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Research paper

Economic impact of treatment-resistant depression: A retrospective observational study

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ABSTRACT

Background: To determine the incidence of Treatment-Resistant Depression (TRD) in Spain and to estimate its economic burden, using real world data.

Methods: A retrospective, observational-study was carried out using data from the BIG-PAC database®. Patients aged ≥18 years with a diagnosis of major depressive-disorder (MDD) who initiated a new antidepressant treatment in 2015–2017 were included. The patients were classified as TRD and non-TRD. Patients were classified as TRD if they had, during the first year of antidepressant treatment: a) failure with ≥2 antidepressants including the prescription of ≥3 antidepressants (N06A) or ≥2 antidepressant and ≥1 antipsychotic (N05A; including lithium) b) antidepressants administered for ≥ 4 weeks each, and c) the time between the end of one treatment and the initiation of the next was ≤ 90 days. Inherent limitations of data collection from databases should also be considered in this analysis (e.g., lack of information about adherence to treatment). Follow-up period: 18 months. The incidence rate was calculated as the number of TRD patients per 1,000 persons-year divided by the population attended. Outcomes: direct healthcare and indirect costs. Two sensitivity analyses were performed varying the index date and the period used to define TRD patients (6 vs.12 months).

Results: 21,630 patients with MDD aged ≥ 18 years (mean age: 53.2 years; female: 67.2%) were analyzed, of whom 3,559 met TRD criteria, yielding a 3-year cumulative incidence of 16.5% (95%CI: 16%-17%) among MDD patients. The annual population incidence rate of TRD in 2015–2017, was 0.59, 1.02 and 1.18/1,000 person-years, respectively (mean: 0.93/1,000 person-year). Overall, mean total costs per MDD patient were €4,147.9, being higher for TRD than for non-TRD patients (€6,096 vs. €3,846; $p<0.001$): a) direct costs (€1,341 vs. €624; $p<0.001$), b) lost productivity (€1,274 vs. €821; $p<0.001$) and c) permanent disability (€3,481 vs. €2,401; $p<0.001$, adjusted). Sensitivity analyses showed no differences with the reported results.

Conclusions: The population based TRD incidence in Spain was similar to recent data from other European countries. TRD is associated with greater resource use and higher costs compared with non-TRD patients.

Abbreviation: ANOVA, Analysis of variance; ATC, Anatomical Therapeutic Chemical Classification System; ICD-10-CM, International Classification of Diseases (10th Edition) Clinical Modification; SD, Standard deviation; non-TRD, Non-Treatment Resistant Depression; TRD, Treatment-Resistant Depression; MAS, Mean annual salary; CI, Confidence interval; INE, Spanish National Institute of Statistics; EMR, Electronic medical records; SPSS, Statistical Package for the Social Sciences.

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1. Introduction

According to Global Data Exchange (Global Health Data Exchange 2021), more than 270 million people in the world would suffer from depression (175 million people specifically from Major Depressive Disorder). In Europe, Major Depressive Disorder would affect 3.15% ot the total population, which accounts for more than 25 million people (GHDx, 2019). In Spain, MDD it is one of the most common psychiatric diagnoses in the general population, with an estimated yearly prevalence of around 4% and a lifetime prevalence of around 10.6% (Gabilondo et al., 2010; Vieta et al., 2021). Prevalence of suicidal ideation in patients with MDD has been estimated at 7.4%, with a 12-month prevalence of suicide attempt of 1.5% (Gabilondo et al., 2010). It is a disabling disease that alters the perceived quality of life, giving rise to an increased health-care resource use (Malhi et al., 2020). The economic impact is significant; different studies show that 21.2–28.6% of costs are direct health costs while indirect or associated costs due to lost occupational productivity (indirect non-health costs) account for up to 78.8% of the total costs of depression in Spain (Salvador-Carulla et al., 2011; Sobocky et al., 2006).

The main goal of the management of depressive disorder is the symptom remission (Malhi et al., 2020; Silverman et al., 2015). However, only 40–60% of patients achieve remission after initial antidepressant treatment, regardless of the drug chosen (Malhi et al., 2020; Silverman et al., 2015; Rush et al., 2006; Sicras-Mainar et al., 2012). A lack of therapeutic response makes it difficult to manage depressive disorder in these patients who do not achieve remission with one or more treatment cycles (McAllister-Williams et al., 2020; Voineskos et al., 2020). Clinical variables (comorbidities), genetics, and sociodemographic factors among others, may influence TRD, although this subject is under-researched (Fugger et al., 2019; Perugi et al., 2019; Mandelli et al., 2016). Lack of remission and treatment-resistant depression (TRD) is associated with a worse quality of life, higher comorbidity, increased resource use, social and occupational disability and worse therapeutic outcomes (Salloum and Papakostas., 2019; Malhi et al., 2020; Silverman et al., 2015). Due to this impact, efforts have been made in recent years to identify factors predicting a lack of response to treatment in these patients (Kautzky et al., 2018; Cepeda et al., 2018). Although TRD appears to have a multifactorial component, the physiopathology remains unclear (Bartova et al., 2019). One of the factors that hinder the research in this area is the lack of consensus on the definition of TRD, as the number of treatment failures considered varies widely between studies (Conway et al., 2017). The definition of TRD, recommended by the European Medicines Agency (EMA) as a non-response to at least two adequate trials with antidepressant agents of the same or different substance class that were administered in adequate daily doses and in adequate duration (at least four weeks for each antidepressant trial) in adherent patients was introduced by the European Group for the Study of Resistant Depression (GSRD) and has been used in the majority of studies on TRD (Schosser et al., 2012; Guideline on clinical investigation of medicinal products in the treatment of depression 2013; Brown et al., 2019). Alternative terminologies to TRD such as major multi-therapy resistant depressive disorder or difficult-to-treat depression (McAllister-Williams et al., 2020), are currently under development and reflect the overall challenge of this condition.

