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Research paper

Is clinician impression of depression symptom severity associated with incremental economic burden in privately insured US patients with treatment resistant depression?

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ABSTRACT

Background: Among patients with major depressive disorder (MDD), those with treatment-resistant depression (TRD) have a higher economic burden. However, the healthcare resource utilization (HRU) and costs may vary by severity status in TRD patients. This study quantified the incremental economic burden of severity status in TRD patients.

Methods: In a US database of privately insured employees and dependents (07/01/2009–03/31/2015), a claims-based algorithm identified adult TRD patients who were stratified into mild, moderate, and severe cohorts based on the information in the last observed MDD ICD-9-CM code. HRU and costs of moderate and severe cohorts were compared to those of the mild cohort during the 2-year follow-up after the first antidepressant claim.

Results: Among 6411 TRD patients, 455 (7.1%) were identified as mild, 2153 (33.6%) as moderate, and 1455 (22.7%) as severe. Moderate and severe patients compared to mild had 45% and 150% more inpatient admissions, 65% and 164% more inpatient days, 18% and 54% more emergency department visits and 8% and 10% more outpatient visits per-patient-per-year (PPPY), respectively (all-cause; all $p < 0.05$). Mean all-cause direct total healthcare costs were $12,123, $16,885, and $18,911 PPPY in mild, moderate, and severe patients, respectively. The all-cause total healthcare cost differences adjusted for baseline characteristics amounted to $3455 in moderate and $5150 in severe versus mild patients, respectively (PPPY; all $p < 0.05$).

Limitations: Not all TRD patients had a severity specifier; the severity specifier was not cross-validated against a depression scale.

Conclusions: Increased severity status is associated with incremental economic burden in TRD patients.

1. Introduction

Major Depressive Disorder (MDD) is a disabling chronic mental health illness that is episodic in nature and is estimated to affect over 16 million Americans annually (Anxiety and Depression Association of America; Kupfer, 1991). Debilitating symptoms associated with MDD often include persistent sadness, feelings of despair, and suicidal ideations (Lasch et al., 2012). MDD typically evolves over time and is characterized by phases of response, relapse, remission, and recurrence which collectively pose a substantial economic burden both from a healthcare and a societal perspective (Mrazek et al., 2014; Posternak et al., 2006; Keller, 1999). For example, in the United States (US), societal costs associated with MDD were $188 billion in 2012, which were greater than other highly-burdensome conditions such as cancer ($131 billion) and diabetes ($173 billion) (Mrazek et al., 2014).

MDD may be classified as mild, moderate, or severe depending on the extent of functional impairment associated with the number and types of symptoms (National Collaborating Centre for Mental Health (UK) 2010; Kroenke et al., 2001; Jia and Lubetkin, 2017). Tools commonly used to measure the severity of symptoms include clinician- and patient-filled questionnaires and rating scales (Kroenke et al., 2001; Zimmerman et al., 2013) often based on criteria delineated in the Diagnostic and Statistical Manual of Mental Disorders (DSM) (American Psychiatric Association, 2013), and/or the International Classification of Diseases of Mental and Behavioral Disorders (ICD) (Lasch et al., 2012; World Health Organization (WHO) 1992). Examples

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of common criteria in the DSM and the ICD include persistent loss of interest in previously enjoyable activities, changes in sleep and weight, the ability to concentrate, and suicidal ideations (American Psychiatric Association, 2013; World Health Organization (WHO) 1992). In addition to diagnostic relevance, severity distinctions dictate therapeutic approaches to care as outlined in various treatment guidelines for acute and long-term management of MDD (American Psychiatric Association, 2010; Moller et al., 2012; European Medicines Agency, 2013). Guidelines from the American Psychiatric Association (APA) and the European Psychiatric Association (EPA) recommend antidepressants or psychotherapy, alone or in combination, for patients with mild to moderate symptoms (American Psychiatric Association, 2010; Moller et al., 2012). For patients with severe MDD without psychotic features, pharmacotherapy with antidepressants alone or together with psychotherapy or a somatic therapy, such as electroconvulsive therapy (ECT), are suggested, however, use of psychotherapy alone is discouraged (American Psychiatric Association, 2010). For patients with severe MDD with psychotic features, antidepressants combined with antipsychotic medications, with or without psychotherapy or ECT, are recommended. Common among both APA and EPA guidelines is the tailoring of treatment regimens based on patient response to therapy with modifications as needed if symptoms do not improve, patients are non-adherent, or if adverse events occur (Davidson, 2010). Examples of treatment modifications include altering the dose of the initially prescribed agent, switching medication, or augmentation with either another antidepressant, antipsychotic agent, or adjunctive therapy (American Psychiatric Association, 2010; Moller et al., 2012).

Although antidepressants are considered the gold standard in treating MDD, not all patients respond to treatment. Results from the large-scale, seminal study, Sequenced Treatment Alternatives to Relieve Depression (STAR*D), demonstrated that only a small portion of patients achieve remission during first-line therapy (Sinyor et al., 2010). Approximately 1 in 3 patients with MDD suffer from treatment resistant depression (TRD) (Little, 2009). Although there is no universal definition for TRD (Agency for Healthcare Research and Quality, 2018), it is commonly defined as the failure to respond to at least two different pharmacological regimens of antidepressant therapies that are of adequate dose (i.e., the minimum dose indicated as effective based on treatment guidelines) (American Psychiatric Association, 2010; European Medicines Agency, 2013; Fife et al., 2018) and duration (i.e., duration of continuous therapy based on treatment guidelines) (American Psychiatric Association, 2010) within the current MDD episode (Sinyor et al., 2010; Little, 2009; Agency for Healthcare Research and Quality, 2018; Berlim et al., 2008; Kubitz et al., 2013). Currently, treatment options for patients with TRD are limited. Guidelines from the APA, EPA, and the European Medicines Agency (EMA), recommend combining antidepressants with non-pharmacological procedures such as ECT and other forms of brain stimulation for patients with TRD, however, apart from this, treatment algorithms and modification strategies (e.g., switching, augmentation) for patients with TRD overlap with recommendations for patients with severe MDD (American Psychiatric Association, 2010; Moller et al., 2012; European Medicines Agency, 2013).

