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Real-world evidence from a European cohort study of patients with treatment resistant depression: Healthcare resource utilization

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ABSTRACT

Background: Treatment resistant depression (TRD) is diagnosed when patients experiencing a major depressive episode fail to respond to ≥2 treatments. Along with substantial indirect costs, patients with TRD have higher healthcare resource utilization (HCRU) than other patients with depression. However, research on the economic impact of this HCRU, and differences according to response to treatment, is lacking.

Methods: This multicenter, observational study documented HCRU among patients with TRD in European clinical practice initiating new antidepressant treatments. Data regarding access to outpatient consultations and other healthcare resources for the first 6 months, collected using a questionnaire, were analyzed qualitatively according to response and remission status. The economic impact of HCRU, estimated using European costing data, was analyzed quantitatively.

Results: Among 411 patients, average HCRU was higher in non-responders, attending five times more general practitioner (GP) consultations and spending longer in hospital (1.7 versus 1.1 days) than responders. Greater differences were observed according to remission status, with non-remitters attending seven times more GP consultations and spending approximately three times longer in hospital (1.7 versus 0.6 days) than remitters. Consequently, the estimated economic impacts of non-responders and non-remitters were significantly greater than those of responders and remitters, respectively.

Limitations: Key limitations are small cohort size, absence of control groups and generalizability to different healthcare systems.

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Conclusion: Patients with TRD, particularly those not achieving remission, have considerable HCRU, with associated economic impact. The costs of unmet TRD treatment needs are thus substantial, and treatment success is fundamental to reduce individual needs and societal costs.

1. Introduction

Major depressive disorder (MDD) is a common mood disorder associated with significant morbidity and mortality, and with elevated risk of suicide (Vos et al., 2020; Cavanagh et al., 2003). Of patients with MDD, approximately 10–30% will have treatment resistant depression (TRD) (Jaffe et al., 2019; Rush et al., 2006; Al-Harbi, 2012; Voineskos et al., 2020), defined as the presence of a major depressive episode (MDE) that fails to respond to a minimum of two different antidepressants, given in adequate dose and duration (European Medicines Agency, 2013). Treatments for MDD include medication, psychotherapy, neurostimulation therapies and combinations of these (European Medicines Agency, 2013). The effectiveness of a treatment is determined according to depression symptoms after treatment, with response referring to reduction of depression symptoms beyond a pre-defined study-specific cut off, while remission is defined as achieving a low threshold of depression symptoms and is typically more stringently defined than response (Rush et al., 2006). Patients with MDD who achieve remission are less likely to relapse, and more likely to show long-term stability and improved psychosocial functioning, thereby supporting remission as the goal of MDD treatment (Mendlewicz, 2008; Rush et al., 2006). Any treatments approved for use in MDD can be applied to treat TRD and clinical management may thus also comprise various combinations of antidepressant and non-antidepressant medications, as well as non-pharmacological therapies (Bennabi et al., 2019; European Medicines Agency, 2013; Voineskos et al., 2020). Regarding European-wide approval, a single pharmacological treatment, esketamine nasal spray (in combination with a selective serotonin reuptake inhibitor [SSRI] or serotonin-norepinephrine reuptake inhibitor [SNRI]) was the first treatment approved specifically for TRD, as defined above (European Medicines Agency, 2013; Mahase, 2019). However, there is no consensus on treatment pathways for TRD and evidence suggests there is wide variation between and within countries in Europe (MacQueen et al., 2017).

Previous literature indicates that patients with TRD have higher levels of healthcare resource utilization (HCRU) than both MDD patients without TRD and the general population, highlighting a clear unmet need in the treatment of this condition (Jaffe et al., 2019; Johnston et al., 2019; Sussman et al., 2019). In a European study of MDD, patients with TRD were consistently found to have significantly greater HCRU than patients without TRD (Jaffe et al., 2019). In another study conducted in the US, annual healthcare payments for patients with TRD in the year following their diagnosis were on average US$3000 higher than those without TRD (Sussman et al., 2019). Evidence further suggests that as the number of treatment failures increases, the direct and indirect healthcare costs for patients with TRD rise, while their health-related quality of life (HRQoL) declines (Johnston et al., 2019). Importantly, a recent study of a TRD patient cohort in France also found that HCRU reduces as patients achieve response, remission and recovery (Yrondi et al., 2020).