The available TRD incidence studies and the economic impact reported may not be comparable, in part due to these wide differences in the definition of TRD (Nemeroff, 2007; Fife et al., 2018). The use of large databases representative of the general population allows observational studies to be conducted, facilitating real world evidence generation and clinical decision-making (Cepeda et al., 2018; Zhdanava et al., 2021; Taipale and Tiihonen, 2021). However, conducting clinical research is challenging with current definitions of TRD, due to the absence of information in the databases such as non-adherence, or the reasons for treatment changes, which makes difficult the classification of patients as resistant to treatment (Cepeda et al., 2018). The objectives of the study were to assess: i) the incidence of TRD, using the definition of TRD based on Cepeda S et al. and Edwards SJ et al., as treatment with ≥3 antidepressants (AD) or ≥2AD and ≥1 antipsychotic/lithium after one year of treatment initiation. Lithium was included in this TRD definition as it is one of the strategies that could be used for treatment resistant patients in daily clinical practice (Edwards et al., 2013; Dold and Kasper, 2017) and ii) the direct and indirect (lost productivity) costs associated with TRD in real world conditions in Spain.

2. Material and methods

2.1. Design and study population

A longitudinal, observational, retrospective study was carried out. Electronic medical records (EMR) were obtained from the BIG-PAC® administrative database (Sicras-Mainar et al., 2019) (data source: secondary; owner: Atrys Health; estimated population: 1.8 million patients; database registration (The European Network of Centers for Pharmacoepidemiology and Pharmacovigilance (ENCePP®); http://www.encepp.eu/encepp/viewResource.htm?id=29236#). Primary data come from the EMR of seven integrated Spanish public health areas (primary care centers, hospitals and specific mental health ambulatory sites). EMR are anonymized prior to export to BIG-PAC in compliance with Organic Law 3/2018, of December 5, on the Protection of Personal Data and guarantee of digital rights (https://www.boe.es/eli/es/lo/2018/12/05/3). Patients who sought care (≥ 1 health records) and initiated new antidepressant treatment between 01/01/2015 and 31/12/2017 (recruitment period, patient selection) for the treatment of depressive disorder (ICD-10-CM: F32 [single episode], F33 [recurring episode], F41.8 [anxiety-hysteria], F34.1 [dysthymic disorder] and F39 [unspecified mood disorder]) were included. The index date was the start of the first antidepressant treatment.

2.2. Inclusion/exclusion criteria

Inclusion criteria were: (a) age ≥ 18 years, (b) depressive disorder diagnosis (c) initiation of a new antidepressant (*The Anatomical Therapeutic Chemical Classification System*; ATC: N06A) (The Anatomical Therapeutic Chemical Classification System with Defined Daily Doses (ATC/DDD) 2021), (d) no antidepressant treatment during the previous 6 months, (e) prescription meeting the minimum treatment criterion (≥ 4 weeks of antidepressant treatment after the first prescription), (f) inclusion in the prescription program (with recorded daily dose, the dosing regimen and duration of each treatment administered, ≥ 2 prescriptions during the follow up), and (g) guaranteed regular monitoring during the follow up (≥ 2 health records in the EMR). Patients transferred to other centers, displaced or out-of-area and permanently institutionalized patients were excluded as were those with terminal illness (Z51.5), dialysis (N18.5), dementia (F01-F03, G30), bipolar depression (F31) and/or psychosis (F20-F29).

2.3. Study and follow-up groups

After 12 months of the index date (AD initiation), patients were classified into two cohorts: a) non-treatment-resistant depression (non-TRD) and b) TRD, and both followed by an additional 6-month period (total follow-up period 18 months).

2.4. Definition of diagnosis and treatment-resistant depression

Depressive disorder was defined as ICD-10-CM, codes F32 [major depressive disorder, single episode], F33 [recurrent episode], F41.8 [depression with anxiety; mixed anxiety-depressive disorder], F34.1 [dysthymic disorder; includes persistent anxious depression, neurotic depression, depressive neurosis, depressive personality disorder], and

F39 [unspecified mood disorder]. who initiated a new antidepressant. TRD was defined as patients who had during the first year of antidepressant treatment: a) failure with ≥2 antidepressants including the prescription of ≥3 antidepressants (N06A) or ≥2 antidepressant and ≥1 antipsychotic (N05A; including lithium) b) antidepressants administered for ≥ 4 weeks each, and c) the time between the end of one treatment and the initiation of the next was ≤ 90 days (Cepeda et al., 2018; Edwards et al., 2013). The diagnostic and treatment criteria were at the discretion of the attending physician.

2.5. Incidence of TRD and non-TRD depressive disorder

Cumulative incidence will be given as the percentage, considering the identified TRD patients among the MDD population (MDD patients initiating treatment) during the 3-year period. The annual incidence rate among health-care users was defined as the newly diagnosed and treated cases of depressive disorder (TRD and non-TRD) per 1000 persons-year in adult patients who sought health care in 2015, 2016, and 2017. Annual incidence rate among general population is also given as newly diagnosed and treated cases of depressive disorder (TRD and non-TRD) per 1,000 persons-year in general adult population in 2015, 2016 and 2017. The results were not standardized due to the similarity of the general study population with the Spanish age pyramid (Sicras-Mainar et al., 2019).