Due to failure to respond to therapy, patients with TRD experience considerably higher clinical and economic burdens compared to patients who respond to treatment (Mrazek et al., 2014; Kubitz et al., 2013; Knickman et al., 2016; Lepine et al., 2012; Amos et al., 2018; Gibson et al., 2010). A 2012 claims study found higher rates of hospitalizations and medication usage, either directly or indirectly related to MDD, among MDD patients with TRD relative to MDD patients who were not resistant to treatment (Lepine et al., 2012). Another study found that MDD patients with TRD had 40% higher medical costs compared to MDD patients who were not resistant to treatment (Gibson et al., 2010). A 2010 interview-based study assessed MDD severity and TRD status among 107 eligible MDD patients and found a correlation between cost and both severity and treatment resistance (Fostick et al., 2010). To the best of our knowledge, recent information regarding the real-world distribution, treatment patterns and economic burden of TRD associated with different severity levels (i.e., mild, moderate, severe) remains limited. The present study was conducted to fill this knowledge gap.

2. Methods

2.1. Data source

This study used data from the OptumHealth Care Solutions, Inc. database (July 1, 2009–March 31, 2015) which includes data for over 19 million privately insured individuals covered by 84 self-insured Fortune 500 companies in the US. The database contains information on all medical claims (i.e., payment; International Classification of Diseases, Ninth Revision, Clinical Modification [ICD-9-CM] diagnoses), prescription drug claims (i.e., supply days, National Drug Codes), and eligibility (i.e., age, sex, enrollment dates). Data are deidentified and comply with the patient confidentiality requirements of the Health Insurance Portability and Accountability Act.

2.2. Study design

The study used a retrospective longitudinal cohort design (Amos et al., 2018). The date of the first antidepressant claim on or after January 1, 2010 was defined as the index date. Baseline characteristics were evaluated during the 6 months that preceded the index date (*baseline period*). Study outcomes were assessed during the follow-up period that spanned from the index date until the end of continuous eligibility or data availability (March 31, 2015) for up to two years after the index date (Fig. 1).

2.3. Inclusion criteria

To be included in the study, patients were required to have ≥1 diagnosis for MDD (ICD-9-CM: 296.21, 296.22, 296.23, 296.24 [MDD – single episode], 296.31, 296.32, 296.33, 296.34 [MDD – recurrent episode]) between July 1, 2009 and March 31, 2015 and ≥1 claim for an antidepressant on or after January 1, 2010. Additionally, patients were required to have ≥1 diagnosis for depression during the baseline period up to 2 years following the index date; depression diagnoses were identified using the following ICD-9-CM diagnostic codes: 296.2x (MDD – single episode), 296.3x (MDD – recurrent episode), 300.4x (dysthymic disorder), 311.x (depressive disorder, not elsewhere classified), 309.0x (adjustment disorder with depressed mood), and 309.1x (prolonged depressive reaction). Patients with diagnoses for specific psychiatric comorbidities (psychosis [ICD-9-CM: 298.xx], schizophrenia [ICD-9-CM: 295.xx], bipolar disorder/manic depression [ICD-9-CM: 296.0x, 296.1x, 296.4x, 296.5x, 296.6x, 296.7x, 296.8x], dementia [ICD-9-CM: 290.xx, 294.1x]), Medicare coverage, < 6 months of continuous eligibility before and after the index date, with claims for an antidepressant during the baseline period, and <18 or >64 years old as of the index date were excluded.

A claims-based algorithm was used to select patients likely to have TRD among the MDD patients. MDD patients were considered likely to have TRD if they failed, within two years of the index date, two antidepressant treatment regimens (including augmentation therapy with anticonvulsant, antipsychotic, lithium, psychostimulant, or thyroid hormone medications) of adequate dose and duration (at least six weeks of continuously available medication with gaps that were not longer than 14 days). Adequate dose and duration of an antidepressant treatment regimen were defined using recommendations from the APA (American Psychiatric Association, 2010). Failure of a treatment regimen was defined as a switch of antidepressant (within 180 days), the addition of an antidepressant, or the initiation of an augmentation therapy. The start of the third treatment regimen had to occur more

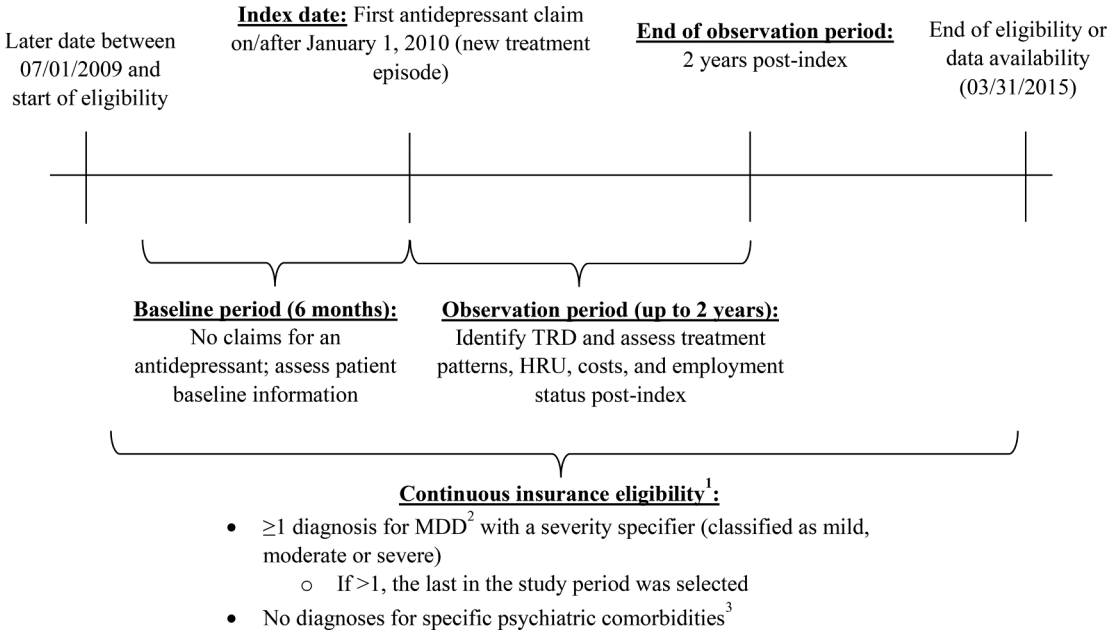

Fig. 1. Study design scheme.
HRU = healthcare resource utilization; MDD = major depressive disorder; TRD = treatment resistant depression.
Notes:
1. Continuous eligibility periods were defined as periods with known health plan coverage, excluding health maintenance organization (HMO) coverage for which complete cost information may not be available.
2. Diagnoses for major depressive disorder include ICD-9-CM: 296.2x (single episode) and 296.3x (recurrent episode). MDD severity was identified using ICD-9-CM codes 296.2x, 296.3x.. Patients were classified as mild (ICD-9-CM 296.21 or 296.31), moderate (ICD-9-CM 296.22 or 296.32) or severe (ICD-9-CM 296.23, 296.24, 296.33 or 296.34).
3. Specific psychiatric comorbidities for exclusion include ICD-9-CM: 298.xx (psychosis), 295.xx (schizophrenia), 296.0x, 296.1x, 296.4x, 296.5x, 296.6x, 296.7x, 296.8x (bipolar disorder/manic depression), 290.xx, and 294.1x (dementia).

than six weeks following the initiation of the first antidepressant treatment.