This paper presents data from the Treatment Resistant Depression Cohort in Europe study (54135419DEP4001), a prospective, multicenter, non-interventional, observational study conducted to collect real-world data from adult patients with TRD being treated in routine clinical practice across a sample of countries in Europe. Overall, the objectives of the study were to describe: the socio-demographic and disease-related characteristics of patients with TRD in a sample of representative European countries; the social and economic burden associated with TRD in a real-world setting; the naturalistic treatment patterns and associated clinical outcomes in TRD in routine clinical practice; and the HCRU of patients in the cohort. Data to support the first three objectives are described in two previously published papers (Heerlein et al., 2021a, 2021b).

As reported by Heerlein et al. (2021a), the mean duration of the current MDE at baseline exceeded 2.5 years. Coupled with high Montgomery-Åsberg Depression Rating Scale (MADRS) scores, this indicates a considerable disease burden for both individuals and society over time. Furthermore, patients had low HRQoL, with a substantial proportion of patients unable to work. Those who were working suffered marked impairment of their abilities in the workplace and lost a substantial amount of time per week to unproductivity as a result of their depression. Furthermore, impairment extended beyond patients' work lives and into their overall everyday activities; the mean overall activity impairment was 73.3%. This highlights the far-reaching impacts of TRD (Heerlein et al., 2021a).

Analysis of treatment patterns and outcomes over time further explored the impact of TRD on patients (Heerlein et al., 2021b). The findings suggested that, for most patients, current treatment options do not result in a clinically significant response. Yet, despite a lack of response, patients may remain on treatments for a prolonged period. The heterogeneity of treatment options identified in this analysis emphasizes the lack of clinical consensus (Heerlein et al., 2021b).

The current paper supports the final objective, describing the HCRU of TRD patients from this cohort, and the estimated economic impact. While evidence indicates that MDD patients achieving remission have better long-term outcomes than those achieving response (Rush et al., 2006; Mendlewicz, 2008), and there is some research to suggest that these differences are reflected in the HCRU (Yrondi et al., 2020), there remains a lack of research from broader European settings and a need for studies which translate HCRU into estimated economic impact. Therefore, in this study, HCRU and its economic impact were analyzed and compared according to patient response and remission status.

2. Methods

2.1. Patients

Male and female patients with TRD aged 18 to 74 years were recruited for the study by their treating physicians during routine clinical practice. Eligible patients had a diagnosis of MDD according to the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) and met the criteria for TRD, defined as failure to respond to at least two different oral antidepressant treatments, taken at an adequate dose and for a sufficiently long duration in the same MDE, in accordance with the Massachusetts General Hospital-Antidepressant Treatment Response Questionnaire (MGH-ATRQ). Patients were required to have a baseline MADRS score of $\geq$20 and were initiating a new antidepressant treatment strategy to treat the current MDE. In the context of this study, a new treatment strategy was defined as any pharmacological or non-pharmacological treatment prescribed to replace, or in addition to, the previous antidepressant treatment. Switches to a biosimilar or changes in dose were not considered as a new treatment.

Patients were excluded if they had a prior diagnosis of psychotic disorder or MDD with psychotic features; displayed homicidal or suicidal ideation or intent within 1 month prior to enrolment and/or had a positive response to Items 4 or 5 on the Columbia Suicide Severity Rating Scale (C-SSRS); a history of suicidal behavior within 1 year of enrolment of the study; moderate to severe substance or alcohol abuse, according to DSM-5 criteria, within 6 months of enrolment (excluding the use of nicotine and caffeine). All patients were required to provide

written informed consent and were excluded if, as per the opinion of the participating physician, they were not considered able to provide such consent. Approval for the study was provided by local ethics review boards, and the study was conducted in accordance with the Declaration of Helsinki.

