurostimulation therapy were being prescribed to 19.2% and 6.6% of patients, respectively. A full description of the baseline characteristics of this patient population has been published previously (Heerlein et al., 2021).

3.2. Overall treatment outcomes at Month 6

At Month 6, 58 patients were reported as discontinued: 1 patient ended the study after 99 days[1]; 37 patients were lost to follow up; 7 withdrew consent; 3 died; 9 discontinued due to 'other' reasons; 1 was of unknown status. Data were excluded from a further 47 patients who were still in the study at Month 6, but whose visits did not meet the defined cut-off dates for a Month 6 visit. All other patients were included in this analysis, irrespective of treatment strategy. Of these patients, 73.5% showed no response, 9.8% showed response without remission

[1] Whilst the protocol recommended a minimum of 6 months follow-up, this patient was reported to have ended the study after 99 days, even though the study was on-going. No data from this patient were recorded after 99 days, so their data are not included in 6 or 12-month analyses.

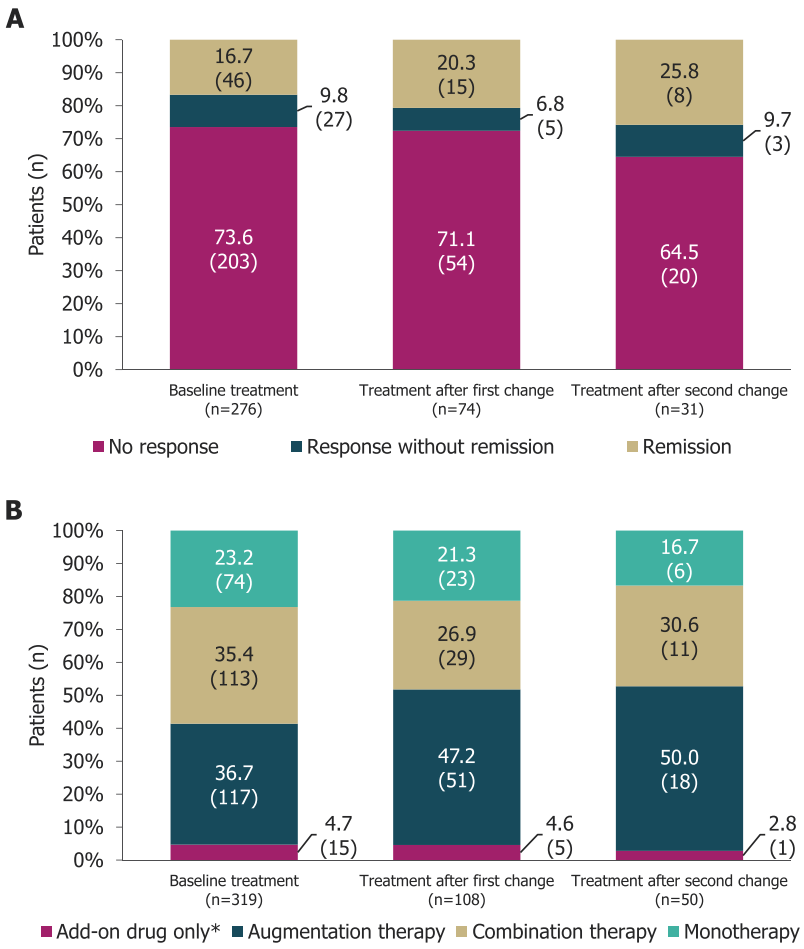

Fig. 2. Pharmacological strategies and treatment outcomes per treatment step during the study. A. Treatment outcomes by treatment step during the study from baseline. B. Pharmacological strategies per treatment step during the study from baseline; data include only patients that were taking ≥1 pharmacological treatment and who had been taking it for ≥30 days. All patients have already experienced at least two treatment line failures prior to study entry, as per study inclusion criteria; since the number of treatment lines prior to enrollment varies across the cohort, the number of treatment changes does not necessarily relate to the total number of treatment lines a patient has been prescribed. Figure shows results from the total population. *Add-on drug only therapy: prescription of an add-on medication in the absence of regular oral antidepressant(s). Augmentation therapy: prescription of an add-on medication in addition to regular oral antidepressant (s). Combination therapy: prescription of ≥2 antidepressant medications. Monotherapy: prescription of 1 antidepressant medication. Remission: MADRS score ≤10; response without remission: MADRS improvement from baseline ≥50% and MADRS score >10; no remission: MADRS improvement from baseline <50% and MADRS score >10. MADRS: Montgomery-Åsberg Depression Rating Scale.

