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Real-world evidence from a European cohort study of patients with treatment resistant depression: Baseline patient characteristics

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ABSTRACT

Background: Treatment resistant depression (TRD; failure to respond to ≥2 treatments) affects ~20% of patients with major depressive disorder (MDD). Real-world data could help describe patient characteristics and TRD disease burden, to assess the unmet needs of TRD patients in Europe.
Methods: This observational study collected data from adults with moderate to severe TRD initiating a new treatment for depression, according to local standards of care. At baseline, socio-demographic characteristics, medical history, prior and current treatments were recorded. Disease severity, health-related quality of life (HRQoL), functionality and productivity were assessed.
Results: Overall, 411 eligible patients were enrolled across seven European countries. Mean (standard deviation [SD]) patient age was 51.0 (10.8) years; 62.3% were female. Long-term sick leave was reported by 19.0% of patients; 30.2% were unemployed. The mean (SD) duration of the current episode was 2.6 (3.9) years. At baseline, mean (SD) HRQoL scores for EuroQoL 5-dimension 5-level (UK tariff) and EQ-Visual Analog Scale were 0.41 (0.25) and 41.1 (18.7), respectively. The Work Productivity and Activity Impairment questionnaire demonstrated mean (SD) absenteeism of 57.0% (44.9%) and presenteeism of 54.7% (29.5%); mean (SD) overall work impairment was 60.5% (29.9%).
Limitations: Key limitations are small cohort size, absence of a control group and generalizability to countries with different healthcare models.
Conclusions: TRD patients had a high disease burden, low HRQoL and reduced function and productivity, with a substantial proportion unable to work. This demonstrates an unmet treatment need in TRD patients that, if addressed, could reduce the heavy personal and societal burden.

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Author Interview

To view an interview with one of the authors, Professor Allan H Young, summarizing this publication, please see the video below, or visit the manuscript on line at doi:10.1016/j.jad.2020.11.124.

1. Introduction

Major depressive disorder (MDD) is a common disorder affecting approximately 15% of the general population, and is associated with substantial morbidity and mortality, including considerable suicide risk (Cavanagh et al., 2003; World Health Organisation, 2008). Globally, unipolar depressive disorders are the leading cause of disability-adjusted life years (Ferrari et al., 2013). Current clinical management of MDD includes pharmacological and non-pharmacological treatments and can include many different combinations of antidepressant drugs as well as non-drug therapies (European Medicines Agency, 2013; National Institute for Health and Care Excellence, 2009). However, around 20% of patients with MDD do not achieve remission after two different treatment lines (European Medicines Agency, 2013).

Treatment resistant depression (TRD) occurs in a subgroup of the MDD population, and is defined by the European Medicines Agency (EMA) as a major depressive episode (MDE) that fails to respond to treatment with two or more different antidepressants, given in adequate dose and duration and with adequate adherence to treatment (European Medicines Agency, 2013). Progress in the identification of new treatment targets and development of drugs with novel mechanisms of action specifically for TRD has been slow. The treatments currently approved for use in MDD can be used in various strategies to treat TRD, namely switching, combining and augmenting medication. However, likelihood of successful treatment is greatly reduced when patients progress to the third or fourth sequential treatment line, or beyond, compared with achieving remission prior to this point (Gaynes et al., 2009). Throughout the European region, only one pharmacological treatment is approved specifically for TRD (Mahase, 2019).

Due to the treatment-resistant and inherent long-term nature of TRD, the condition has a greater patient and societal burden than non-TRD MDD, including lower health-related quality of life (HRQoL), higher comorbidity, and reduced functionality (Amos et al., 2018; Mrazek et al., 2014). While a number of studies on the burden of TRD have been carried out in the US, research in Europe has been comparatively lacking, and there are few reports of patient characteristics and disease burden for TRD in European standard clinical practice (Amos et al., 2018; Kubitz et al., 2013). To analyze the extent of this unmet need in Europe, a solid evidence base of real-world data from clinical practice in European countries is required in addition to clinical trial data. In fact, while clinical trials represent a well-controlled setting with a narrowly-defined patient population that is followed closely, outside this setting, patient populations are more diverse, have a higher level of comorbidities, and adherence to treatment regimens may be lower. Therefore, real-world evidence can provide additional data that complements clinical trial findings.