2.4. Definition of study cohorts

TRD patients were further stratified into three cohorts according to severity status. Severity status was identified based on ICD-9-CM codes; patients were classified as mild (ICD-9-CM: 296.21 or 296.31), moderate (ICD-9-CM: 296.22 or 296.32), or severe (ICD-9-CM: 296.23, 296.24, 296.33 or 296.34). Among patients with multiple severity codes, the last severity code in the study period was selected as this may be the most relevant from a payer's perspective. Patients with an unspecified severity status (ICD-9-CM: 296.20 or 296.30) or without a severity status in the study period were excluded from the analysis.

2.5. Study measures

Baseline characteristics included demographics (i.e., age, sex, year of index date, geographical region, type of healthcare plan, relationship to healthcare plan holder), physical and behavioral comorbidities, baseline treatment patterns, healthcare resource use (HRU), and costs.

Economic outcomes were measured per-patient-per-year (PPPY); costs were reported in 2015 US dollars. Behavioral health-related HRU and medical costs were identified using ICD-9-CM diagnostic codes 290.xx – 319.xx. Psychiatric pharmacy costs included costs of anxiolytics, antidepressants, antipsychotics/antimanics, anticonvulsants, and other mood stabilizers (e.g., lithium). Depression-related HRU and medical costs were identified using the ICD-9-CM diagnostic codes 296.2x, 296.3x, 300.4x, 309.0x, 309.1x, and 311.xx. Suicide-related HRU and medical costs were defined using ICD-9-CM diagnostic codes E95x, and V62.84. Antidepressant pharmacy costs included costs of selective serotonin reuptake inhibitors (SSRIs), norepinephrine-dopamine reuptake inhibitors (NDRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), serotonin modulators (i.e., nefazodone, trazodone, vilazodone, venlafaxine), tricyclics and tetracyclics, norepinephrine-serotonin modulators, monoamine oxidase inhibitors (MAOIs), and other agents (i.e., olanzapine-fluoxetine).

2.6. Statistical analysis

The balance of baseline characteristics was assessed between cohorts using standardized differences (below 10% indicated a balance between the cohorts) (Austin, 2011). Treatment use during the follow-up period was compared using Wilcoxon rank-sums tests for continuous variables and chi-square tests for categorical variables. HRU was compared between cohorts using generalized linear models with a negative binomial distribution based on the results of the overdispersion test; results were reported as incidence rate ratios (IRRs), 95% confidence intervals (CIs) and *p*-values. Mean costs differences between cohorts were estimated using ordinary least squares regressions; corresponding 95% CIs with *p*-values were obtained using a non-parametric bootstrap procedure ($N = 499$ replications). Models were adjusted for baseline characteristics including age, sex, year of index date, geographical region, type of healthcare plan, relationship to healthcare plan holder and Quan-Charlson comorbidity index (Quan-CCI) (Quan et al., 2005).

3. Results

3.1. Baseline characteristics

Among 39,479 medication-treated MDD patients, using the claims-based algorithm, 6411 (16%) were identified to likely have TRD (Amos et al., 2018). Of these 6411 patients, 455 (7.1%) were mild, 2153 (33.6%) moderate, and 1455 (22.7%) severe; the remaining either

had an unspecified severity status or no MDD diagnosis during the baseline and follow-up periods and thus were excluded from the study. The mean age was 39.1, 40.4 and 41.1 years in mild, moderate, and severe patients, respectively. Across all three cohorts, patients were predominantly female (63.4–65.1%). A higher proportion of patients in the moderate and severe cohorts used psychiatric medications during the baseline period relative to patients in the mild cohort: 39.1% (severe) and 39.5% (moderate), versus 33.8% (mild). The mean all-cause medical and pharmacy costs during the baseline period were higher among patients in the severe cohort compared to patients in the moderate and mild cohorts (Table 1). The mean duration of the observation period was 21.4, 20.9, and 20.8 months for the mild, moderate, and severe cohorts, respectively.

3.2. Treatment patterns

During the follow-up period, antidepressant use was similar across all three cohorts (Fig. 2A). The three most commonly used antidepressants were SSRIs (90.1% [mild], 86.6% [moderate], 87.2% [severe]), NDRIs (56.0% [mild], 54.7% [moderate], 51.1% [severe]), and SNRIs (47.0% [mild], 48.4% [moderate], 50.3% [severe]). The mean duration of the antidepressant therapy was 229.1 days, 240.4 days, and 229.2 days in mild, moderate and severe patients, respectively. Higher proportions of patients in the severe cohort relative to patients in the mild cohort appeared to use adjunctive medication (Fig. 2B). Specifically, 73.9% versus 65.3% of patients used anxiolytics, 39.2% versus 28.6% used anticonvulsants/mood stabilizers, and 42.5% versus 24.8% used antipsychotics, in severe and mild cohorts, respectively. Non-pharmacological therapy was similar across the cohorts, with 40.2%, 46.6% and 43.8% of patients using psychotherapy in the mild, moderate and severe cohorts, respectively.

3.3. HRU and costs

Patients in the moderate and severe cohorts had significantly higher HRU during the follow-up period relative to patients in the mild cohort. In terms of all-cause adjusted HRU differences, patients with moderate and severe status had 45% and 150% more inpatient admissions, 65% and 164% more inpatient days, 18% and 54% more emergency department (ED) visits, and 8% and 10% more outpatient visits PPPY, respectively compared to patients whose status was mild (all p-values < 0.05; Fig. 3). The magnitude of adjusted differences in behavioral health-related HRU among severe and mild patients was even greater. Specifically, patients in the severe cohort had 274% more inpatient admissions, 249% more inpatient days, 102% more ED visits PPPY versus patients in the mild cohort (all p-values < 0.001; Fig. 4). Similar

Table 1
Baseline[1] characteristics stratified by severity status[2].

