

Prospective Service Use and Health Care Costs of Medicaid Beneficiaries with Treatment-Resistant Depression

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Abstract

BACKGROUND: Although the clinical and health economic characteristics of commercially insured adults with treatment-resistant depression (TRD) have been well characterized, little is known about TRD in the Medicaid population.

OBJECTIVE: To describe clinical and health economic characteristics of adult Medicaid beneficiaries with TRD.

METHODS: Retrospective longitudinal cohort analyses were performed with Truven Health MarketScan Medicaid Database (2008-2014), focusing on adults with major depressive disorder (MDD) following an index antidepressant prescription. TRD was operationally defined as starting a third treatment regimen after 2 adequate regimens of antidepressants or augmentation therapy within 12 months of an index antidepressant prescription. Among patients with and without TRD, percentages with inpatient admissions, emergency department visits, and outpatient visits (all cause, mental health related, and depression related) were determined. Logistic regression models were used to examine associations between TRD status and use of

inpatient, outpatient, and emergency services. Separate analyses were performed for the first and second year after the index antidepressant prescription.

RESULTS: Approximately one quarter (25.9%) of pharmacologically treated adults with MDD met criteria for TRD. In relation to MDD patients without TRD, patients with TRD were proportionately more likely to be older, male, and white. Compared with MDD patients without TRD, patients with TRD were also significantly more likely to receive inpatient care for any cause (31.0% vs. 21.6%; $P < 0.001$), a mental health-related reason (12.7% vs. 7.6%; $P < 0.001$), or depression (10.1% vs. 6.1%; $P < 0.001$) during the first year following their index antidepressant prescription. Over the second follow-up year, patients with TRD continued to be more likely than patients without TRD to receive inpatient care for any reason (26.7% vs. 19.5%; $P < 0.001$), a mental health-related reason (5.6% vs. 2.7%; $P < 0.001$), and depression (3.7% vs. 1.7%; $P < 0.001$). The mean health care costs of patients with TRD were also significantly higher than the costs of patients without TRD during the first year (\$18,982 [SD \pm \$35,276] vs. \$11,642 [SD \pm \$29,203]) and second year (\$17,997 [SD \pm \$34,146] vs. \$10,325 [SD \pm \$28,224]) following the index antidepressant prescription.

CONCLUSIONS: In the U.S. Medicaid program, adults with TRD have substantially and persistently higher health care costs than their counterparts who do not meet criteria for TRD. The service use and health care cost patterns of patients with TRD in the Medicaid program highlight challenges of developing interventions and care coordination strategies to meet their complex clinical needs.

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Study concept and design were contributed by Amos, Olfson, Marcus, Benson, and McRae. Data analysis was performed by all the authors. The manuscript was primarily written by Olfson, along with the other authors, and revised by McRae, Benson, Amos, Marcus, and Olfson.

A different data cut from the same database was presented previously at the 2017 Annual Meeting of the International Society for Pharmacoeconomics and Outcomes Research; May 20-24, 2017; Boston, MA; and the 2017 AcademyHealth Annual Research Meeting; June 25-27, 2017; New Orleans, LA.

What is already known about this subject

- Treatment-resistant depression (TRD) is major depressive disorder (MDD) in patients who have not responded adequately to at least 2 different antidepressants of adequate dose and duration.

Commercially insured patients with TRD have health care costs that are roughly twice as high as those with treatment-responsive depression.

What this study adds

• Within the U.S. Medicaid program, patients with MDD who have evidence of TRD have substantially higher health care costs than their counterparts who do not meet criteria for TRD.

• Health care cost differences between depressed patients with TRD and those without TRD persist during the first year following the year in which TRD developed.

• The persistence of health care cost differences over the year following development of TRD suggests that depression treatment resistance is often an enduring clinical characteristic.

Major depressive disorder (MDD) is one of the most common, disabling, and costly health conditions in the United States.¹⁻³ Unfortunately, approximately half of depressed patients do not respond to an adequate trial of an antidepressant medication, and a significant proportion of these patients do not respond to multiple antidepressant treatments.⁴ Treatment-resistant depression (TRD), which is often defined as MDD that does not respond to at least 2 adequate treatments in an MDD episode,⁵ is common in clinical practice. Depending on the patient population and specific TRD definition, TRD has been reported to occur in 7%-35% of adults who are treated for depression.⁶⁻¹⁰

Adults with TRD bear a heavy burden of disease. According to recent literature reviews, adults with TRD as compared with those with treatment-responsive depression tend to have longer episodes of depression, more previous psychiatric hospital admissions, higher symptom severity, and a greater risk of comorbid anxiety disorders.^{11,12} The prevalence of suicidal ideation in TRD (15%) is over twice as high as its prevalence in treatment-responsive depression (6%).¹³ In addition, adults with TRD report significantly poorer quality of life and an earlier age of onset of depression than patients with treatment-responsive depression.^{13,14}

Because of their complex health care needs, patients with TRD place heavy demands on health care resources. According to 1 analysis, for example, the costs of TRD patients for office visits to psychiatrists and for emergency department visits were each over 5 times greater than their respective costs for patients with non-TRD depression.⁸ With 1 exception,¹⁵ the overall health care costs of TRD have been reported to be nearly twice or more than twice as high as those with treatment-responsive depression.^{6-8,16,17} Our understanding of the clinical characteristics and economic implications of TRD has been built up from clinical data and from claims records of commercially insured patients.^{6-8,11,14,17,18} Much less is known about the demographic and clinical characteristics, predictors, and health care economic burden of TRD among adult Medicaid beneficiaries. Because Medicaid is the largest single source of financing for mental health services in the United States,¹⁹

Medicaid patients with TRD represent a large, impaired, and expensive-to-manage, but poorly characterized, patient group.