To address the need for real-world evidence in Europe, a patient cohort study was established to collect information from patients with TRD being treated in routine clinical practice across a sample of European countries. This cohort study followed treatment outcomes for up to 21 months in patients with moderate to severe TRD starting a new therapy. The objectives of the study were to describe the socio-demographic and disease-related characteristics of patients with TRD; the social and economic burden associated with TRD in a real-world setting; the long-term treatment patterns used in routine clinical practice in European countries and their associated clinical and economic outcomes.

This paper reports baseline data supporting the first two objectives. Here, we describe the baseline socio-demographic, disease- and treatment-related characteristics, as well as social and work-related burden among patients from this cohort.

2. Methods

2.1. Participants

Patients aged 18 to 74 years with a diagnosis of MDD (according to 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 fulfill the criteria for diagnosis of TRD (defined by failing to respond to two or more different oral antidepressants, given at an adequate dose and for a sufficiently long period in the same MDE, as determined using the Massachusetts General Hospital-Antidepressant Treatment Response Questionnaire [MGH-ATRQ]) (European Medicines Agency, 2013). A Montgomery-Åsberg Depression Rating Scale (MADRS) score of 20 or more was also required for inclusion.

Both inpatients and outpatients were enrolled in a patient cohort study (registry number 54135419DEP4001). All patients were initiating a new antidepressant treatment according to standard care in their treatment setting, with choice of treatment, and dose and administration (if applicable) at the discretion of the prescribing clinician. For the purposes of this study, initiation of a new antidepressant was defined as any pharmacological and/or non-pharmacological treatment (including deep brain stimulation, electroconvulsive therapy, transcranial magnetic stimulation and specific psychotherapy) prescribed or recommended in addition to, or to replace, the previous treatment. Dose increases or a switch to a biosimilar were not considered to be a new antidepressant treatment.

Patients with a current or prior diagnosis of a psychotic disorder, MDD with psychotic features, bipolar or related disorders, or intellectual disability, also according to DSM-5 or ICD-10, were excluded. Other key exclusion criteria included homicidal ideation/intent or suicidal ideation with some intent to act within one month prior to enrollment per physician's clinical judgment and/or positive response to Item 4 ('active suicidal ideation with some intent to act, without specific plan') or Item 5 ('active suicidal ideation with specific plan and intent') on the Columbia Suicide Severity Rating Scale. Patients with a history of suicidal behavior within one year prior to enrollment, or moderate or severe alcohol or other substance use disorder (except for nicotine and caffeine) according to DSM-5 criteria, within six months prior to enrollment, were also excluded.

All participants were considered to be capable of providing written informed consent, based on the opinion of the participating physician. The study adhered to the Declaration of Helsinki. Country-specific ethics review boards provided approval for the study.

2.2. Study design

A prospective, multicenter, observational cohort study of patients with TRD in Europe was conducted. The study consisted of baseline data collection, a 6–12 month observational period and an extended observation period up to a maximum of 6 months from enrolment of the last patient (the main study endpoint) (Fig. 1). Eligible patients enrolled were 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 medical records, clinician-rated assessments, and questionnaires completed by patients, either on paper or in digital format, to record self-assessed quality of life and functional status. These data were collected at baseline, at scheduled six-monthly patient visits, and at the main study endpoint. In case of premature

end of the observation period, and during any patient visits due to a clinically relevant event, data were also collected. Baseline clinical assessments were performed within 14 days before and 7 days after the date on which a new antidepressant treatment was started; other baseline data were collected within 14 days before or after initiation of new treatment.

At baseline, the following socio-demographic data were documented: educational level; employment status (irrespective of income level); living status; economic status (as measured by income level); marital status; legal status. Patient characteristics and disease history were also documented at baseline including: age; age at diagnosis of MDD; start of current MDE; number of previous episodes; medical/psychiatric history; confirmation of MDD diagnosis; TRD criteria (MGH-ATRQ); depressive symptom spectrum and severity (MADRS, Clinical Global Impression of Severity [CGI-S] score and Clinical Global Impression of Change [CGI-C]); suicidality; psychiatric comorbidities (lifetime and current).