2.2. Study design

This study was a prospective, multicenter, observational cohort study of patients with TRD, documenting outcomes in routine clinical practice across seven countries in Europe. Patients were enrolled from the United Kingdom, Italy, the Netherlands, Germany, Belgium, Portugal and Spain. The study design has been described in previous publications (Heerlein et al., 2021a, 2021b). It included baseline data collection, an observational period of 6–12 months and an extended observational period of up to 6 months after enrolment of the final patient. Scheduled data collection periods occurred at baseline, 6-monthly scheduled visits and at the end of the study or, in the case of premature end, at the end of the observation period. The study was closed for all patients when the last included patient reached a follow-up of 6 months, so that each included patient could have a minimum follow-up of approximately 6 months (Fig. 1).

2.3. Study procedures and evaluations

At baseline, data were collected on patient socio-demographics, disease history and current clinical characteristics, as well as details of all treatments used to treat the current MDE prior to study entry. The remission or response status of each patient was assessed at approximately 6 and 12 months after initiation of a new treatment at baseline. Response was defined as MADRS improvement from baseline ≥50% while remission was defined as MADRS score ≤10. As such, all patients who achieved remission were also responders, but not all patients who achieved response also achieved remission.

HCRU data were collected from baseline to Month 6 (150–216 days after enrolment) using a HCRU questionnaire, completed by physicians on behalf of their patients. The questionnaire asked for the type and frequency/duration of visits, between baseline and Month 6, to outpatient healthcare practitioner (HCP) consultations, inpatient hospital care, intensive care units (ICUs) and day/night clinics which were triggered by any clinically relevant worsening or improvement in the current depressive episode. The average cost (in Euros [€]) of HCRU per patient across the 6-month period from baseline to Month 6, was estimated via an economic impact model using published 2020 cost input data from Spain (Osakidetza, 2019; Boletín Oficial de la Región de, 2020), the second largest country cohort in the study. The cost input data for each healthcare resource type are presented in **Supplementary Table 1**. By applying these estimated costs to all instances of HCRU throughout the study, the estimated economic impact of HCRU over 6 months was calculated for all patients, as well as separately for each of the responder/remitter groups, to assess the impact of these health states.

2.4. Statistical analysis

Descriptive analyses of HCRU from baseline to Month 6 were presented for all patients that had data recorded in the HCRU questionnaire up to Month 6. The number and percentage of patients (overall, and within each of the responder/remitter groups) using each healthcare resource at least once from baseline to Month 6 were calculated. The baseline and Month 6 visits were excluded from these calculations to ensure that differences in HCRU between groups could be adequately characterized (inclusion of these visits would lead to 100% of patients across all groups having at least one visit with a psychiatrist/neurologist). The mean, standard deviation (SD), median, minimum and maximum number of uses for each healthcare resource were also calculated. The exception was hospitalizations, for which the total length of stay was calculated, instead of number of uses. In cases where hospitalizations of an undefined duration were reported (i.e., start/end dates of admission were unavailable), the median duration of defined hospitalizations was imputed.

The mean, SD, median, and minimum and maximum values were calculated for the estimated cost (€) of HCRU per patient (overall and within responder/remitter groups) over the 6 months starting at baseline. The baseline and Month 6 visits were included in these calculations, since the estimation of economic impact by the model was facilitated if all patients had a cost input of >€0. Formal statistical analyses were conducted to evaluate whether differences between health states were significant: a generalized linear model was fitted, with log-link function and gamma distribution, in line with previously published methods (Flórez-Tanus et al., 2018). A two-sided p-value <0.05 was considered statistically significant.