2.6. Demographic variables and comorbidity

Demographic and comorbidity recorded variables were age (continuous and by range), gender, high blood pressure, diabetes mellitus, dyslipidemia, obesity, active smoking, ischemic heart disease, cerebrovascular accident, heart failure, kidney failure, anxiety, and malignancies (all obtained at the index date). As summary variables of general comorbidity, we used the Charlson's comorbidity index (Charlson et al., 1987) and the number of chronic comorbidities.

2.7. Medication administered

Drug dispensing records according to the ATC/DDD classification were recorded. The mean of depressive disorder medications (different active substances, N06A), antipsychotics (N05A) and anxiolytics/sedatives (N05C) were obtained.

2.8. Resource use and cost analysis

Direct healthcare costs (medical visits, days of hospitalization, emergencies, diagnostic or therapeutic requests, pharmaceutical prescriptions), and indirect (non-health costs), related to temporary and permanent occupational disability were collected. Costs were expressed as the mean cost per patient and resource (mean/patient/resource) during the 18-month follow up. The study concepts and their unit costs (in 2017) are detailed in Table 1. Rates were obtained from hospital accounting, except for medication and days of occupational disability. Prescriptions were quantified according to the retail price per pack (according to Bot Plus, General Council of Official Pharmacist Colleges of Spain).

2.9. Calculation of temporary and permanent disability

The data source used to carry out this analysis contains information on both temporary and permanent disabilities of the subjects included in this database. In the case of temporary disabilities, the number of days that the patient has been in this condition is counted. If the patient has a permanent disability, he is marked as such in the database. Days of occupational disability were considered indirect non-health costs and were estimated using average annual earnings (AAE) (*Instituto Nacional de Estadística*, INE, 2017). The mean age of active workers with disability according to gender was considered to select the mean annual salary (€ 21,792.70 in females and € 28,912.87 in males). Lost work productivity was quantified according to the days of occupational disability and the corresponding mean annual salary. Likewise, for permanent disability, the period of disability was 365 days/year. Considering the mean age of patients with permanent work disability, the mean annual salary selected was € 22,367.70 in females and € 29,711 02 in males.

Table 1
Direct and non-health indirect unit costs used in the study (in € 2019).

Health and non-health resources	Unit costs (€)
Medical visits	
Primary care visit	23.19
Hospital emergency visit	117.53
Hospitalization (one day)	420.90
Specialized care visit*	65.00
*Complementary tests***	
Laboratory tests	32.30
Conventional radiology	28.50
Diagnostic/therapeutic tests	47.12
Computed axial tomography	96.00
Magnetic nuclear resonance	177.00
Electroconvulsive therapy***	190.00
Pharmaceutical prescription	Retail price
Temporary work disability (non-health costs; women-men)	MAS (€ 59.7–79.2/day)
Permanent work disability (non-health costs; women-men)	MAS (€ 61.3–81.4/day)

Source of health resources: hospital accounting and Spanish National Statistical Institute (INE).
Values expressed in euros (year 2019).
MAS: mean annual salary (Source: INE, 2017).
* Only in psychiatry, psychotherapy, and psychology services.
** Related to depressive disorder.
***Does not include hospital admission, which is counted as a day of hospitalization.

2.10. Other follow-up outcomes

All-cause deaths and codes potentially related to suicidality/harm (ICD-09-CM: V62.84 [Suicidal ideation], V62.85 [Homicidal ideation], V71.89 [Suicide attempt, alleged], 300.9 [At risk for suicide], 960–979 [Poisoning by drugs, medicinal and biological substances] and E950-E959 [Suicide and self-inflicted injury] were recorded.

2.11. Statistical analysis

A descriptive univariate statistical analysis was performed. Qualitative data were expressed as absolute and relative frequencies and quantitative data as means and standard deviation (SD), medians and 25th and 75th percentiles of the distribution (interquartile range), and 95% confidence intervals (CI) for parameter estimation. In the bivariate analysis comparing the two study cohorts, ANOVA and the chi-squared tests for independent groups were used. A logistic regression model was performed to estimate demographic variables and comorbidities associated with TRD, mortality, and suicide attempt considering the variables that were statistically significant in the bivariate analysis as covariates (method: consecutive steps; statistical: Wald). A covariance model (ANCOVA) was performed to adjust the different cost components, with Bootstrap resampling methods (bootstrapping; method: estimation of marginal means, statistical: Bonferroni. Bootstrap resampling (bootstrapping): the initial sample random resampling is based on 1000 stratified sampling simulation samples (with bias reduction and variance approximation). Covariates: variables that were statistically significant in the binary regression model were included. Dependent variable: health costs, lost occupational productivity, permanent disability, and total cost, respectively. The SPSSWIN version 23 program was used, and statistical significance was established as $p<0.05$.

2.12. Sensitivity analysis

Two sensitivity analyses were made to determine the proportion of patients with TRD, resource use and costs: (a) the start of the 18-months follow-up period to estimate costs begins with the date of second treatment failure (instead of the date of first treatment received); as the observation period for these patients starts later, for some patients the 18-month follow-up period would not be complete and were not included in this analysis; and b) the second sensitivity analysis used a different period for the definition of TRD (6 months vs 12-months in the general analyses). As for the main and first sensitivity analysis, a 18-month follow-up period was used to compare TRD and non-TRD costs.