Antidepressant treatments used for the current MDE up to enrollment were documented, including treatment type (pharmacological; non-pharmacological psychotherapeutic treatments; non-pharmacological neurostimulation treatments). In the case of pharmacological treatment, the medication, daily dose and route, frequency, start and stop date along with the reason for both, were recorded. Antidepressant treatment used during the observation period was documented to the same extent but with additional details of any dose adjustment and reason for adjustment (except in the case of psychotherapeutic treatment). Patients were permitted to change treatments at any time during the study at the discretion of the treating physician, and all changes were documented.

Antidepressant pharmacological treatment classes were categorized as: selective serotonin reuptake inhibitors (SSRI), serotonin-norepinephrine reuptake inhibitors (SNRI), tricyclic antidepressants (TCA), monoamine oxidase inhibitors (MAOI), and 'other' (e.g. trazodone, bupropion, mirtazapine, vortioxetine). Non-antidepressant drugs were categorized as add-on or augmentation medications (e.g. quetiapine, brexpiprazole, aripiprazole, lithium). Combination therapy was defined as more than one antidepressant medication in the absence of add-on medication. Augmentation therapy was defined as antidepressant medication(s) plus at least one add-on medication.

HRQoL was assessed using the EuroQoL 5-dimension 5-level (EQ-5D-5L) patient-reported questionnaire, which includes the EuroQoL Visual Analog Scale (EQ-VAS), and the Quality of Life in Depression Scale (only completed in Germany; not reported here). For EQ-5D-5L, a health state index score was calculated using the UK specific value set, resulting in an index score between <0 and 1, where 1 represents perfect health, 0 represents a health state equivalent to death, and values below 0 represent a state worse than death (Herdman et al., 2011). The EQ-VAS score ranges from 0 (the worst imaginable health) to 100 (the best imaginable health). Functional impairment and associated disability were measured using the Sheehan Disability Scale (SDS) patient-reported questionnaire. Impairment in work, productivity and activity was assessed using the Work Productivity and Activity Impairment (WPAI) patient-reported questionnaire. The WPAI includes some questions that are only answered by patients in paid employment, while the SDS questionnaire includes patients doing both paid and unpaid work. These patient-reported questionnaires were measured and documented at baseline and patient visits during the study.

Following initiation of the new antidepressant treatment (baseline), observational data were collected at pre-scheduled time points at approximately six-monthly intervals from baseline date, and/or the premature end of the observational period. The study was planned to run until 6 months after the last patient was enrolled. Patients still in the study at 12 months were invited to enter an extended observational period until the final data cut-off (6 months after the last patient was enrolled). During the study, events indicating clinically relevant worsening or improvement triggered a physician-lead assessment, namely: appointment or consultation with treating physician in response to improvement or worsening of the current MDE (confirmed by CGI-C $\leq$3 or $\geq$5); admission to, or discharge from, inpatient care; relapse of depressive symptoms (including suicidality); remission of the current MDE (confirmed by MADRS score of 10 or less); any change in the antidepressant pharmacological treatment, including dose changes (except titration), medication switch, initiation of augmentation therapy; any change in non-pharmacological antidepressant treatment. Planned and event-triggered assessment included documentation of depressive symptom spectrum and severity; suicidality; HRQoL; functional impairment and disability in work and other activities. For patients who did not complete the study, as much data were collected as possible as per the planned data collection for study end.

In this paper, patient baseline data are reported; treatment outcomes will be described in a future publication.

2.4. Statistical analysis

Analyses were carried out on the data from the final data cut taken 30 March 2020. Descriptive statistics (N, mean, standard deviation [SD], median, minimum and maximum) were used to summarize continuous variables. Frequency distribution (number and percentage of patients in each category) was used to summarize categorical variables.