	Mild to moderate classification			Mild to severe classification	
	Mild $N = 455$	Moderate $N = 2153$	Std. diff.[3]%	Severe $N = 1455$	Std. diff.[3]%
Observation period (months), mean ± SD [median]	21.4 ± 4.6 [24.0]	20.9 ± 5.0 [24.0]	10.0%	20.8 ± 5.1 [24.0]	12.0%
Age at index date (years), mean ± SD [median]	39.1 ± 13.3 [40.9]	40.4 ± 13.2 [41.4]	10.5%	41.1 ± 13.4 [42.9]	15.5%
Age Categories, *n* (%)					
18–24	108 (23.7)	413 (19.2)	11.1%	268 (18.4)	13.1%
25–34	73 (16.0)	340 (15.8)	0.7%	227 (15.6)	1.2%
35–44	96 (21.1)	496 (23.0)	4.7%	301 (20.7)	1.0%
45–54	121 (26.6)	549 (25.5)	2.5%	404 (27.8)	2.6%
55–64	57 (12.5)	355 (16.5)	11.3%	255 (17.5)	14.0%
Female, *n* (%)	296 (65.1)	1364 (63.4)	3.5%	945 (64.9)	0.2%
Year of index date[4], *n* (%)					
2010	174 (38.2)	813 (37.8)	1.0%	560 (38.5)	0.5%
2011	107 (23.5)	456 (21.2)	5.6%	322 (22.1)	3.3%
2012	82 (18.0)	418 (19.4)	3.6%	271 (18.6)	1.6%
2013	68 (14.9)	348 (16.2)	3.4%	218 (15.0)	0.1%
2014	24 (5.3)	118 (5.5)	0.9%	84 (5.8)	2.2%
Geographical region, *n* (%)[5]					
Northeast	89 (19.6)	518 (24.1)	10.9%	314 (21.6)	5.0%
Midwest	137 (30.1)	573 (26.6)	7.8%	316 (21.7)	19.2%
South	141 (31.0)	682 (31.7)	1.5%	587 (40.3)	19.6%
West	83 (18.2)	355 (16.5)	4.6%	230 (15.8)	6.5%
Unknown	5 (1.1)	25 (1.2)	0.6%	8 (0.5)	6.1%
Type of healthcare plan, *n* (%)					
Preferred provider organization	364 (80.0)	1622 (75.3)	11.2%	1096 (75.3)	11.2%
Point of service plan	48 (10.5)	302 (14.0)	10.6%	217 (14.9)	13.1%
Indemnity plan (i.e., fee-for-service)	33 (7.3)	189 (8.8)	5.6%	114 (7.8)	2.2%
Other healthcare plan[6]	10 (2.2)	40 (1.9)	2.4%	28 (1.9)	1.9%
Quan-CCI, mean ± SD [median][7]	0.2 ± 0.7 [0.0]	0.3 ± 0.8 [0.0]	12.1%	0.3 ± 0.9 [0.0]	14.2%
Number of unique behavioral health diagnoses, mean ± SD [median]	1.0 ± 1.2 [1.0]	1.0 ± 1.2 [1.0]	1.4%	1.2 ± 1.3 [1.0]	12.0%
Other psychiatric medication use[8], *n* (%)	154 (33.8)	851 (39.5)	11.8%	569 (39.1)	10.9%
Top 5 most frequent physical comorbidities, *n* (%)[9]					
Hypertension	44 (9.7)	258 (12.0)	7.4%	212 (14.6)	15.1%
Hypothyroidism	28 (6.2)	123 (5.7)	1.9%	85 (5.8)	1.3%
Chronic pulmonary disease	16 (3.5)	125 (5.8)	10.9%	102 (7.0)	15.7%
Diabetes	22 (4.8)	124 (5.8)	4.1%	84 (5.8)	4.2%
Other neurological	9 (2.0)	65 (3.0)	6.7%	72 (4.9)	16.3%
Top 5 most frequent behavioral comorbidities, *n* (%)[10]					
Depression[11]	181 (39.8)	860 (39.9)	0.3%	616 (42.3)	5.2%
Anxiety disorders	87 (19.1)	402 (18.7)	1.1%	296 (20.3)	3.1%
Trauma- and stressor-related disorders	57 (12.5)	225 (10.5)	6.5%	139 (9.6)	9.5%
Sleep-wake disorders	38 (8.4)	156 (7.2)	4.1%	130 (8.9)	2.1%
Substance-related and addictive disorders	15 (3.3)	105 (4.9)	8.0%	113 (7.8)	19.6%

(*continued on next page*)

Table 1 (*continued*)

	Mild to moderate classification			Mild to severe classification	
	Mild *N* = 455	Moderate *N* = 2153	Std. diff.[3]%	Severe *N* = 1455	Std. diff.[3]%
Baseline costs and resource use					
Had ≥1 healthcare visit/service, *n* (%)					
Inpatient	38 (8.4)	226 (10.5)	7.3%	243 (16.7)	25.4%
ED	95 (20.9)	543 (25.2)	10.3%	424 (29.1)	19.2%
Outpatient	403 (88.6)	1948 (90.5)	6.2%	1327 (91.2)	8.7%
Other	153 (33.6)	742 (34.5)	1.8%	530 (36.4)	5.9%
Total healthcare costs (US $2015), mean ± SD [median]	9917 ± 36,717 [2156]	11,818 ± 35,186 [2540]	5.3%	18,015 ± 78,815 [3232]	13.2%
Pharmacy costs	1508 ± 4832 [178]	1528 ± 5912 [256]	0.4%	1546 ± 4453 [264]	0.8%
Medical costs	8410 ± 35,890 [1452]	10,290 ± 34,281 [1616]	5.4%	16,469 ± 77,535 [2037]	13.3%

ED = emergency department; Quan-CCI = Quan-Charlson comorbidity index; SD = standard deviation; std. dif. = standardized difference; US = United States.

Notes:

[1] The baseline period was defined as the 6-month period prior to the index date.

[2] MDD severity was identified using ICD-9-CM codes 296.2x, 296.3x.. Patients were classified as mild (ICD-9-CM 296.21 or 296.31), moderate (ICD-9-CM 296.22 or 296.32) or severe (ICD-9-CM 296.23, 296.24, 296.33 or 296.34).