3. Results

3.1. General

The population (aged ≥ 18 years) attended in the health system between 2015 and 2017 was 1280,284 patients, of whom 28,796 had a new diagnosis of depressive disorder. Of these, 21,630 patients initiated a new antidepressant treatment (6897, 7155 and 7578 patients in 2015, 2016 and 2017, respectively) (Fig. 1). Of these patients, 3559 were defined as TRD, yielding a 3-year cumulative incidence of 16.5% (95% CI: 16%−17%). Among health care users, the annual incidence rate of TRD per 1000 person-years was 0.59 (752/1279,532), 1.02 (1301/1280,196) and 1.18 (1506/1281,125), in 2015, 2016 and 2017, respectively (mean incidence rate in 2015–2017: 0.93‰ (95%CI: 0.7–1.1). For the general population, the incidence rate of TRD per 1000 person-years was 0.51 (752/1469,559), 0.89 (1301/1469,559) and 1.02 (1506/1470,624) in 2015, 2016 and 2017, respectively (mean incidence rate in 2015–2017: 0.81‰ (95%CI: 0.7–0.9).

The mean age for the population was 53.2 (SD: 17.3) years; 67.2% were female and the mean Charlson index was 0.8 points. Anxiety (39.8%), dyslipidemia (28.8%) and high blood pressure (27.4%) were the most frequent comorbidities. Both groups were similar in baseline demographic variables but patients with TRD presented a higher frequency of anxiety (OR 1.63; $p<0.001$), smoking (OR 1.14; $p<0.05$) and excessive drinking (OR 1.94; $p<0.001$) (Table 2a). At follow-up, cumulative mortality and suicide-related behaviors were also significantly higher in TRD than in non-TRD patients (OR 1.92; $p<0.001$) and (OR 1.30; $p<0.001$) respectively (Table 2b).

During the 18-month follow up after the initiation of the first AD treatment, mean total cost per DD patient was €4147.9. Patients with TRD used more health resources, specifically in primary care visits (21.7 vs. 13.1; $p<0.001$), specialist visits (2.9 vs. 0.8; $p<0.001$) and hospital stays (0.7 vs. 0.3; $p<0.001$). They also had more days of occupational disability (17.6 vs. 11.7; $p<0.001$), and higher percentage of permanent disability (13.6% vs. 9.8%; $p<0.001$). Table 3 shows the mean direct and indirect cost per patient during the 18-month follow up period. The total direct and non-indirect cost was € 89.7 million (21,630 patients x € 4147.9), of which 17.9% corresponded to direct health costs and 82.1% to indirect non-health costs. The distribution of indirect non-health costs was 19.8% temporary occupational disability and 62.4% permanent disability. Total costs were higher in patients with TRD (€ 6096 vs. € 3846, $p<0.001$; difference: € 2250). These proportions were also maintained in the different cost components: direct health costs (€ 1341 vs. € 624, $p<0.001$), lost occupational productivity (€ 1274 vs. € 821, $p<0.001$) and permanent disability (€ 3481 vs. 2401, $p<0.001$). (Table 3, Fig. 2).

3.2. Sensitivity analysis

When the index date was considered the date of TRD diagnosis, fewer patients could be followed for 18-month resulting in fewer study patients (20,863) (Table S1). Their median age was 53.3 (SD:17.3) years, 67.2% were female and the mean Charlson index was 0.8. The mortality rate was 1.4%. According to these criteria, 2792 patients with TRD (13.4%, 95% CI: 12.9%−13.9%) were identified. In TRD patients, mortality was higher (OR 1.42, $p<0.001$) as were cases with suicide-related codes (OR 2.06, $p<0.001$). The mean total cost per patient was € 4228.6. Total costs were higher in patients with TRD (€ 6597 vs. € 3930, $p<0.001$; difference: € 2073). These proportions were maintained in the different cost components: direct healthcare costs (€ 1227 vs. € 624, $p<0.001$), lost occupational productivity (€ 1226 vs. € 854, $p<0.001$) and permanent disability (€ 3335 vs. € 2452, $p<0.001$). Comparison between the main analysis and the first sensitivity one showed no substantial differences between TRD patients (difference of € 93 in the total mean cost per patient).

A second sensitivity analysis was performed varying the criterion of follow-up length for TRD definition (from 12-months to 6 months after treatment initiation) (Table S2). The 21,630 patients with a new diagnosis who started treatment in 2015–2017 were analyzed and the two study groups were 20,362 non-TRD, and 1628 TRD patients. According to this criterion, 5.8% of patients were identified as TRD at 6 months. As in the main analysis, total costs were higher in patients with TRD vs non-TRD (€ 6486 vs. € 4079, $p<0.001$). These proportions were maintained in the different cost components: direct healthcare costs (€ 11,708 vs. € 682, $p<0.001$), lost occupational productivity (€ 1230 vs.€ 878, $p<0.001$) and permanent disability (€3548 vs. € 2519, $p<0.001$). Number of TRD patients according to this sensitivity analysis was lower,

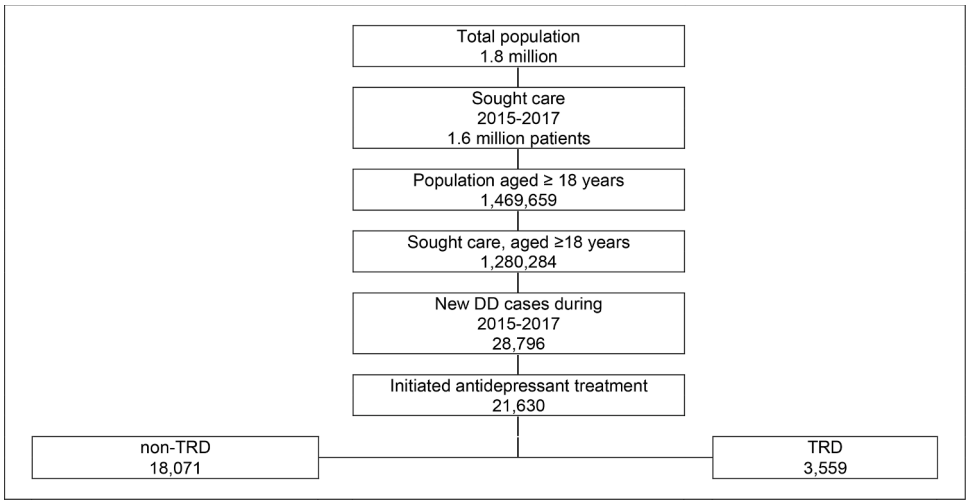

Fig. 1. Study flow diagram.