3. Results

3.1. Patient socio-demographics

In total, 411 patients with TRD were included in the final analysis set. Seven European countries were represented, with Italy representing the largest proportion of patients in the cohort (30.2%, **Supplementary Figure 1A**). The mean (SD) age of patients was 51.0 (10.8) years, and 62.3% were female. 56.0% had not progressed beyond secondary education, and 30.2% of patients were unemployed. Nineteen percent of patients were on long-term sick leave. Across patients, 54.3% were married or had an official partner, and 78.6% were living with a partner,

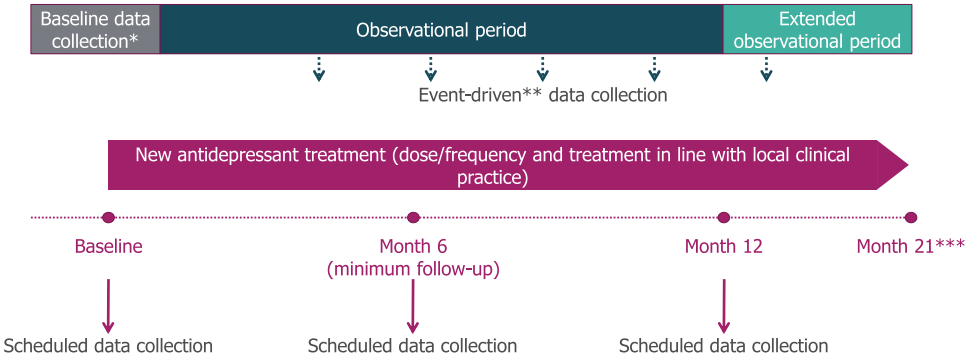

Fig. 1. Study design *Baseline data were documented +/- 14 days of the date on which new treatment started. **Any clinically relevant worsening/improvement in the current MDE.
***21 months was the maximum time enrolled in the study for any individual patient; all patients had a minimum of 6 months follow-up. MDE: major depressive episode.

Table 1
Patient demographics

Category	Subcategory	N=411
Age, mean (SD)		51.0 (10.8)
Sex, n (%)	Male	155 (37.7)
	Female	256 (62.3)
Education level, n (%)	University	70 (17.0)
	High school	111 (27.0)
	Secondary school	148 (36.0)
	Primary school	65 (15.8)
	No formal education/unknown/other	17 (4.1)
Marital status, n (%)	Married/official partner	223 (54.3)
	Not married/no official partner	98 (23.8)
	Divorced	65 (15.8)
	Widowed	17 (4.1)
	No information provided/other	8 (1.9)
Employment status, n (%)	Full time employed	97 (23.6)
	Part time employed	36 (8.8)
	Sheltered work	3 (0.7)
	Long-term sick leave	78 (19.0)
	Unemployed (seeking work)	29 (7.1)
	Unemployed (not seeking work)	95 (23.1)
	Retired	48 (11.7)
	Student/in training	9 (2.2)
	Other	16 (3.9)
Living status, n (%)	At home, alone	85 (20.7)
	At home, with partner, family, or friends	323 (78.6)
	Other	3 (0.7)
Legal status, n (%)	Legal representative (yes)	7 (1.7)

SD: standard deviation.

Table 2
Patient clinical characteristics

Category	**Subcategory**	**N=411**
Clinical evaluation at baseline		
Total MADRS score, mean (SD)		31.8 (6.0)
Disease severity, MADRS category, n (%)	Moderate depression	277 (67.4)
	Severe depression	134 (32.6)
Disease change*, CGI-C, n (%)	No change	267 (65.0)
	Minimally worse	83 (20.2)
	Much/very much worse	61 (14.8)
Psychiatric and medical history		
Age (years) at diagnosis with MDD, mean (SD)		37.2 (13.1)
Years since diagnosed with MDD, mean (SD)		13.7 (11.2)
Duration of current MDE in weeks, mean (SD)		136.3 (203.8)
First or recurrent episode, n** (%)	First episode	93 (22.6)
	Recurrent episode	310 (75.4)
Previous depressive episodes, mean (SD)		3.4 (5.6)

*Relative to assessments carried out at the time point the previous treatment was initiated. **Data only obtained for 403 patients; no data were obtained from 8 patients. CGI-C: Clinical Global Impression of Change; MADRS: Montgomery-Åsberg Depression Rating Scale; MDD: major depressive disorder; MDE: major depressive episode; SD: standard deviation.

family or friends (Table 1). Of patients who provided yearly income level data (68.6%), the largest group earned 20,000–49,999€ (32.6%, **Supplementary Figure 1B**).