[3] For continuous variables, the standardized difference is calculated by dividing the absolute difference in means of the mild cohort and the moderate and severe cohorts by the pooled standard deviation of both groups. The pooled standard deviation is the square root of the average of the squared standard deviations. For dichotomous variables, the standardized difference is calculated using the following equation where *P* is the respective proportion of participants in each group: (Pmoderate or severe-Pmild)/√[(Pmoderate or severe(1-Pmoderate or severe) + Pmild(1 − Pmild))/2].

[4] The index date was defined as the date of the first prescription fill for an antidepressant.

[5] Based on U.S. census regions (http://www2.census.gov/geo/pdfs/maps-data/maps/reference/us_regdiv.pdf).

[6] Other healthcare plans include locked-in and independent practice association health insurance plan types.

[7] Quan H, Sundararajan V, Halfon P et al. Coding Algorithms for Defining Comorbidities in ICD-9-CM and ICD-10 Administrative Data. Medical Care 2005;43:1130–1139.

[8] Includes anxiolytics, anticonvulsants/mood stabilizers, antipsychotics, psychostimulants, thyroid hormone (T3), and lithium. Agents were grouped according to the generic name.

[9] Elixhauser A, Steiner C, Kruzikas. D. HCUP Methods Series Report # 2004-1. ONLINE February 6, 2004. U.S. Agency for Healthcare Research and Quality. [Internet]. Comorbidity Software Documentation. Rockville, MD, USA; 2004 [cited 2013]. p. 12–5. Available from: http://www.hcup-us.ahrq.gov/reports/ComorbiditySoftwareDocumentationFinal.pdf.

[10] American Psychiatric Association. Diagnostic and statistical manual of mental disorders: DSM-V. Amer Psychiatric Pub Inc; 2013.

[11] Depression diagnoses included the following diagnoses ICD-9-CM: 296.2x (MDD – single episode), 296.3x (MDD - recurrent episode), 300.4x (dysthymic disorder), 309.0x (adjustment disorder with depressed mood), 309.1x (prolonged depressive reaction), and 311.x (depressive disorder, not elsewhere classified). Patients were required to have ≥ 1 depression diagnosis in either the baseline or observation period.

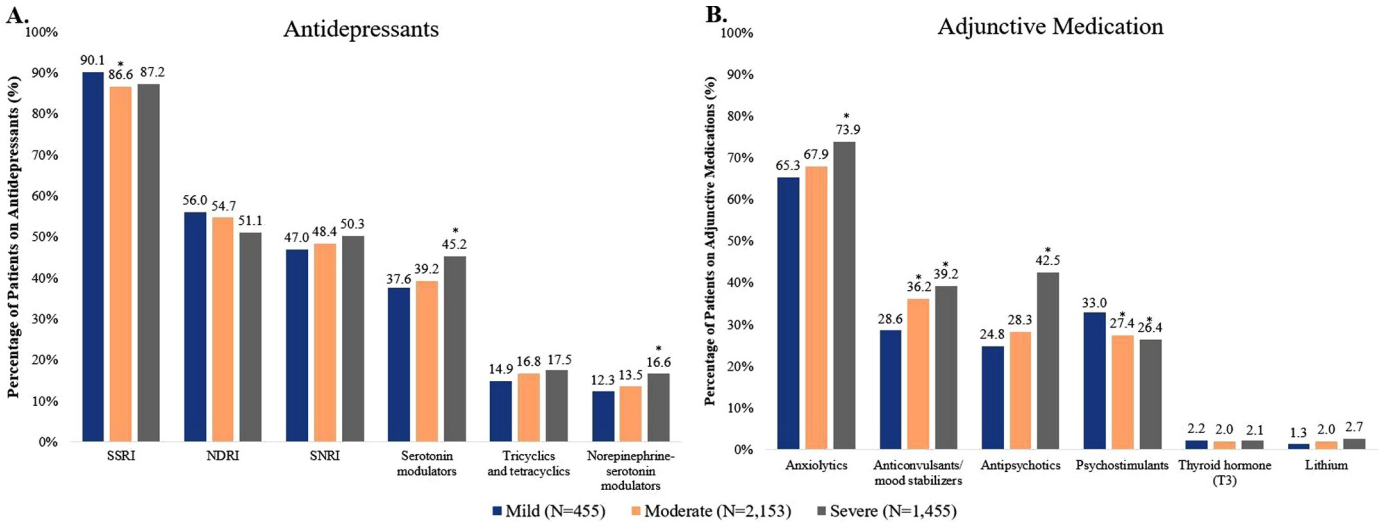

Fig. 2. Treatment use during the observation period, stratified by severity status[1].

APs = antipsychotics; NDRIs = norepinephrine-dopamine reuptake inhibitors; SNRIs = serotonin-norepinephrine reuptake inhibitors; SSRIs = selective serotonin reuptake inhibitors.

Notes:

*Significant at the 5% level, relative to the mild cohort.

1. MDD severity was identified using ICD-9-CM codes 296.2x, 296.3x.. Patients were classified as mild (ICD-9-CM 296.21 or 296.31), moderate (ICD-9-CM 296.22 or 296.32) or severe (ICD-9-CM 296.23, 296.24, 296.33 or 296.34).