Table 2a
Baseline characteristics of the depressive disorder (DD) patients of the study, according to Treatment Resistant status.

Study groups (depressive disorder) Number of patients,%	Total DD No=21,630 (100%)	non-TRD No=18,071 (83.5%)	TRD* No=3559 (16.5%)	p	OR (95% CI)[a]
Demographics					
Mean age, years (SD)	53.2 (17.3)	53.2 (17.3)	53.6 (17.2)	0.209	0.94 (0.87 - 1.01)
Ranges: 18–44 years	7708 (35.6%)	6472 (35.8%)	1236 (34.7%)	0.667	
45–64 years	8113 (37.5%)	6761 (37.4%)	1352 (38.0%)		
65–74 years	2893 (13.4%)	2412 (13.3%)	481 (13.5%)		
≥ 75 years	2916 (13.5%)	2426 (13.4%)	490 (13.8%)		
Sex (female)	14,538 (67.2%)	12,178 (67.4%)	2360 (66.3%)	0.210	0.93 (0.86 - 1.01)
Comorbidity (quantitative)					
Mean diagnoses (SD)	1.6 (1.4)	1.5 (1.3)	1.7 (1.4)	<0.001	0.99 (0.95 - 1.04)
Mean Charlson Index (SD)	0.8 (1.3)	0.8 (1.3)	0.8 (1.2)	0.362	0.97 (0.93 - 1.02)
0	13,197 (61%)	11,016 (61.0%)	2181 (61.3%)	0.235	
1	4323 (20.0%)	3618 (20.0%)	705 (19.8%)		
2	1283 (5.9%)	1056 (5.8%)	227 (6.4%)		
3+	2827 (13.1%)	2381 (13.2%)	446 (12.5%)		
Comorbid conditions					
High blood pressure	5922 (27.4%)	4959 (27.4%)	963 (27.1%)	0.639	
Diabetes mellitus	2011 (9.3%)	1679 (9.3%)	332 (9.3%)	0.944	
Dyslipidemia	6240 (28.8%)	5205 (28.8%)	1035 (29.1%)	0.738	
Obesity	2572 (11.9%)	2117 (11.7%)	455 (12.8%)	0.072	
Active smoking	2339 (10.8%)	1874 (10.5%)	445 (12.5%)	<0.001	1.14 (1.01 - 1.29)*
Excessive drinking	240 (1.1%)	167 (0.9%)	73 (2.1%)	<0.001	1.94 (1.45 - 2.59)‡
Ischemic heart disease	674 (3.1%)	568 (3.1%)	106 (3.0%)	0.605	
Cerebrovascular accident	677 (3.1%)	577 (3.2%)	100 (2.8%)	0.230	
Heart failure	520 (2.4%)	444 (2.5%)	76 (2.1%)	0.252	
Kidney failure	681 (3.1%)	569 (3.1%)	112 (3.1%)	0.996	
Anxiety	8612 (39.8%)	6856 (37.9%)	1756 (49.3%)	<0.001	1.63 (1.49 - 1.78)‡
Neoplasms	2615 (12.1%)	2195 (12.1%)	420 (11.8%)	0.563	

Table 2b
Death (all-causes, and suicide-related codes) of the depressive disorder (DD) patients of the study, according to Treatment Resistant status.

Study groups (depressive disorder) Number of patients,%	Total DD No=21,630 (100%)	non-TRD No=18,071 (83.5%)	TRD* No=3559 (16.5%)	p	OR (95% CI)[a]
Death (all causes)	320 (1.5%)	235 (1.3%)	85 (2.4%)	<0.001	1.92 (1.49 - 2.49)‡
18–44 years	8 (0.04%)	6 (0.03%)	2 (0.1%)		
45–64 years	33 (0.2%)	25 (0.14%)	8 (0.2%)		
65–74 years	124 (0.6%)	92 (0.5%)	32 (0.9%)		
≥ 75 years	155 (0.7%)	112 (0.6%)	43 (1.2%)		
Suicide-related codes	760 (3.5%)	596 (3.3%)	164 (4.6%)	<0.001	1.30 (1.08 - 1.56)†

* TRD index date: start date of the first antidepressant treatment administered. Values expressed as percentage (N,%) mean (SD: standard deviation), p: statistical significance. TRD: Treatment-resistant depression. non-TRD: non-treatment-resistant depression.

[a] Binary logistic regression model; method: consecutive steps; Statistician: Wald. OR: odds ratio, CI: confidence interval.

‡ $p<0.001$.

† $p<0.01$* $p<0.05$ Covariates: variables that were statistically significant in the bivariate analysis were included. Dependent variable: TRD.

as expected because of the shorter period to fulfill TRD criteria. Cost per TRD patient was slightly higher in this sensitivity analysis vs the main one (€ 390 above per TRD patient).

4. Discussion

The study results show that during the first year after a diagnosis of depressive disorder up to one in six patients have at least two changes in their AD treatment regimen, as indication of treatment resistant depression (TRD). The resource use, total costs associated with TRD (especially costs due to lost occupational productivity), mortality and suicidality were higher in TRD patients.