and 16.7% were in remission (Fig. 1**A**). As per the definitions used to stratify patients by outcome status, the mean (SD) MADRS score for patients achieving remission was 6.0 (2.6) compared to 14.1 (2.7) in patients with response without remission and 26.2 (7.5) in patients with no response (Table 1). Using KW tests followed by post-hoc Dunn's tests to analyse mean change from baseline, greater change was seen across EQ-5D-5L, EQ-VAS and SDS in patients achieving remission compared to those with no response ($p<0.001$ for all comparisons; Table 1). Greater mean change was also observed for patients achieving response without remission in the same comparison ($p<0.05$ or $p<0.01$; Table 1).

3.3. Overall treatment outcomes at Month 12

At Month 12, 244 patients in total were not included in the analysis set: for 164 patients the study ended prior to their 12-month assessment; 45 were lost to follow up; 9 withdrew consent; 4 died; 22 discontinued due to 'other' reasons; 1 was of unknown status. Data were excluded from a further 21 patients who were still in the study at Month 12, but whose visits did not meet the defined cut-off dates for a Month 12 visit. All other patients were included in this analysis, irrespective of treatment strategy. Of these patients, 69.2% had not responded, 11.6% showed response without remission and 19.2% were in remission (Fig. 1**A**). Using KW tests followed by post-hoc Dunn's tests to analyse mean change from baseline, greater changes in EQ-5D-5L, EQ-VAS and SDS were observed in patients who had achieved remission at Month 12 than for those who had not responded ($p<0.001$; Table 2), and changes in EQ-5D-5L and EQ-VAS were greater in patients achieving response without remission when compared to those with no response ($p<0.05$; Table 2).

3.4. Changes in remission or response status between Month 6 and 12

Maintenance of remission or response was analysed in patients for whom data at both timepoints were available. Of patients who had not achieved remission at Month 6, 86.6% of those that were assessed again at Month 12 still had not achieved remission (Fig. 1**B**). Among patients who achieved remission at Month 6, 33.3% of those that were assessed again at Month 12 were no longer in remission (Fig. 1**B**). When these patients were stratified by response vs non-response, 51.7% of Month 6 responders had lost response by Month 12, and among non-responders at Month 6, 72.9% remained unresponsive at Month 12 (Fig. 1**C**).

3.5. Treatment patterns and response by number of treatments since enrolment

Data from patients taking ≥1 pharmacological treatment with a duration ≥30 days were included in this analysis. The rate of response to treatment increased with the number of treatment changes after baseline (Fig. 2**A**). With treatment implemented at baseline, 26.4% of patients responded, while response was achieved in 35.5% of patients completing a third treatment since entering the study (Fig. 2**A**). For baseline treatment, the proportions of patients on combination or augmentation strategies were 35.4% and 36.7%, respectively, 23.2% were on monotherapy (Fig. 2**B**). The proportion of patients on a monotherapy decreased as treatment was changed, with 16.7% on monotherapy in the third treatment since starting the study (Fig. 2**B**). There was a concurrent increase in the percentage of patients on augmentation therapy that accounted for 50.0% of patients completing a third treatment since starting the study (Fig. 2**B**).