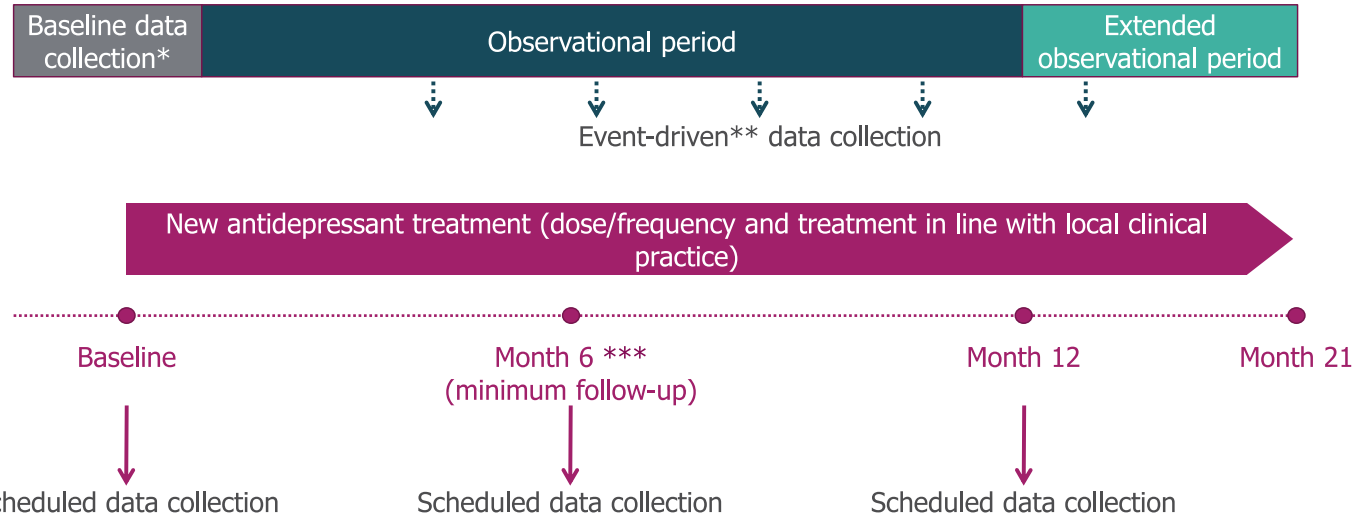

Fig. 1. Study design. *Baseline data were documented +/- 14 days of the date on which new treatment started. **Any clinically relevant worsening/improvement in the current MDE. ***HCRU data were analyzed from baseline to Month 6. HCRU: healthcare resource utilization; MDE: major depressive episode.

3. Results

3.1. Baseline characteristics and response to treatment at month 6

Since HCRU data were only collected for the first 6 months, only 6-month treatment outcomes are included here. Baseline characteristics for the total patient cohort, including prescribed treatments, as well as full details on outcomes of treatment up to Month 12, have been described elsewhere (Heerlein et al., 2021a, 2021b) Of the 411 patients that were included in the study, 306 had data recorded in the HCRU questionnaire up to Month 6 and were included in this analysis. For this sub-group of patients, the mean (SD) age of patients at baseline was 51.0 (10.4) years and 61.1% (187/306) were female. The mean (SD) MADRS score was 31.9 (5.8), with 68.0% (208/306) of patients with moderate depression (MADRS score of 20–34) and 32.0% (98/306) with severe depression (MADRS score >34). The percentage of patients who had experienced two and three previous treatment failures was 55.2% (169/306) and 30.7% (94/306), respectively. At Month 6, 73.5% (225/306) of patients showed no response, 9.8% (30/306) showed response without remission and 16.7% (51/306) of patients achieved remission.