As far as we know, this is the first publication about the incidence of TRD in Spain based on real-life data. Similar information available from other countries is also scarce. One of the reasons that explains the absence of updated information in this regard could be the fact that TRD does not have a diagnosis entity, being the analysis usually conditioned by other factors (heterogeneity in the evaluation tools and patient characteristics). Although these challenges lead to widely varying estimates (Demyttenaere and Van Duppen, 2019; Voineskos et al., 2020; Thomas et al., 2013), it is crucial for both, clinicians and health policy, makers to count on updated information regarding the frequency of this condition.

We found that 16.5% of patients with a new diagnosis who had started a new antidepressant treatment in 2015–2017 developed TRD, with an annual population incidence rate of 0.59, 1.02 and 1.18 persons/year, respectively. If we compare our data with studies using large patient databases in other countries, we find that, for example, Cepeda (Cepeda et al., 2018) found that 10.4% of newly diagnosed subjects developed TRD per year. In this work, they found that TRD patients were younger and had a higher frequency of substance use, anxiety, psychiatric conditions (eating disorders, insomnia, attention deficit disorders) and pain than non-TRD patients (Cepeda et al., 2018). An analysis by Gronemann of the Danish national patient registry found that about 15% of patients with depressive disorder developed TRD during the first year. The incidence was higher in patients with severe depression and was relatively stable over time, being serotonin (SSRIs) and noradrenaline reuptake inhibitors (SNRIs) part of most combinations of treatments (Gronemann et al., 2018, 2021). In a recent French study of a prescription database, the annual incidence of TRD was estimated at 5.8 and 7.8 patients per 10,000 persons in the first 3 or 6 months after starting treatment, respectively (Bosco-Lévy et al., 2021).

To date, TRD incidence information is still scarce. Our TRD incidence results (0.93 per 1000 person-years) are consistent with those recently published by Bosco-Lévy and Gronemann (Bosco-Lévy et al., 2021; Gronemann et al., 2018) and somewhat higher than the estimate by

Table 3
Health-care direct and non-health indirect costs by study group.

Study groups (depressive disorder)	Total DD	non-TRD	TRD*	p
Number of patients,%	*N* = 21,630 (100%)	*N* = 18,071 (83.5%)	*N* = 3559 (16.5%)	
Primary care visits	335.9 (307.7)	303.0 (275.2)	503.3 (396.7)	<0.001
Hospital emergency visits	45.3 (119.0)	41.8 (116.7)	63.1 (128.7)	<0.001
Specialist visits	72.1 (233.8)	49.0 (174.4)	189.0 (401.7)	<0.001
Hospital stays	75.4 (878.1)	62.5 (801.9)	140.9 (1190.3)	<0.001
Laboratory tests	52.6 (75.3)	51.1 (74.9)	60.3 (76.7)	<0.001
Conventional radiology	10.9 (40.5)	10.7 (40.7)	11.7 (39)	0.184
Axial tomography	0.9 (10.3)	0.8 (9.8)	1.5 (12.6)	<0.001
Magnetic nuclear resonance	2.5 (23.4)	2.3 (22.7)	3.2 (26.7)	0.045
Other complementary evidence	3.5 (82.6)	3.2 (79.1)	5.1 (92.3)	<0.001
Electroconvulsive therapy	5.9 (92.1)	5.4 (92.3)	8.2 (90.9)	0.132
Antidepressants	136.0 (382.7)	95.6 (222.3)	340.9 (767.4)	<0.001
Health costs	741.0 (1186.0)	625.5 (985.3)	1327.2 (1791.3)	<0.001
Lost occupational productivity	819.6 (2670.2)	754.8 (2537.1)	1148.5 (3247.5)	<0.001
Permanent disability	2587.3 (4119.5)	2421.5 (3686.6)	3403.1 (4607.4)	<0.001
Total costs	4147.9 (3199.3)	3801.8 (2985.5)	5878.8 (3998.3)	<0.001

Adjusted cost model (ANCOVA) **			***Difference***
Health costs	624	1341	717‡
95% CI	609–643	1278–1404	649–784
Lost occupational productivity	821	1274	453‡
95% CI	773–871	1140–1409	304–604
Permanent disability	2401	3481	1080‡
95% CI	2271–2532	3155–38,14	727–1440
Total cost	3846	6096	2250‡
95% CI	3702–3999	5714–6503	1837–2698

* TRD index date: start date of the first antidepressant treatment administered. Values expressed in mean (SD: standard deviation), p: statistical significance. TRD: Treatment-resistant depression non-TRD: non-treatment-resistant depression.

** *Analysis of covariance (ANCOVA) with Bootstrap resampling methods (bootstrapping);* Method: estimation of marginal means, statistical: Bonferroni. Bootstrap resampling (bootstrapping): the initial sample random resampling is based on 1000 stratified sampling simulation samples (with bias reduction and variance approximation). CI: confidence interval.

‡ *Significance:* $p<0.001$. Covariates: variables that were statistically significant in the binary regression model were included. Dependent variable: health costs, lost occupational productivity, permanent disability and total cost, respectively.

Cepeda (Cepeda et al., 2018), although some methodological differences can be found among the different studies (definition, time period analyzed, time to meet TRD criteria, etc.). As an example, in Cepedaś analysis, cases and non-cases were matched on age, gender and other characteristics, while our study did not include any matching procedure.