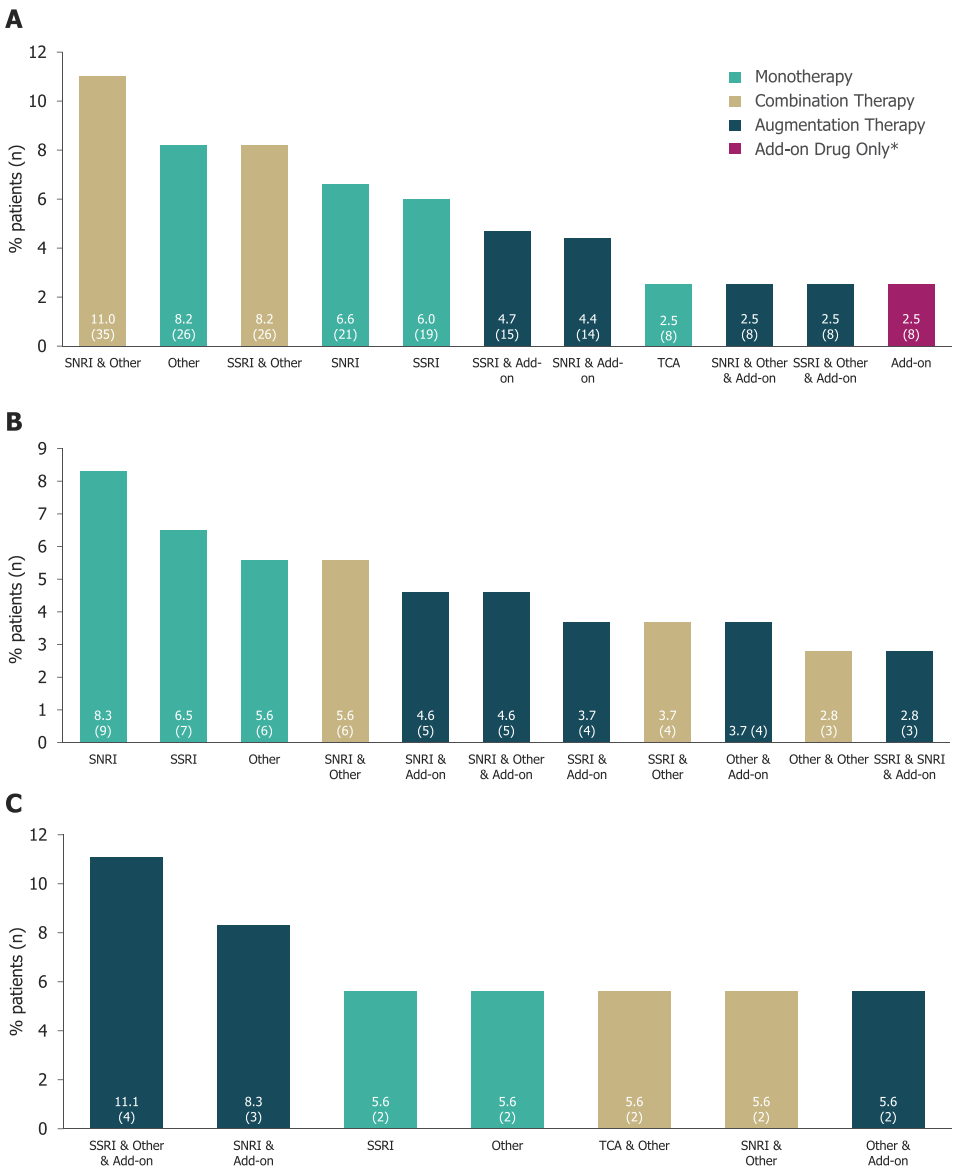

Fig. 3. Treatment strategies used at each treatment step, by treatment classes. *Add-on drug only therapy: the use of an add-on medication in the absence of regular oral antidepressant(s). **A.** Baseline treatment. **B.** Treatment after first treatment change in the study. **C.** Treatment after second treatment change in the study. All patients have already experienced ≥2 treatment line failures prior to study entry, as per study inclusion criteria. Augmentation therapy: the prescription of an add-on medication in addition to regular oral antidepressant (s). Combination therapy: the prescription of ≥2 antidepressant medications. Figure shows most common treatment classes prescribed in ≥2%, ≥5% and >2 patients (**A,** **B** and **C,** respectively). SNRI: serotonin-norepinephrine reuptake inhibitor; SSRI: selective serotonin reuptake inhibitor; TCA: tricyclic antidepressant.

Together, the top five treatments, taken by patients at baseline defined according to drug classes, accounted for 40.0% of all treatments used at that timepoint (Fig. 3**A**). The most common treatment at baseline was the combination of an SNRI plus "other" antidepressant, used in 11.0% of patients. "Other" antidepressants as monotherapy and SSRI plus "other" antidepressant were both taken by 8.2% of patients (Fig. 3**A**). In patients whose treatment was changed following failure of baseline treatment, the top two individual treatment classes taken on changing were SNRIs (8.3%) and SSRIs (6.5%) both used as a monotherapy (Fig. 3**B**). The top two treatment classes and combinations used for patients changing treatment a second time in the study were a combination of SSRI plus "other" antidepressant plus an add-on drug (11.1%) and an SNRI plus add-on medication (8.3%; Fig. 3**C**).