3.2. Use of outpatient HCP consultations

3.2.1. Response versus no response

Overall, most patients across both non-responder and responder groups accessed at least one outpatient consultation from baseline to Month 6 (77.1% [172/223] and 78.3% [65/83], respectively). However, the difference between the two groups was due to a greater proportion of responders reporting at least one consultation with a psychiatrist/neurologist than non-responders. For other HCP types (general practitioners [GPs], psychologists, therapists and psychiatric nurses), higher proportions of non-responders accessed at least one outpatient consultation than responders (Supplementary Fig. 1A).

With regards to number of consultations, from baseline to Month 6 non-responders accessed all types of healthcare professionals with a greater mean frequency than responders. Non-responders accessed on average (mean [SD]) five times as many consultations with a GP (1.5

Fig. 2. Mean number of outpatient HCP consultations between baseline and Month 6 (excluding baseline and Month 6 visits). **A.** Mean outpatient consultations stratified by response at Month 6. **B.** Mean outpatient consultations stratified by remission at Month 6. Response: MADRS improvement from baseline ≥50% or MADRS score >10; remission: MADRS score ≤10. GP: general practitioner; HCP: healthcare practitioner; MADRS: Montgomery-Åsberg Depression Rating Scale; SD: standard deviation.

[5.6] versus 0.3 [0.9]), and nine times as many consultations with a therapist and with a psychiatric nurse (respectively, 0.9 [6.8] versus 0.1 [0.3] and 0.9 [5.6] versus 0.1 [0.6]) than responders. Despite a greater proportion of responders reporting at least one consultation with a psychiatrist/neurologist, the overall mean (SD) frequency of visits with this HCP group was also higher among non-responders than responders (3.8 [7.4] versus 2.8 [2.6]); Fig. 2A).

3.2.2. Remission versus no remission

In both non-remitter and remitter groups, most patients accessed at least one outpatient consultation, with a higher proportion among non-remitters than remitters (78.0% [199/255] versus 74.5% [38/51], respectively). Compared with patients who achieved remission, greater proportions of non-remitters reported at least one consultation with all HCP types except psychiatrists/neurologists (Supplementary Fig. 1B).

Patients who did not achieve remission accessed, on average (mean [SD]), a higher number of consultations with all five types of healthcare professionals than remitters. In particular, non-remitters reported seven times as many GP consultations than patients in remission (1.4 [5.3] vs 0.2 [0.9]). Further, despite a lower overall proportion of non-remitters accessing at least one consultation with a psychiatrist/neurologist than remitters, non-remitters had a higher mean (SD) frequency of consultations with this HCP type (3.7 [7.0] versus 2.5 [2.3], respectively; Fig. 2B).

3.3. Visits to hospital, ICU, and day/night clinics

3.3.1. Response versus no response

From baseline to Month 6, hospital admissions, and visits to ICU and day clinics were reported among both responders and non-responders.