3.2. Patient clinical characteristics

Mean (SD) age at diagnosis of MDD was 37.2 (13.1) years, which was on average (SD) 13.7 (11.2) years prior to enrolling in the study. The mean (SD) number of previous episodes was 3.4 (5.6). The current MDE had a mean (SD) duration of 2.6 (3.9) years, and was, for most patients (75.4%), a recurrent episode (Table 2). At baseline, 32.6% of patients had severe depression (defined as MADRS >34), with the remainder classified as experiencing moderate depression (MADRS 20–34). The mean (SD) MADRS score was 31.8 (6.0; Table 2). CGI-S (evaluated on a scale of 0–7) categorized 50.4% of patients as markedly ill (CGI-S 5), 14.1% as severely ill (CGI-S 6), and 1.0% among the most extremely ill patients (CGI-S 7); together, these categories accounted for 65.6% of the patients (Fig. 2**A**). Based on the clinician-rated CGI-C assessment, 20.2% of patients showed minimal worsening of their condition during the previous treatment, with 14.8% of patients recorded as being much or very much worse.

At baseline, 99.5% of patients had failed on at least two antidepressant drugs (according to the MGH-ATRQ criteria) in the current episode,[1] with 45.7% having failed on three or more, and 14.6% on four or more (Fig. 2**B**). Prior to enrolment, SSRIs were the most commonly prescribed medication (77.1%). Treatment failure on at least one SSRI during the current episode had been experienced by 76.2% of patients at baseline, followed by SNRIs, on which 55.7% of patients had failed (Fig. 2**C**).

Pharmacological treatments described as "other" were prescribed to 56.0% of patients at baseline. The next most common treatments prescribed at baseline were SNRIs (42.8%) and SSRIs (37.5%). In total, 54 different pharmacological treatments were prescribed to patients at baseline, either as monotherapy, or as part of combination or augmentation therapy. Augmentation therapy was prescribed for 40.4% of patients and combination therapy was prescribed for 41.4% of patients at baseline. Additionally, 19.2% and 6.6% of patients were undergoing psychotherapeutic treatment or neurostimulation therapy, respectively, either as an on-going or new treatment, at baseline.

3.3. Patient HRQoL, functioning and productivity

EQ-5D-5L and EQ-VAS scores were obtained at baseline from 96.6% and 98.1% of patients, respectively. Mean (SD) index values were 0.41 (0.25) and 41.1 (18.7) for EQ-5D-5L and EQ-VAS, respectively (Table 3).

As a result of their depression, 61.6% of patients were experiencing marked or extreme work impairment, measured by the SDS (Fig. 3). The mean (SD) number of workdays lost or unproductive in the previous week, as measured by the SDS, was 4.3 (3.0) and 4.9 (2.6), respectively (Table 3). Using the WPAI questionnaire to assess productivity, the mean (SD) work time missed (absenteeism) and impairment while working (presenteeism) due to depression was 57.0% (44.9%) and 54.7% (29.5%), respectively, while the overall work impairment due to depression was 60.5% (29.9%). The mean (SD) overall activity impairment, including both employed work and household activities, such as chores, was 73.3% (19.9) (Table 3).

4. Discussion

The study described here assessed the socio-demographics and clinical characteristics, as well as HRQoL and functional impairment, of patients with TRD. The cohort was followed for up to 21 months to measure the disease burden, treatment patterns and treatment outcomes, as well as medical resource utilization, for these patients over time. At baseline, patients had reduced functionality both in and outside of work and poor HRQoL; a considerable number were on long-term sick

[1] Two patients who had experienced one treatment failure according to the MGH-ATRQ criteria also had a second treatment failure recorded in their concomitant medication details. After medical review, they were considered to fulfil the eligibility criteria.