A number of works using alternative sources of information (different from large patient databases) have focused on prevalence of TRD. Jaffe (Jaffe et al., 2019) described 3308 patients with Major Depressive Disorder selected from a population survey conducted in five European countries in which 18.8% of patients with Major Depressive Disorder had TRD. TRD was more prevalent in women and was associated with comorbidities such as anxiety and attempted suicide. A review of treatment-resistant depression in the United States by Mrazek et al. included 62 articles published between 1996 and 2013 with a total of 59,462 in and outpatients". The prevalence of TRD was 12–20%. The authors highlighted the high economic burden of the disease, the need to investigate the mechanisms associated with depressive disorder and the need to improve treatment adherence (Mrazek et al., 2014).

The mean total cost per patient during the 18 months of follow up after initiation of antidepressant treatment was € 4147.9. Patients with TRD had significant higher costs (€ 6096 vs. € 3846; p <0.001; difference: € 2250). These differences between TRD and non-TRD patients were maintained across all the cost components: direct health costs (€1341 vs. € 624, p <0.001), lost occupational productivity (€1274 vs. € 821; p <0.001) and permanent disability (€ 3481 vs. € 2401; p <0.001). Sensitivity analyses showed similar results. Our results are in line with other publications that show that direct costs of depression are the tip of the iceberg, with indirect costs having, by far, the greatest weight. A review by Johnston et al. (Johnston et al., 2019) reported that TRD places a high economic and human burden on the health system, patients, and their families. That review showed wide variations in the costs attributable to TRD, mainly due to geography, and therefore to the different associated costs. However, the review also showed a clear and consistent trend between higher levels of treatment resistant and higher associated costs (both direct and indirect ones), as well as a worse quality of life.

A direct cost-only analysis by Sussman et al. found that patients with TRD in the US Health Care System have more emergency department visits, outpatient visits and prescriptions. Annual costs per patient were € 9890 vs. € 6848 in non-TRD patients. The authors recommended improving the care of these patients to help reduce the economic burden of the disease (Sussman et al., 2019). Our results are similar to those described above, although comparisons of costs between countries with different health systems and unit costs face important limitations. In our study the increase of direct costs in the TRD population is mainly due to an increased number of visits to specialists, drug treatments and hospitalizations. The only differences with Sussman's work would be the greater use of hospitalizations in TRD vs non-TRD population in Spain vs. higher emergency visits in the US population.

Other reviews also show that failure to respond to first-line pharmacotherapy for MDD is also associated with greater risk of unemployment and reduced work productivity (Johnston et al., 2019). Greenberg et al. showed that the associated costs for both lost occupational productivity due to disability and absenteeism in treatment-resistant patients were approximately twice as high as those associated with non-treatment resistant patients (Greenberg et al., 2004). Amos et al. found costs € 6709 higher in TRD patients than in non-TRD patients (Amos et al., 2018). Costs due to lost productivity in patients with TRD were €1811 higher than in non-TRD patients and accounted for 46% of the total mental health-related direct costs. These differences are even more evident when patients have cardiovascular, metabolic, or respiratory disease or cancer (Zhdanava et al., 2020).

Our results also show that lost productivity (both temporary and long-term) is the largest cost component of depression, which amounts up to 82% of the total cost. The greater weight of indirect costs is maintained when the costs are analyzed according to whether patients are treatment resistant, and it is proportional in patients with and without TRD. In TRD patients, the costs increase in all categories, with a cost difference during the 18-month follow up of € 2250 (of which € 717 are due to direct costs, and € 1533 to indirect costs). This is not surprising as the relationship between the severity of depressive symptoms and functionality at work has been established, and the fact that even mild depression is associated with lost productivity (Beck et al., 2011). The important weight that the loss of labor productivity has in the economic burden of depression has also been shown in recent studies carried out in other countries. According to Zhdanava et al., treatment-resistant depression is responsible for 48% and 32% of the economic burden of MDD due to unemployment and loss of productivity respectively (Zhdanava et al., 2021). TRD is associated with an elevated risk for DP compared to other patients with depression, with large potential costs for the affected patients and for society. This information is aligned with the result of a recent publication showing that TRD is

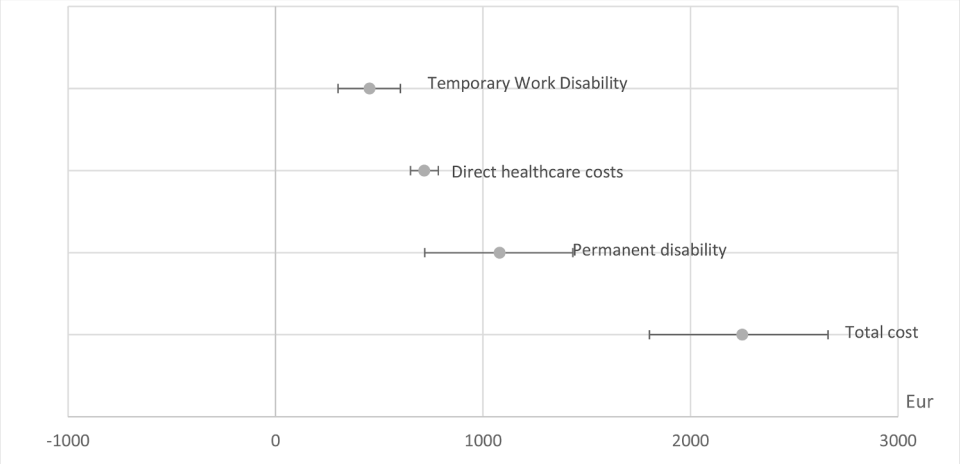

Fig. 2. Mean differences in costs (95% CI) between TRD and non-TRD patients, by cost category (2019 Euro).

associated with an elevated risk for disability pension compared to other patients with depression (Taipale et al., 2020).