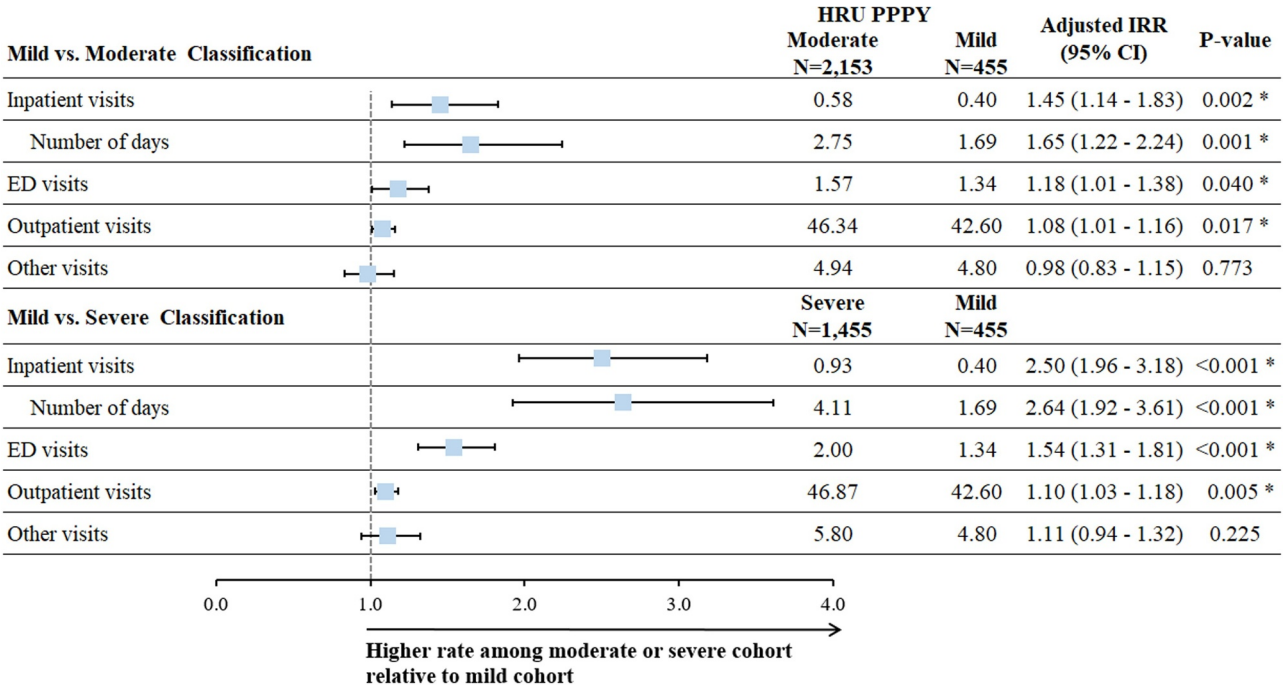

Fig. 3. All-Cause HRU Per-Patient-Per-Year during the observation period[1].
CI = confidence interval; ED = emergency department; HRU = healthcare resource utilization; IRR = incidence rate ratio; PPPY = per-patient-per-year.
Notes:
*Significant at the 5% level.
1. Adjusted for baseline demographics.

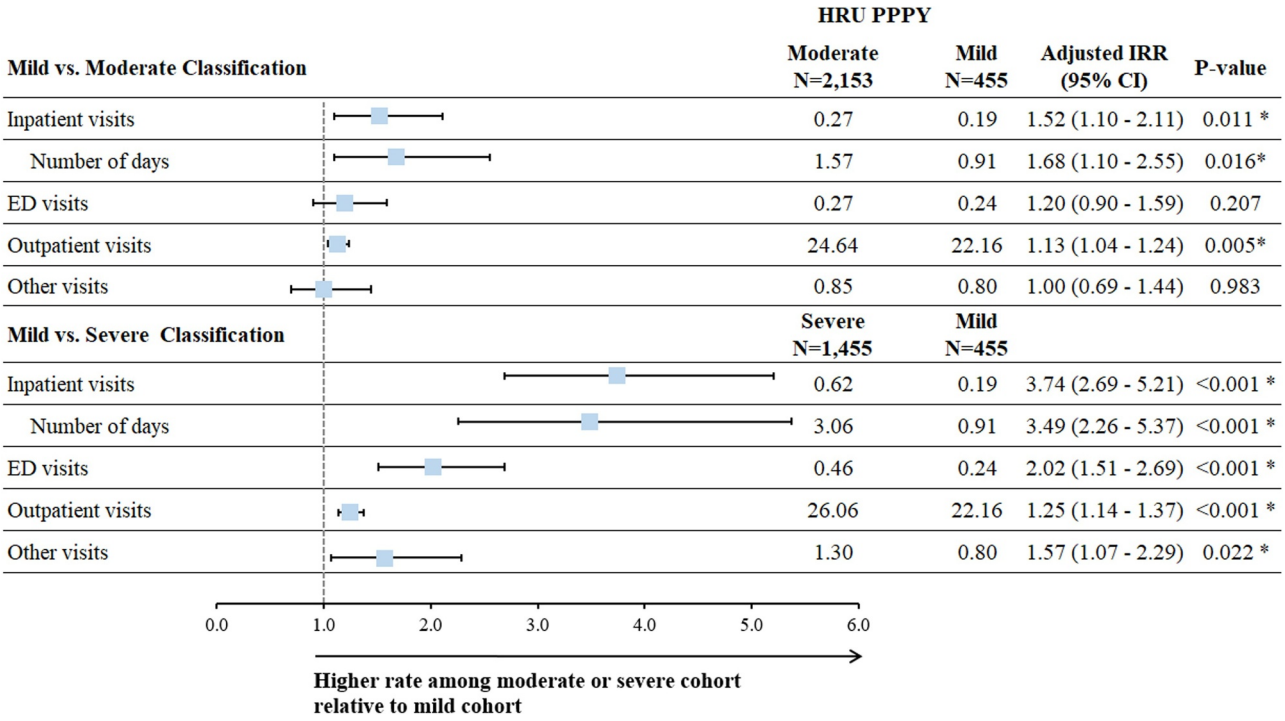

Fig. 4. Behavioral Health-Related[1] HRU Per-Patient-Per-Year during the observation period[2].
CI = confidence interval; ED = emergency department; HRU = healthcare utilization; IRR = incidence rate ratio; PPPY = per-patient-per-year.
Notes:
*Significant at the 5% level.
1. Behavioral health-related HRU were identified using the following ICD-9 CM diagnostic codes: 290.xx – 319.xx.
2. Adjusted for baseline demographics.