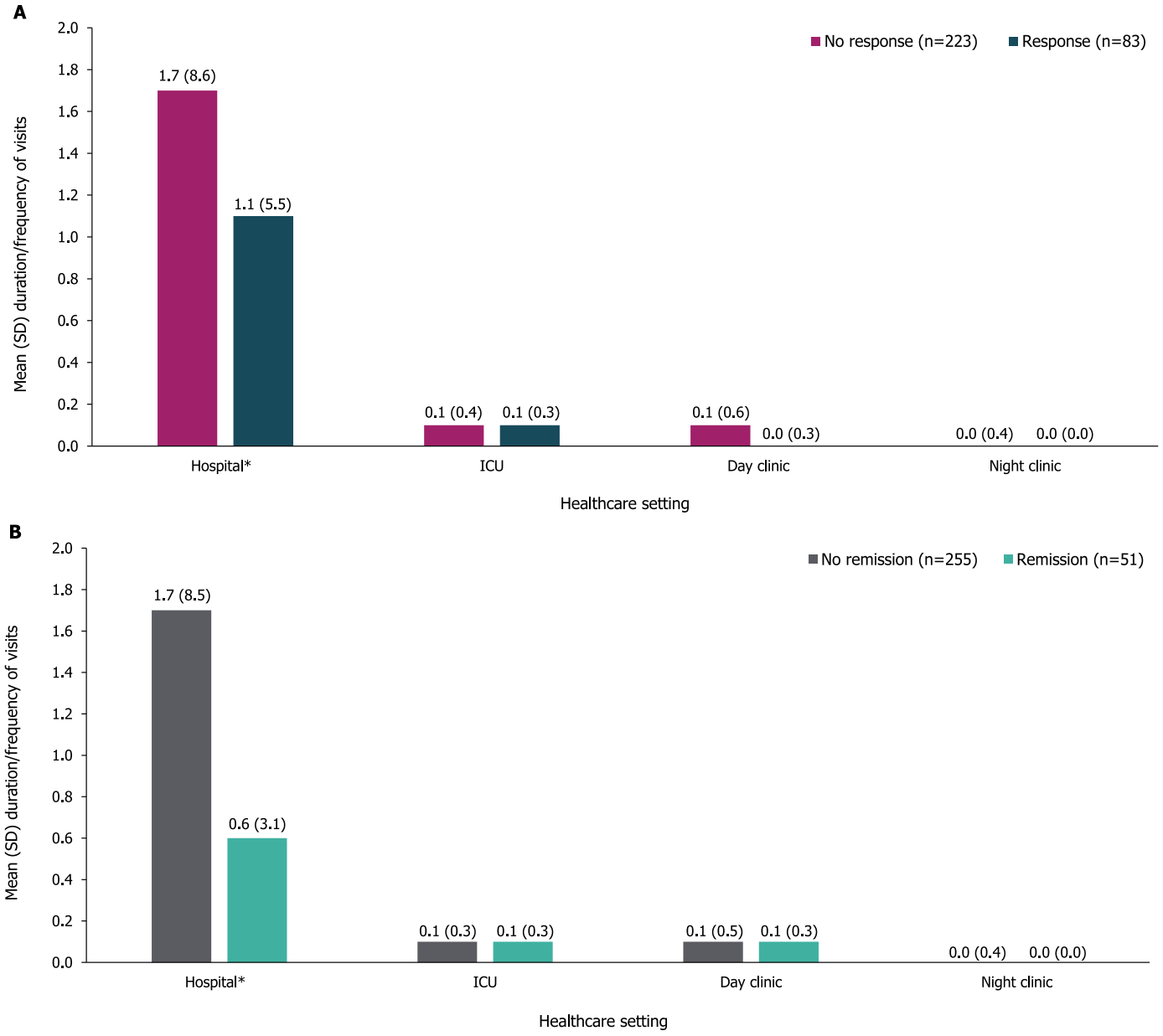

Fig. 3. Mean duration (number of days) or frequency of visits to hospital, ICU and day/night clinics between baseline and Month 6 (excluding baseline and Month 6 visits). *For patients who did not specify the duration of hospital stay, the median duration for patients who did report start and/or stop dates (7 days) was imputed. **A.** Mean number of days/visits to healthcare settings stratified by response. **B.** Mean number of days/visits to healthcare settings stratified by remission. Response: MADRS improvement from baseline ≥50% or MADRS score >10; remission: MADRS score ≤10. ICU: intensive care unit; MADRS: Montgomery-Åsberg Depression Rating Scale; SD: standard deviation.

At least one hospital admission was reported by 8.4% (7/83) of responders and 8.5% (19/223) of non-responders. Higher proportions of non-responders than responders reported visits to ICU (7.2% [16/223] versus 4.8% [4/83]) and day clinics (4.9% [11/223] versus 3.6% [3/83], respectively). One non-responder (0.4% [1/223]), but no responders, accessed night clinics from baseline to Month 6 (Supplementary Fig. 2A). Further, non-responders reported a greater mean (SD) duration and/or frequency of visits than responders, overall (Fig. 3A). Specifically, patients who did not respond to treatment remained in hospital, on average, for more days (1.7 [8.6] vs. 1.1 [5.5]) and had more day clinic visits (0.1 [0.6] vs. 0.0 [0.3]), than responders.