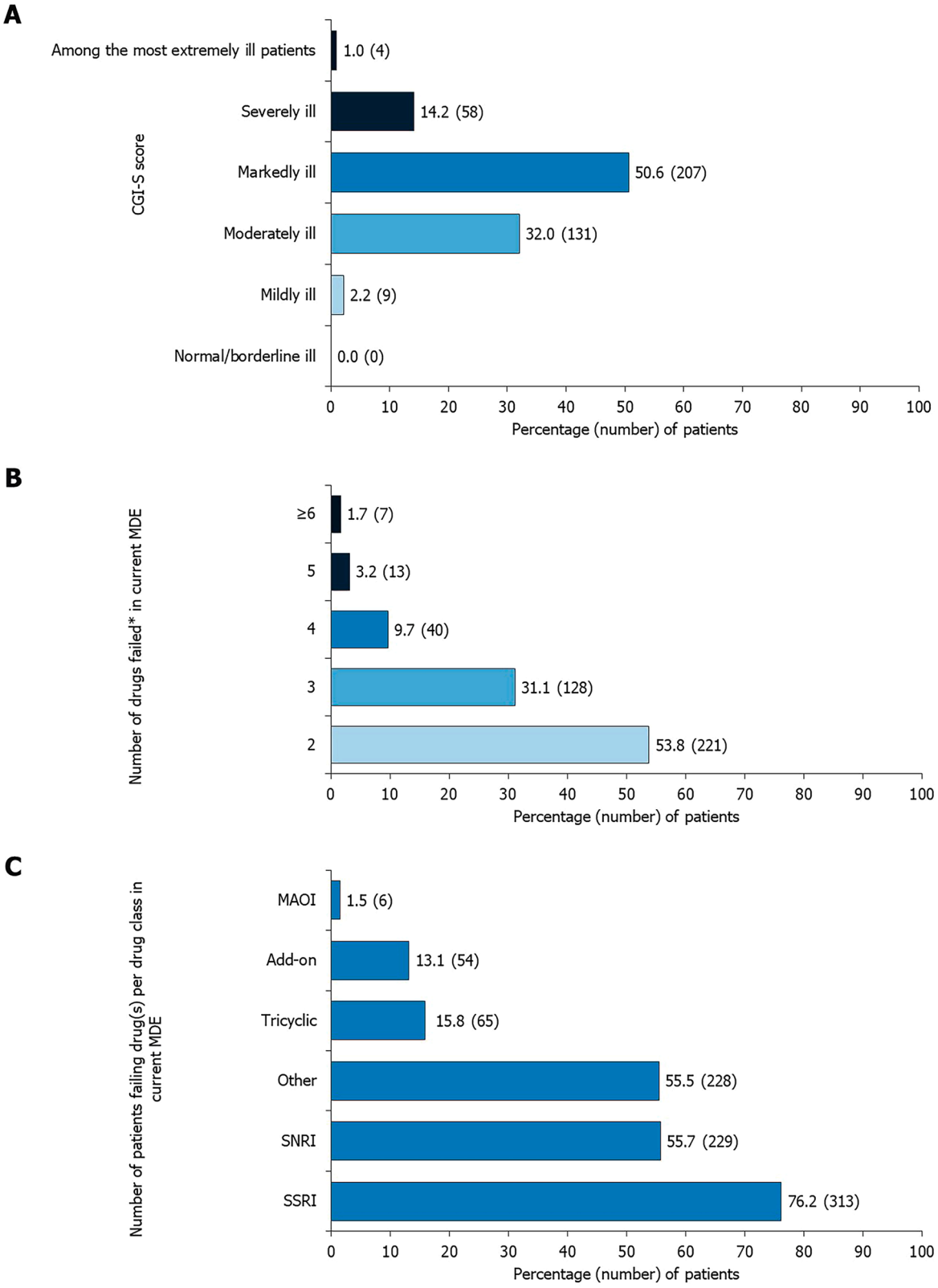

Fig. 2. Baseline clinical characteristics A. CGI-S score; **B.** Number of drugs failed in the current MDE; **C.** Number of patients failing drug(s) per drug class in the current MDE. *According to the MGH-ATRQ. Add-on medications: antipsychotic (aripiprazole, quetiapine, brexpiprazole, alisulpride, amisulpride, asenapine, clozapin, levosulpiride, lurasidone, olanzapine, lanzapine/fluoxetine combination, paliperidon, risperidone); mood stabilizer (depamide, lamotragine, lithium, oxcarbamazepine, oxcarbazepine, quilonum, topiramate, valproate, valproate sodium, valproate acid); other: methylphenidate, modafinil. CGI-S: Clinical Global Impression of Severity scale; MAOI: monoamine oxidase inhibitors; MGH-ATRQ: Massachusetts General Hospital-Antidepressant Treatment Response Questionnaire; SNRI: serotonin-norepinephrine reuptake inhibitor; SSRI: selective serotonin reuptake inhibitor.