Differences found with other studies, both in the total costs (usually higher than ours).and in their proportions (typically lower proportion of indirect costs), may be due to the differences in the methodology used to estimate indirect costs and to the definition of TRD used. We think that an important part of the costs variation may be due to differences in the following: unit costs applied; health organizational model that determines resource use and supply of services; and different social policies governing absenteeism and lost productivity in different countries. From a methodological point of view, according to the approved study protocol, we have estimated the costs for RTD patients considering the 18-months follow-up, period starting from the initial MDD diagnosis (study inclusion). Also, per protocol, we carried out a first sensitivity analysis, in which the estimation of costs started at the time the patient was considered to have TRD. The latter is more in line with other relevant studies carried out in this area (Reutfors et al., 2018), and might prevent immortal time bias (Yadav and Lewis, 2021a,b). Importantly results of both analyses are very similar. Despite methodological differences among studies, an increased resource use and unmet need for care of TRD patients is consistent, which supports the need to conduct specific studies in each geographical area, and according to the determinants of each country, accurately estimating the reality of the problem. More accurate information could have an impact in improving intervention and resource-providing strategies, making this type of study a useful reference for health decision-making process (Mahlich et al., 2018).

Our study shows that TRD has an important social impact. In addition to direct and lost productivity costs, patients with TRD had a higher frequency of alcohol dependence, smoking and anxiety, mortality, and suicide-related cases, in line with most studies reviewed (Amos et al., 2018; Cepeda et al., 2018; Gronemann et al., 2018; Jaffe et al., 2019; Mrazek et al., 2014). Also, the association between treatment-resistant depression and general medical conditions (both prior and subsequent to TRD diagnosis) has recently been studied in detail (Madsen et al., 2021). All these issues may have added an additional intangible cost to the disease burden. The impact and burden of Major Depressive Disorder and TRD are immense and go beyond economic costs, due to its association with increased mortality (associated or not with suicide) that, in some countries, is associated to demands for assisted dying (Demyttenaere and Van Duppen, 2019).

Some limitations of our study deserve discussion. First, inherent to its retrospective design, under recording of depression is likely resulting in a possible underestimation of untreated depressive disorders and therefore, in a possible underestimation of TRD. This is due to the fact that a subgroup of patients even with a severe depression may not be using health care services, or receiving adequate treatment (Gabilondo et al., 2011). On the contrary, it should be taken into consideration that the fact of having carried out the study including different diagnostic codes related to depressive disorder, means that we have estimated the costs of the whole treatment-resistant population, but not specifically of those with treatment-resistant major depression. Second, an important limitation of this study is the classification of patients as TRD within a database, as it is not possible to consider the severity of the depressive disorders nor the treatment adherence, as these characteristics not usually available in structured databases. This limitation could have led to an overestimation of the TRD population. Furthermore, the costs of lost productivity due to presenteeism or to unpaid productivity were not included. The results and conclusions regarding the costs of this analysis are limited to direct costs in the public health system, as well as indirect costs due to productivity losses (work disabilities and premature death), so it should not be understood as the totality of the costs of depression. Finally, as TRD is not a diagnosis per se and, case definition depends on the criteria used. Therefore, although the lack of a diagnosis code for TRD is not an inherent limitation of the study, it makes incidence and prevalence estimates published in different databases difficult to compare and interpret (Fife et al., 2018). Having this into account, the operational definition used in this study was therefore chosen because it had showed the ability to nicely discriminate between subjects with and without proxies for TRD (Cepeda et al., 2018).

Notwithstanding these limitations, a major interest of the study is the novelty of its results, not previously available in Spain due to the lack of observational studies related to depression in this specific patient population. This makes comparison of results with populations with similar characteristics and environment difficult, but also enhances their interest. The large sample size and its representativeness of the general population strengthens the results of this study.

In conclusion, TRD in adults in Spain accounts up to 16% of patients with depressive disorder that initiate an AD treatment, and it is associated with 58,5% higher total costs (adjusted). These results, although quantitatively not easily comparable, are in line with studies recently conducted in other geographic areas and suggest that there is unmet medical need that would need to be addressed and would provide useful information when establishing specific strategies and allocating resources that allow comprehensive or multidisciplinary treatment, with the aim of optimizing clinical outcomes patients with TRD.

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Authors contributions

All authors conceived and designed the manuscript; data collection and statistical analysis carried out by ASM, ASN and BH; and interpretation of the data, drafting, review and approval of the submitted manuscript, by all authors.

Disclosures

TH and BH are full-time employees of Janssen-Cilag S.A. ASM and ASN are independent consultants at Atrys Health regarding the development of this study. EV has received grants and served as consultant, advisor or CME speaker unrelated to the present work for the following entities: AB-Biotics, AbbVie, Allergan, Angelini, Dainippon Sumitomo Pharma, Ferrer, Gedeon Richter, GH Research, Janssen, Lundbeck, Otsuka, Sage, Sanofi-Aventis, Sunovion, and Takeda. VP has been a consultant to or has received honoraria or grants from AB-Biotics, AstraZeneca, Bristol-Myers-Squibb, CIBERSAM, FIS- ISCiii, Janssen Cilag, Lundbeck, Otsuka, Servier and Pfizer. MR has received grants or served as advisor or speaker unrelated to the present work for Janssen, Lundbeck and Pfizer.

Data availability

The data that support the findings of this study are available on request from the corresponding author, AS. The data are not publicly available as they contain information that could compromise the privacy of research participants.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jad.2021.08.036.

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