3.6. Treatment strategy duration, per treatment strategy used since baseline

Data from 392 treatment strategies were available for analysis, after excluding non-pharmacological strategies. Of these, outcomes (remission, response, non-response) were assigned based on CGI-S and/or CGI-C in 3.6% (14/392) of treatment strategies where a corresponding MADRS score was not available. Pharmacological strategies ≥30 days duration were analysed. Where a treatment strategy resulted in response (including remission), the mean (SD) duration of treatment was 250.6 (136.0) days. When patients did not achieve a response, the mean (SD) treatment strategy duration before changing was shorter (196.2 [128.3] days; $p<0.001$; repeated measures model; Fig. 4**A**). Kaplan-Meier analysis was used to analyse time-to-treatment change endpoints. After approximately 6 months of treatment, 68.4% of patients had not changed treatment strategy (including prescription of an additional drug) since enrolment. At Month 12, approximately 60.0% of patients had not changed their treatment strategy since entry into the study (Fig. 4**B**).

4. Discussion

This study assessed the naturalistic treatment patterns and clinical outcomes of 411 patients with TRD in Europe. Results at 6 months after initiating a new treatment strategy, as per routine clinical practice, showed most patients did not respond to treatment or achieve remission, remained very unwell and had poor HRQoL and reduced function. The number of different treatment strategies reported was high; the top five treatment types accounted for only 40.0% of treatments, suggesting that current treatment strategies employed for patients with TRD are very heterogeneous. Importantly, and considering that there is no consensus

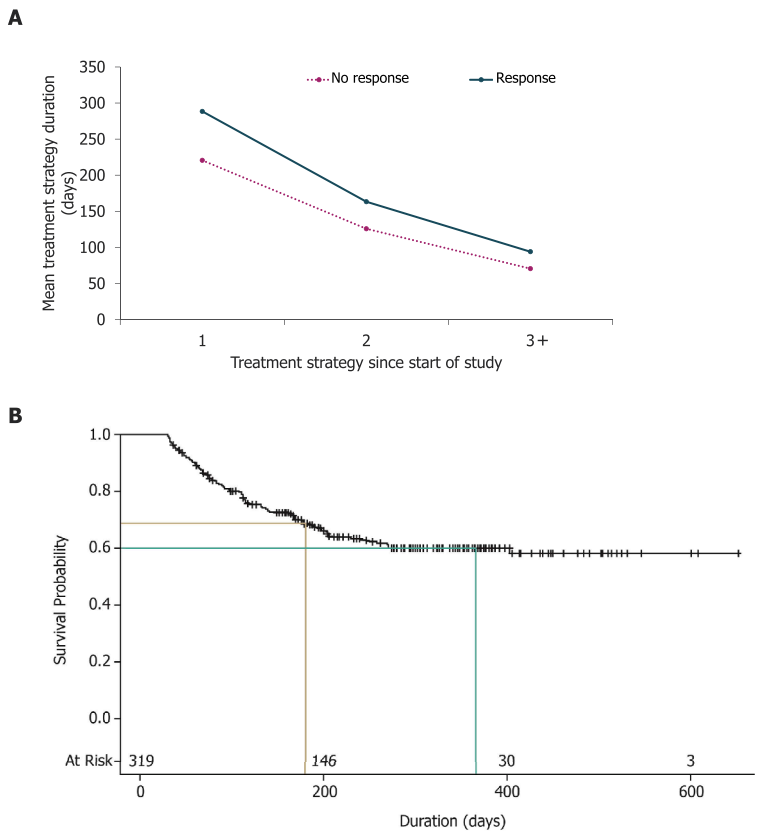

Fig. 4. Pharmacological treatment duration and time to first treatment change. **A.** Least square mean plot of treatment number and duration, by outcome. Treatment outcome based on MADRS score, or CGI-C/S where a MADRS score was unavailable (14/392 [3.6%]). Treatment durations were right censored at the time corresponding to the last study visit. Since some patients (most likely) continued treatment after the study had ended, their treatment durations would in fact be longer; this analysis therefore underestimates treatment duration. **B.** Time to first treatment change from study entry (excluded treatment lines <30 days in duration and non-pharmacological treatments). Censoring was applied to treatments not stopped at the moment corresponding to the last study visit. Response: MADRS improvement from baseline ≥50% or MADRS score >10, or (if MADRS score unavailable) CGI-C score ≤2 or CGI-S score ≤2; no response: MADRS improvement from baseline <50% and MADRS score >10, or (if MADRS score unavailable) CGI-C score >2 or CGI-S score >2. CGI-C: Clinical Global Impression of Change; CGI-S: Clinical Global Impression of Severity; MADRS: Montgomery-Åsberg Depression Rating Scale.

strategy across Europe for treating TRD, the wide variation in treatment strategies being used in clinical practice makes it difficult to build a robust evidence base of which strategies are most efficacious to inform clinical guidelines. This, in turn, makes it more challenging for clinicians to make informed treatment decisions.