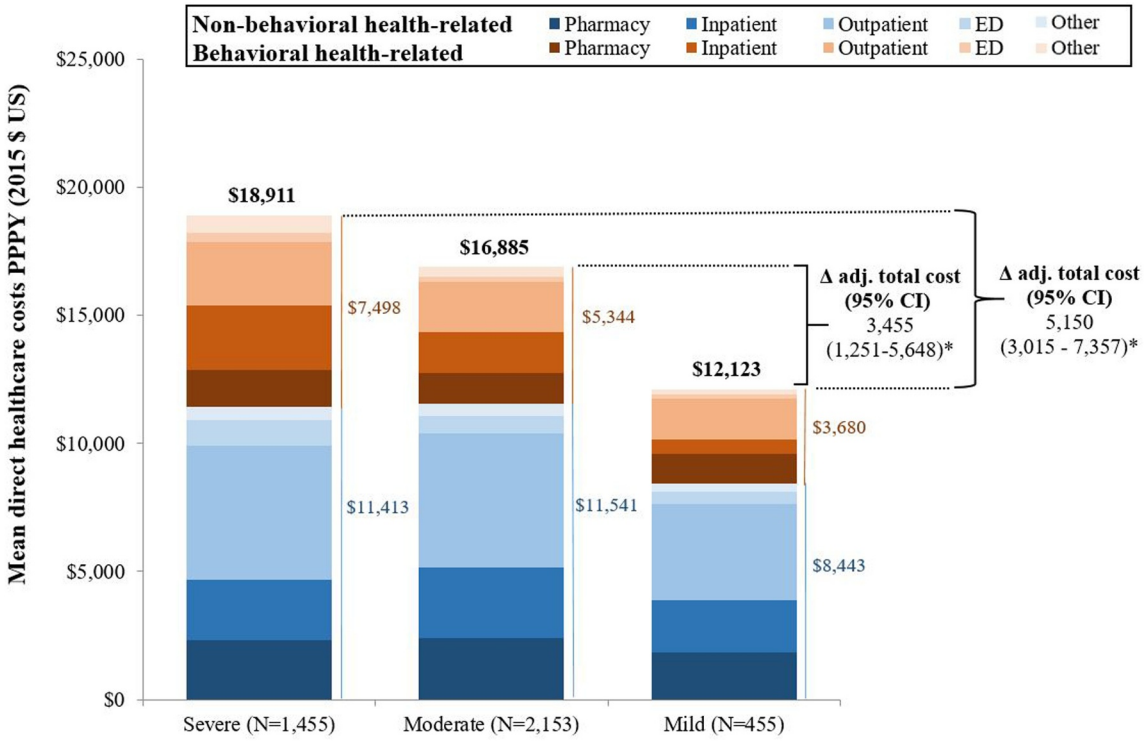

Fig. 5. Healthcare costs Per-Patient-Per-Year during the observation period[1].
CI = confidence interval; ED = emergency department; PPPY = per-patient-per-year; US = United States.
Notes:
*Significant at the 5% level.
1. Adjusted for baseline demographics.

magnitudes of differences were observed between severe and mild cohorts in depression-related HRU. The mean total all-cause healthcare costs were $12,123, $16,885, and $18,911 PPPY in the mild, moderate, and severe cohorts, respectively. After adjusting for baseline characteristics, the incremental HRU among patients in the moderate and severe cohorts compared to mild resulted in all-cause incremental total health care costs of $3455 (moderate vs. mild) and $5150 (severe vs. mild) PPPY (all p-values < 0.001). Incremental all-cause inpatient costs of $1490 (moderate vs. mild) and $1814 (severe vs. mild) PPPY (all p-values < 0.05) and outpatient costs of $1242 (moderate vs. mild) and $1750 (severe vs. mild) PPPY (all p-values < 0.05) were the main drivers of the incremental all-cause total healthcare costs between the cohorts (Fig. 5).

4. Discussion

Results from this retrospective longitudinal cohort study demonstrated that patients with TRD and moderate and severe status incurred greater HRU and costs compared to patients with TRD and mild severity status. Differences in all-cause and behavioral health-related HRU observed in moderate and severe statuses relative to mild were particularly pronounced with regard to inpatient admissions and inpatient days. Incremental all-cause total healthcare costs between patients with moderate and severe status relative to patients with mild status were driven by inpatient and outpatient costs, and differences were not exclusive to behavioral health-related resource utilization. This finding may explain the gap between all-cause and behavioral health-related costs, consistent with findings in Kessler et al. which showed that poor behavioral health has a downstream impact on patients' overall physical health (Kessler, 2012). In the current study, as severity increased, the incremental behavioral health-related costs comprised a larger proportion of the incremental all-cause cost difference: 47% in moderate versus mild patients, and 74% in severe versus mild patients. The increasing proportion of all-cause costs that are behavioral health-related suggests that as severity increases, costs of specialized care for behavioral health grow to dominate costs of care for comorbid physical conditions.

Despite the differences in HRU and medical costs, use of antidepressants, predominantly SSRIs, served as the mainstay therapy, and antidepressant pharmacy costs were similar across the severity cohorts in TRD patients. This finding may reflect clinician perception of similarity regarding the efficacy across different antidepressants. Although different classes of antidepressants have been recommended, either in monotherapy or combination therapy with augmentation and switching as needed, a considerable portion of patients still do not achieve remission, particularly those that fail to respond to the first and second lines of therapy (Fournier et al., 2010). For example, in the STAR*D study, no specific medication was found superior among patients who were resistant following one or more lines of therapy (Gaynes et al., 2009).

In contrast to antidepressants, differences among adjunctive treatments in this analysis were more substantial across the different severity cohorts, which aligns with findings from prior studies (Gaynes et al., 2009; Johnston et al., 2018). In the present study, the use of psychostimulants decreased with increasing severity. Although some studies suggested the adjunctive use of psychostimulants for patients with increased symptom severity (Pary et al., 2015; Huang et al., 2008; Orr and Taylor, 2007), there is a relative paucity of evidence in this area. Clinically, psychostimulants can provide a rapid and dramatic amelioration of depressive symptoms but their use for the treatment of depression is a growing concern due to a short-lived relief as well as a lack of the understanding of long-term benefits and risks (Malhi et al., 2016). Results of this study suggest that unlike augmentation with other classes of medications such as anxiolytics, anticonvulsants/mood

stabilizers and antipsychotics, the adjunctive use of psychostimulants was not a common strategy to address depression severity in real-world patients.

The increased cost burden associated with TRD relative to patients with or without MDD is consistently supported by earlier studies (Kubitz et al., 2013; Lepine et al., 2012; Amos et al., 2018; Corey-Lisle et al., 2002; Russell et al., 2004; Greenberg et al., 2004). For example, results from two separate studies reported that the mean annual costs for patients who were likely to have TRD were approximately twice as high as the costs for patients unlikely to have TRD ($10,954 versus $5025 (Corey-Lisle et al., 2002); $14,490 versus $6665 (Greenberg et al., 2004)) while in another study the costs for patients with TRD were over six times as high as the costs for patients who were not treatment resistant ($42,344 versus $6512 (Crown et al., 2002)). However, most studies evaluating the costs of TRD relative to non-TRD MDD or non-MDD have not stratified patients according to severity status. Although the number of studies that have examined TRD by severity status are limited, the findings reported in the present study regarding the incremental burden of TRD with severity status align with prior studies (Fostick et al., 2010; Birnbaum et al., 2010). A 2010 study conducted by Fostick et al. assessed severity status stratifying patients based on the presence of treatment resistance, and found that higher costs correlated with increased severity and presence of treatment resistance (Fostick et al., 2010). Another study conducted in 2010 by Birnbaum et al. found that costs for patients with severe MDD were generally at least twice those for patients with mild MDD, and were similar to costs for patients with moderate MDD, however, patients with TRD were not evaluated (Birnbaum et al., 2010). In light of the limited recent real world examination of the economic burden associated with TRD by severity status, the present study offers valuable insight. Furthermore, changes in treatment strategies to manage depression in real-world practice, as well as ongoing updates to clinical guidelines, highlight the need for more up-to-date information that this study provides regarding the treatment and cost patterns among these patient populations.