Table 3
Health-related quality of life, functioning and productivity

Category	
EQ-5D-5L score (UK-based algorithm)	
N	397
Mean (SD)	0.41 (0.25)
Median	0.42
Min, Max	-0.26, 0.88
EQ-VAS score	
N	403
Mean (SD)	41.1 (18.7)
Median	40.0
Min, Max	0, 90
SDS total score (no imputation)*	
N	341
Mean (SD)	22.4 (5.5)
Median	23.0
Min, Max	2, 30
SDS: number of workdays lost in last week	
N	395
Mean (SD)	4.3 (3.0)
Median	5.0
Min, Max	0, 7
SDS: number of days unproductive in last week	
N	392
Mean (SD)	4.9 (2.6)
Median	7.0
Min, Max	0, 7
WPAI: percent work time missed due to depression**	
N	132
Mean (SD)	57.0 (44.9)
Median	77.5
Min, Max	0, 100
WPAI: percent impairment while working due to depression**	
N	86
Mean (SD)	54.7 (29.5)
Median	60.0
Min, Max	0, 100
WPAI: percent overall work impairment due to depression**	
N	76
Mean (SD)	60.5 (29.9)
Median	68
Min, Max	0, 100
WPAI: percent activity impairment due to depression	
N	390
Mean (SD)	73.3 (19.9)
Median	80.0
Min, Max	0, 100

*Only patients answering **all** questions in the SDS questionnaire (341) were included in the data set for SDS total score; SDS total score was not imputed. **Only patients in paid employment (133 in total) were eligible to complete these sections of the WPAI questionnaire. EQ-5D-5L: European Quality of Life (EuroQol) 5-dimension 5-level; EQ-VAS: EuroQol-Visual Analog Scale; SD: standard deviation; SDS: Sheehan Disability Scale; WPAI: Work Productivity and Activity Impairment questionnaire.

leave or unemployed. Patients had remained unwell for several years, and not only failed to improve despite treatment with multiple different medications but, in many cases, their condition worsened on their last treatment before entering the study. This paper is limited to reporting the baseline characteristics of the patient cohort. Treatment patterns and treatment outcomes over time, as well as healthcare resource utilization during follow-up, will be presented in subsequent papers. However, the data presented here add to the body of real-world evidence demonstrating significant disease burden in patients with TRD in Europe.

Although there is no globally-accepted definition of TRD, in this study TRD was defined according to the EMA Guideline on Clinical Investigation of Medicinal Products in the Treatment of Depression (European Medicines Agency, 2013). The incidence and prevalence of depression is known to be higher in women than men (Piccinelli and Wilkinson, 2018), and our cohort had a similar degree of gender disparity as described for patients with depression in the recently-published 2017 National Health and Wellness Survey (NHWS) (Jaffe et al., 2019). Highlighting the individual and societal impact of TRD, our cohort had low levels of full-time employment at baseline, when compared with recent EU employment rates (Eurostat Statistics Explained, 2019), and almost one fifth of the patients were on long-term sick leave.

The patients with TRD recruited for this study scored highly for depression at baseline. Although baseline data provide only a single time-point measure of the current disease burden, given that the mean duration of the current MDE in these patients was more than 2.5 years without successful response to treatment, this is likely to represent a substantial disease burden over time. Consistently, patients had both high levels of functional impairment and poor HRQoL, with high SDS and WPAI scores, indicating high disease burden. Moreover, WPAI scores for overall activity impairment were substantially higher than those relating solely to employment, indicating that the burden extends beyond work activities. On enrolment, depression had worsened in more than a third of patients over the current MDE, highlighting that patients not only fail to improve, but a substantial proportion may deteriorate further without successful treatment.

Our patient population is similar to the population in the TRANSFORM-2 study, a randomized controlled clinical trial of patients with TRD (Popova et al., 2019). While patients in TRANSFORM-2 reported, on average, a higher level of depression severity (as determined by total mean MADRS score), patient-reported outcomes, including HRQoL scores, were remarkably similar to those from the present observational study (Popova et al., 2019). The data described here also align broadly with results published recently from the 2017 NHWS (Jaffe et al., 2019). This retrospective, observational study examined characteristics of patients from five European countries, and compared patients with TRD with patients whose depression was not treatment resistant, as well as with the general population (Jaffe et al., 2019). While not all measures employed in the current study were comparable with those used in the 2017 NHWS, the comparisons that were possible revealed that the population in the current cohort scored slightly lower for HRQoL, and had higher levels of impairment, as measured by WPAI. The current study cohort also had lower educational status and full-time employment level compared with the 2017 NHWS study population (Jaffe et al., 2019; Rosenthal et al., 2012).