The results reported here largely align with other studies, in terms of the variety of treatments used and treatment outcomes (Rush et al., 2006b, Ionescu et al., 2015).

In this study, most patients failed to achieve or sustain a clinical response, with less than 20% of patients in remission at 12 months. In a 2-year observational study of patients with TRD in which patients received a variety of treatments ('treatment as usual'), that could be changed at any time during the study, a 12-month remission rate of 3.6% was reported (Dunner et al., 2006). This is considerably lower than the remission rate observed in the current study. Notable differences that may have contributed towards the lower remission rate include the inclusion of patients with bipolar disorder, higher number of mean treatment failures and longer mean duration of the current MDE, indicating a cohort with more difficult to treat depression. Furthermore, in that study the self-rated 30-item Inventory of Depressive Symptomatology-Self-Report was used to assess changes in the degree of depression. Other studies of long-term outcomes for TRD patients in routine clinical practice have also reported lower remission rates than the current study. As in this study, the US Treatment-Resistant Depression Registry study (Aaronson et al., 2017) used clinician rated assessments (MADRS), and the baseline depression severity was comparable. However, only 12% of patients achieved remission after 1 year, possibly because the cohort included patients with bipolar disorder and overall had a considerably worse clinical history with a mean of 7.3 treatment failures. Regarding treatment practices in Europe, a long-term study of UK TRD patients in routine clinical practice reported an 18-month remission rate of 6.5%, decreasing to 4.4% after 42 months (Fonagy et al., 2015). Compared with the current study, patients in this cohort had a greater mean number of prior treatment failures, as well as greater mean current MDE duration. Notwithstanding differences in the baseline clinical characteristics of these other patient cohorts, the higher rates of remission reported in the current study may also be explained by low patient numbers at Month 12, possibly reflecting differential loss to follow up. In the current study, one third of Month 6 remitters were no longer in remission at Month 12, suggesting that treatment efficacy was lost. Remission was lost by an even higher proportion of patients (75%) between Month 12 and 24 in another observational study, possibly due to key differences in the patient baseline characteristics and study, as was highlighted above (Dunner et al., 2006). When analyzed in terms of response, rather than remission, more than 50.0% of Month 6 responders lost response by Month 12, suggesting response is a less stable outcome for patients than remission. Both analyses support the argument that current treatment strategies are inadequate to maintain long-term treatment success in many TRD patients, but that remission is a more robust target outcome than simply response. That remission should be the aim of treatment strategies is further supported by the greater improvement in functioning/disability in patients who achieved remission compared to those who only achieved a response without remission in this study. Others have also acknowledged that failure to achieve full remission is associated with an increased risk of relapse and recurrent episodes, as well as the personal and societal burden resulting from residual symptoms (Mendlewicz, 2008; Rush et al., 2006a).

Despite high levels of non-response, patients continued with pharmacological treatments for long time periods. The mean length of time on the baseline treatment strategy was 220.1 days and after one year, 60.0% of patients were still on their first treatment strategy since entering the study. Given all patients in this study had already experienced at least two treatment failures prior to enrolling, and their continued lack of response, this finding is unexpected. The factors that contributed to the continuation of treatments by patients for such long periods in this study are not clear. One possibility is that treating physicians have low expectations of

added treatment responses. Following change of treatment strategy, low levels of patient response were observed, with only 20.3–25.8% of patients responding. This was despite a wide range of different treatment strategies employed, further indicating the inefficacy of treatment strategy alternatives in this population.