3.3.2. Remission versus no remission

Overall, greater proportions of non-remitters reported at least one admission to hospital (9.0% [23/255] versus 5.9% [3/51]), to ICU (7.1% [18/255] versus 3.9% [2/51]) and to night clinics (0.4% [1/255] versus 0) compared to remitters. The reverse was true for day clinics, for which a lower proportion of non-remitters reported at least one attendance than remitters (4.3% [11/255] versus 5.9% [3/51], respectively; Supplementary Fig. 2B). Compared to those who achieved remission, the mean (SD) duration of hospital stays of non-remitters was almost three times as long (1.7 [8.5] days versus 0.6 [3.1] days). Similar differences were not observed for ICU admissions or day/night clinics (Fig. 3B).

3.3.3. Estimated cost of trd patient HCRU

Over 6 months, the mean (SD) estimated cost of HCRU per TRD patient, regardless of response or remission status, was €1421.6 (€3403.4; Table 1). When patients were stratified by response status, non-responders had a significantly higher mean (SD) estimated cost per patient than responders (€1575.4 [€3743.2] versus €1008.3 [€2216.2]; $p = 0.002$; Table 1). Differences in costs between health state groups were even more pronounced when patients were stratified by remission status. For non-remitters, the mean (SD) estimated HCRU cost per patient was €1548.2 (€3672.0) while the cost for a patient achieving remission was estimated to be €788.2 (€1292.4; $p < 0.001$; Table 1).

4. Discussion

In this study, we assessed the HCRU of patients with TRD over 6 months from the initiation of a new TRD treatment. The results support the findings of previously published studies, which suggest high HCRU among TRD patients (Jaffe et al., 2019; Johnston et al., 2019; Sussman et al., 2019). However, compared to a previous study of European patients with TRD, patients in the current study were found to report lower mean values for the number of GP consultations and overall HCP visits (Jaffe et al., 2019). This could reflect a wide variation in HCRU, possibly dependent on patient response to treatment as well as the specific healthcare system studied.

Importantly, here it was found that HCRU was higher in patients who did not respond to treatment compared to those who did, with non-responders spending more days in hospital and having more outpatient HCP consultations than patients who did respond to treatment. Comparisons according to remission status revealed even more pronounced differences in HCRU. This aligns with previous work, which has shown that as the number of treatment failures rise the direct and indirect costs associated with TRD also increase (Johnston et al., 2019) and that as patients achieve response, remission and recovery, HCRU decrease (Yrondi et al., 2020). Such findings demonstrate the importance of achieving treatment success, not only for individual patients but also for healthcare providers and society as a whole.

In line with these HCRU results, the economic impact analysis using previously published costing data from Spain showed that from baseline to Month 6, the mean cost per patient for responders was significantly less (on average €567.1 less; $p = 0.002$) than that of non-responders. The mean cost difference between non-remitters and remitters was even greater (mean costs were €760.0 less for remitters; $p < 0.001$). Notably, although higher proportions of responders/remitters reported at least one consultation with psychiatrists/neurologists than non-responders/non-remitters, the latter had a higher mean frequency of these consultations. This suggests that, while responders and remitters were more likely to attend a psychiatrist or neurologist appointment, they were less likely to return within 6 months of starting a new treatment; they visited these HCPs less regularly than non-responders and non-remitters.

Along with these direct costs of TRD to healthcare systems, previously reported results from this study have shown that TRD has a substantial indirect cost, too. Much of this expenditure is likely associated with the marked or extreme work impairment, substantial absenteeism and presenteeism, and reductions in overall activity and productivity both inside and outside of work (Heerlein et al., 2021a). Notably, patients achieving remission reported better functioning than non-remitters (Heerlein et al., 2021a).