This study used ICD severity specifiers to quantify the treatment patterns and the economic burden associated with severity status in TRD patients. However, severity measures, such as the Patient Health Questionnaire (PHQ-9), a 9-question tool administered to patients to determine the presence and severity of symptoms, are emerging as useful instruments to assess severity. The value of PHQ-9 is its ability to identify patients across a range of clinical settings with varying severity levels that would not otherwise be identified for inclusion in research (Gilbody et al., 2007; Diez-Quevedo et al., 2001; Lowe et al., 2004; Griffith et al., 2015). Another measure based on a standard self-rated depression scale is the Quick Inventory of Depressive Symptomatology Self-Report (QIDS-SR). Specifically, in the study of Birnbaum et al. conducted among a sample of MDD patients, MDD severity (as measured by the QIDS-SR) was significantly associated with increased resource usage and costs (Birnbaum et al., 2010). However, unlike the current study, Birnbaum et al. suggested that the use of antidepressants increased with severity. This discrepancy could be explained by the differences in MDD and TRD populations as well as the time period evaluated as the survey period in the prior study was February 2001–December 2002 (Birnbaum et al., 2010). Thus changes in treatment availability, such as the approval of atypical antipsychotic agents and other adjunctive therapies, since this study was conducted could contribute to the treatment pattern differences observed. In addition, the distribution of patients across severity categories also varied. While the 2010 study by Birnbaum and colleagues had 13.8%, 38.5%, and 47.7% of patients classified as mild, moderate, and severe, respectively (Birnbaum et al., 2010), in the present study, more patients were diagnosed as “moderate” (33.6%) relative to “mild” (7.1%) and “severe” (22.7%). While part of the difference may be explained by differences in populations (TRD vs. MDD) or methods of severity measurement, one or more of the severity cohorts may be underrepresented in the current sample given that 36.6% had an unspecified or missing severity classification.

Future studies are needed to help improve our understanding of the relationship between the diagnostic code severity specifiers and well-accepted severity measures (i.e., the Hamilton Depression Rating Scale (Worboys, 2013), the PHQ (Kroenke et al., 2001) the Beck Depression Inventory (Beck et al., 1961), and QIDS-SR). Additional studies that can offer real-world evidence regarding the economic, health-related quality of life, and clinical differences across different severity levels in TRD patients have the potential to help direct interventions aimed at improving care and reducing the economic and societal burden. Specifically, studies assessing the predictive value of severity specifiers among TRD patients and the implications of various treatment strategies (including augmentation therapy), patterns of resource use or future costs could be of interest and will have a practical value for health care decision makers.

Despite recommendations in the guidelines from the APA, EPA and EMA, it is not clear how widely used measurement-based care is in clinical practice. Findings from this study demonstrate that real-world outcomes of TRD patients are associated with the diagnostic code severity specifier, confirming that this measure of severity is consistently used. Moreover, unlike other severity measures, the diagnostic code severity specifier is also widely available in secondary data. It contains valuable information on patient severity for researchers and health care decision makers, which is essential to payers in order to ensure appropriate use of emerging therapies targeting depression (i.e., ICD-9-CM MDD codes are used to support the medical necessity for transcranial magnetic stimulation, recommended for patients with TRD) (Institute for Clinical and Economic Review (ICER) 2012). It will be important to consider how modifications to ICD, such as transitions from ICD-9-CM to ICD-10-CM and the newly released ICD-11, may affect indicators of MDD severity.

5. Limitations

Results of this study should be interpreted within the context of important limitations. First, the algorithm used to identify patients with TRD and further stratify by severity relied exclusively on claims information rather than clinical evidence. While a common definition of TRD (i.e., failure of two antidepressant treatment regimens) was chosen, there is no universal definition of TRD. Second, while all patients had a depression diagnosis during the baseline and observation periods and a diagnosis of MDD between July 1, 2009 and March 31, 2015, not all patients had an MDD diagnosis during the baseline and observation periods. Additionally, not all patients had an MDD ICD-9-CM code explicitly classifying them as mild, moderate, or severe during the baseline and observation periods, therefore, the results may not capture the true economic burden across severities for patients with TRD. Third, the severity specifier could not be cross-validated with a depression scale commonly used in clinical trials such as the Montgomery–Asberg Depression Scale. Fourth, this study defined TRD as a minimum of two treatment failures within two years of the first antidepressant claim, and patients who showed evidence of treatment resistance after a period of time exceeding two years were not captured. Fifth, although multivariable adjustments were used in an effort to help mitigate potential confounding, the comparisons made in this study may be subject to residual confounding resulting from unmeasured factors. In particular, an unmeasured correlate of depression severity could be driving the outcomes examined, hence results should be interpreted as associations rather than causal effects. Sixth, as with all claims-based studies, there are inherent limitations due to coding inaccuracies and potential omission. Lastly, this study focused on employees and their dependents, who were commercially insured, therefore, the findings might not be generalizable to the overarching patient population with TRD insured by Medicaid, Medicare, or the Veteran's Health Administration or the uninsured population.

6. Conclusions

Results of this study demonstrated that increased severity was associated with incremental economic burden among patients with TRD. In light of the similarities in antidepressant treatment patterns across the severity status, the findings of this study highlight the need for novel treatments for patients with moderate-to-severe symptoms.

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Data statement

The claims database (OptumHealth Care Solutions, Inc.) is proprietary, provided by a third-party vendor.

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CRediT authorship contribution statement

Dominic Pilon: Conceptualization, Data curation, Writing - original draft. **John J. Sheehan:** Conceptualization, Data curation, Writing - original draft. **Holly Szukis:** Conceptualization, Data curation, Writing - original draft. **Laura Morrison:** Conceptualization, Data curation, Writing - original draft. **Maryia Zhdanava:** Conceptualization, Data curation, Writing - original draft. **Patrick Lefebvre:** Conceptualization, Data curation, Writing - original draft. **Kruti Joshi:** Conceptualization, Data curation, Writing - original draft.

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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.2019.04.100.

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