Treatment patterns in the study described here will be analyzed in more detail in a follow-up publication. However, a couple of points regarding treatments used *before* enrolling in the study warrant comment. Across the current MDE, SSRIs were the most common drug class prescribed and failed, followed by SNRIs and “other” medications. By contrast, at the moment of enrolment, when at least two different treatments had failed, SSRIs were the third most prescribed medication, after “other” medications and SNRIs, revealing a shift towards later-line antidepressant treatments. Nevertheless, this suggests that guidelines for first- and second-line treatment of MDD in European countries are largely being followed in routine clinical practice, although their effectiveness in TRD is questionable (Bennabi et al., 2019; Cleare et al., 2015; National Institute for Health and Care Excellence, 2009).

With additional results on patient outcomes at 6 months and beyond, data from this cohort will provide further evidence, gained in a real-world setting, for the burden of TRD and the potential need for new treatments. Data from this study will also enhance understanding of the current treatment patterns of TRD in European clinical practice by providing insight into whether current guidelines are being followed by healthcare professionals and if particular treatment patterns are effective in reducing the disease burden for patients with TRD.

5. Limitations

The limitations of the current study include its relatively small size

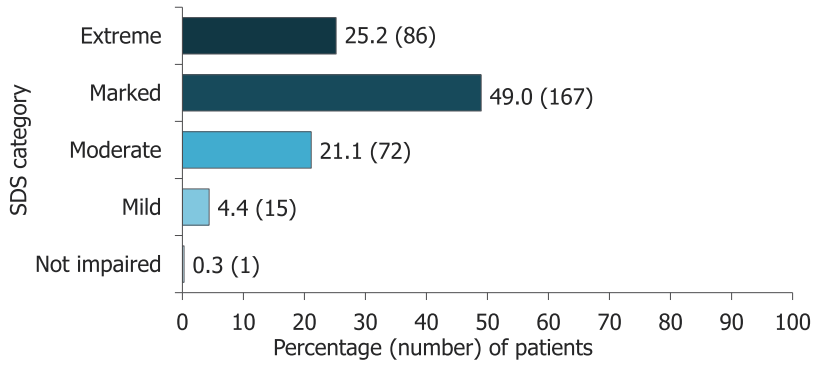

Fig. 3. Patient functioning: Sheehan Disability Scale category. No imputation. SDS: Sheehan Disability Scale.

when compared to other studies such as STAR*D (Rush et al., 2004), and the absence of a control group for comparison. The poor completion rate for patient-reported outcome questionnaires is another limitation. However, given the reduced functionality experienced by patients in this TRD cohort, it is perhaps unsurprising to observe low completion rates of patient-reported outcome questionnaires.

The exclusion of patients with suicidal ideation and alcohol/substance abuse limits the generalizability of the results, as do differences in organization and access to healthcare across the different countries represented in this study. Differences in the availability of fully state-funded care versus private insurance-funded care (or combinations of these healthcare models), drug reimbursement as well as the agreed cost between manufacturers and payers, and differences in access to specialist clinics and clinicians may have introduced bias. Due to the small numbers of patients in this cohort from each European country, it is not feasible to rule out the influence on baseline characteristics resulting from differences in healthcare models. Furthermore, given differences in healthcare models across Europe, extrapolation of these findings to other European countries may be misleading.

6. Conclusions

The TRD patient population assessed in this cohort study was roughly similar to that in previously published literature (Jaffe et al., 2019, Popova et al., 2019). Baseline results demonstrate that the burden of TRD is high, with patients reporting substantial functional impairment and reduced HRQoL.

Data sharing statement

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

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Authors' contributions

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

Declaration of Competing Interest

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Supplementary materials

Supplementary material associated with this article including an interview with one of the authors, Professor Allan H Young, summarizing this publication, can be found, in the online version, at doi:10.101

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