In the European region, there are few specific recommendations for medication strategies to treat TRD as market approval submissions for most MDD treatments have not included efficacy and safety studies on the TRD subpopulation. An extended-release formulation of quetiapine is indicated in the EU for use as an add-on treatment for patients with MDD in which a first antidepressant has failed (European Medicines Agency, 2020). In December 2019, esketamine nasal spray, an N-methyl-D-aspartate receptor (NMDAR) antagonist and new mechanism of action, was granted EU market approval for the treatment of TRD in adults, when used in combination with either an SSRI or a SNRI (European Medicines Agency, 2020). The same drug had already obtained FDA approval for use in combination with an oral antidepressant for TRD earlier that same year (FDA, 2019). In the US, an olanzapine/fluoxetine hydrochloride combination was granted FDA approval for the treatment of TRD in 2009 (FDA, 2020) and aripiprazole and brexpiprazole are also approved in this indication (FDA, 2020; FDA, 2018). However, none of these treatments have EMA approval for use in the TRD subpopulation. Since the 1950s, pharmacological treatments for MDD have targeted the monoamine pathway (Hillhouse and Porter, 2015), but the results described here suggest that, for many patients with TRD, treatment strategies involving these drugs may be ineffective. The poor HRQoL experienced by TRD patients in whom treatment continues to be ineffective points to an urgent need for investigators to develop alternative treatments for TRD and investigate new treatment strategies. A pipeline of drugs to treat MDD are in development that target the glutamate pathway. These alternative mechanisms of action may open new possibilities for treating TRD, if there is sufficient evidence to support the need for efficacy and safety trials that include the TRD subpopulation as a separate entity.

The data presented here, together with those previously described on HRQoL and functionality in TRD in the first paper published from this study (Heerlein et al., 2021) demonstrate the substantial impact of TRD on patients and society. These data add to the body of real-world evidence demonstrating that treatment strategies currently employed in routine clinical practice in Europe, lack efficacy in most patients with TRD.

To allow more in-depth analysis of the relationship between different treatment strategies used in routine clinical practice and clinical outcomes for patients with TRD, it would be valuable to conduct larger-scale observational studies with a similar design to the current study. As more treatments gain market approval in Europe for TRD specifically, it will be important to assess how these impact patient outcomes in a real-world setting, beyond the controlled environment of clinical trials. Newer treatments require safety and efficacy studies in well-defined TRD cohorts to support market approval and improve access to potentially beneficial treatments for these patients.

4.1. Limitations

The limitations of the current study include its relatively small size compared with other studies, and the absence of a control group to allow comparison of the cohort with patients not starting on a new treatment strategy. For analysis of treatment strategies, a small proportion of outcomes were assigned based on CGI rather than MADRS scores. Furthermore, since the number of treatment lines failed prior to enrolment varies across the cohort, the number of treatment changes in the study does not relate directly to the total number of treatments a patient had been prescribed during the current MDE. As expected in a real-world study, patients for whom data were available for analysis decreased over time, but this was for many reasons and only a small number were true patient drop out. Of note, the study design meant that the later a patient enrolled in the study, the less likely they were to reach 12 months before the study end date; this was the case for approximately 70% of patients. A small proportion of Month 6 or Month 12 visits did not happen within the post-study defined cut-off dates, and in those that did, some did not have a MADRS score (or other outcome measures) recorded at one or more visits. Furthermore, some assessments and/or questionnaires were not completed fully, so numbers of responses for some outcome measures vary. A number of patients were lost to follow up after attending only some visits, possibly due to reduced functioning caused by TRD. Thus, overall, patient numbers are much lower for analysis of Month 12 data than for data collected at Month 6, and results for Month 12 should therefore be interpreted with caution. Finally, comparisons of patient subgroups did not take confounding variables, such as country of origin, into account. Importantly, since patient numbers in the study were approximately proportional to the population of each country, this led to substantial variations in absolute numbers across the countries studied.

5. Conclusions

In this study, patients with TRD were treated with many different treatment strategies suggesting that there is no consensus on the standard of care to be used in this population. Despite the wide range of treatments used in these patients, treatment response rates were low, regardless of the number of treatment steps tried, indicating that overall treatment outcomes for patients with TRD are poor. Additionally, data presented here suggest that patients may spend a substantial amount of time on each treatment without a response.

Authors' contributions

Substantial contributions to study conception and design: KH, GP, WH, AJOM, VPS, SR, GR, SM, JM, CV, BG, AHY; substantial contributions to acquisition, analysis or interpretation of the data: KH, GP, CO, TF, GD, WH, AJOM, VPS, SR, GR, SP, SM, JM, CV, BG, AHY; drafting the article or revising it critically for important intellectual content: KH, GP, CO, TF, GD, WH, AJOM, VPS, SR, GR, SP, SM, JM, CV, BG, AHY; final approval of the version of the article to be published: KH, GP, CO, TF, GD, WH, AJOM, VPS, SR, GR, SP, SM, JM, CV, BG, AHY.

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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