The substantial indirect costs associated with TRD have also been captured in other published works. In a US-based study, for example, patients with TRD were more likely than non-TRD MDD patients to claim government healthcare support offered to those whose employment status has changed (i.e. due to termination or reduced hours) (Amos et al., 2018). While TRD alone did not significantly impact employment termination, these findings indicate that the condition may be associated with higher rates of employment status change, for example transitioning from full-time to part-time employment. Such status changes may then in turn lead to additional indirect costs. Corresponding findings from European settings have also been reported. A registry study in Sweden examined TRD as a potential risk factor for being granted disability pension, demonstrating that TRD patients were twice as likely to be granted disability support than non-TRD MDD patients (Taipale et al., 2020), highlighting the additional strain placed on resources even relative to other patients with non-TRD MDD. Similarly, a registry study of patients living in Denmark found TRD patients to be twice as likely to receive disability pension than non-TRD depressed patients (Bang-Madsen et al., 2020). The data from Denmark also indicated that TRD patients were three times more likely to prematurely leave the workforce than those without TRD, losing on average six work-years (Bang-Madsen et al., 2020).

Together with the previously published findings of this study, these results demonstrate that the economic burden of TRD is not restricted to direct impacts of HCRU; rather, this condition can also result in substantial, indirect costs to patients and the wider societies of broad

Table 1
Economic analysis of HCRU over 6 months.

Total healthcare costs, €*			
By response status at Month 6	All	No response	Response
n	306	223	83
Mean (SD)	1421.6 (3403.4)	1575.4 (3743.2)	1008.3 (2216.2)
Median	541.0	541.0	511.0
Min, Max	253, 29,075	253, 29,075	253, 18,214
Difference in mean cost between health states; p-value	–	567.1; $p = 0.002$	
By remission status at Month 6	**All**	**No remission**	**Remission**
n	306	255	51
Mean (SD)	1421.6 (3403.4)	1548.2 (3672.0)	788.2 (1292.4)
Median	541.0	569.0	476.9
Min, Max	253, 29,075	253, 29,075	253, 8888
Difference in mean cost between health states; p-value	–	760.0; $p<0.001$	

* Includes baseline and Month 6 visits. The cost of the baseline visit was assumed to be equal to a first psychiatrist visit (€167); the cost of the Month 6 visit was assumed to be equal to a follow-up psychiatrist visit (€86); the minimum cost for all patient groups was equal to the sum of the baseline and Month 6 visits (€253). HCRU: healthcare resource utilization; SD: standard deviation.

geographical regions. That said, it is important to consider when examining findings from different study cohorts that there are currently no rigid diagnostic criteria for TRD within DSM-5 or International Classification of Diseases (ICD-10). Similarly, lack of response to antidepressive treatments exists on a continuum, and there is no clear cut-off point at which MDD transitions into TRD (Amos et al., 2018). As a result, the definition used can vary between different studies and make it challenging to define clear TRD/non-TRD patient subgroups.

5. Limitations

A limitation of the current study is its relatively small sample size, particularly for some of the included countries and some of the presented analyses. Additionally, as is the case for many real-world evidence studies, there was no control group for comparison. Furthermore, while HCRU data were collected over a longer period, analysis was only completed on data from baseline to Month 6. Importantly, comparisons of patient subgroups were descriptive and did not take confounding variables into account. Moreover, economic costs were estimated based on local costs in Spain, though the cost structure may vary between countries and healthcare systems represented in the study. Finally, definitions of different types of healthcare appointment, such as a day clinic, may vary between the different European countries included in this study. This limitation is difficult to avoid when using real-world data from countries with different healthcare systems.

6. Conclusion

Overall, non-responders had greater HCRU and significantly greater associated costs than responders. Such differences were observed to an even higher degree in comparisons between non-remitters and remitters. As such, the study highlights the economic impact of the condition and the importance of effective treatments for patients, to reduce individual needs to access healthcare resources, thus also benefiting society as a whole.

Data sharing statement

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

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