In light of recent advances in the treatment of TRD and the recent expansion of Medicaid under the Affordable Care Act,²⁰ it is important to increase our understanding of readily identifiable demographic and clinical risk factors for TRD and its health care economic burden in the Medicaid population. In an effort to help fill these gaps in our knowledge of TRD, we identified predictors and health care cost consequences of TRD among nonelderly Medicaid beneficiaries. To assess the persistence of service demands, we also compared patients with and without TRD with respect to service use and health care costs during the first and second years following initiation of treatment for a depressive episode.

Methods

Data Source

The analyses used Truven Health Analytics MarketScan Medicaid Database between the dates of January 1, 2008, and July 31, 2014. This database includes person-specific demographic, enrollment, expenditure, and clinical utilization information from approximately 8-12 million Medicaid enrollees within each year from multiple states. The clinical utilization data includes inpatient, emergency department, outpatient, and prescription data. Because the data were stripped of personal identifiers, this project was exempted from human subjects review by the institutional review board of the New York State Psychiatric Institute.

Sample Selection

This was an observational study with a retrospective cohort design that used administrative claims data. The initial inclusion criteria captured Medicaid adult patients who were aged 18-64 years and had continuous pharmacy benefit and mental health/substance use coverage for 12 months before and 24 months after starting an antidepressant prescription that occurred after ≥ 6 months without an antidepressant prescription claim. We refer to this antidepressant prescription, which marks the beginning of the depression treatment episode used to define either TRD or non-TRD, as the index antidepressant prescription. In order to help limit the cohort to patients receiving antidepressants for the treatment of depression, patients were required to have ≥ 1 diagnosis for depression (*International Classification of Diseases, Ninth Revision, Clinical Modification* [ICD-9-CM] codes 296.2, 296.3, 300.4, 311, 309.0, and 309.1) within 30 days before or after the index antidepressant prescription fill. In addition, patients were required to have ≥ 1 diagnosis of MDD (ICD-9-CM codes 296.2 and 296.3) during the 12 months before or after the index antidepressant fill. Patients with ≥ 1 claim for schizophrenia (ICD-9-CM code 295.xx), psychosis (298.xx), bipolar disorder/manic depression (296.0x-296.1x, 296.4x-296.8x), or dementia (290.xx

and 294.1x) were excluded from the cohort. Patients with Medicare coverage during the 12 months before or 24 months after the index antidepressant fill were also excluded from the cohort ([Appendix A](#), available in online article).

Study Design and Study Period

This analysis characterized patients with MDD during 3 different time periods in relation to the initiation of their index treatment episode: (1) a 12-month baseline period before antidepressant treatment initiation, (2) a 12-month period following antidepressant initiation, and (3) a 12-month extension period following period 2. In the first period, demographic and clinical characteristics, described in the following sections, were collected during the 12-month baseline period immediately before the date of the index antidepressant prescription.

This analysis focused on identifying characteristics during the 12-month period before the depression treatment episode that predict subsequent development of TRD. The second 12-month period following antidepressant initiation was the incidence observation used to identify patients with MDD who met the criteria for TRD. In this period, we compared the service utilization pattern and direct health care costs of patients with and without TRD during the 1-year period following initiation of their depression treatment episodes.

The third period describes short-term downstream service utilization and health care cost consequences of developing TRD during the following year (i.e., 13-24 months following the index antidepressant prescription fill).

These analyses were performed with patients who were aged 18-64 years and had continuous pharmacy and medical coverage for 12 months before and 24 months after an index antidepressant prescription that occurred after ≥ 6 months without an antidepressant prescription claim. Within 30 days before or after the index antidepressant prescription fill, patients were required to have ≥ 1 diagnosis for depression (ICD-9-CM codes 296.2, 296.3, 300.4, 311, 309.0, and 309.1), along with meeting the other previously described eligibility criteria.

Treatment-Resistant Depression

Study patients were classified as TRD or non-TRD using a claims-based algorithm for identifying TRD. We used the concept that an antidepressant treatment trial required at least 6 weeks of antidepressant availability at an adequate dose, which was adapted from the Massachusetts General Hospital Antidepressant Treatment Response Questionnaire.²¹ TRD was defined as initiating a third regimen of depression treatment after 2 different regimens of antidepressants or augmentation therapy at adequate dose and duration in the 12 months after the index antidepressant prescription. Treatment regimens included use of the same antidepressant or augmentation medication (anticonvulsant, antipsychotic, lithium, psychostimulant, or thyroid hormone) at adequate dose for at least 6 weeks without gaps of longer than 14 days. Adequate dose was defined by the recommended minimal dosage in the American Psychiatric Association practice guidelines or in the product

package inserts approved by the U.S. Food and Drug Administration.²² A list of adequate antidepressant doses and augmentation therapies appears in [Appendix B](#) (available in online article).

Independent and Dependent Variables

In the analysis of the 12-month baseline period, patient background characteristics were the independent variables, and TRD served as the dependent variable ([Table 1](#)). These background characteristics included age group (aged 18-34, 35-44, 45-54, and 55-64 years); sex; race/ethnicity (white, black, Hispanic, and other); and health plan type (indemnity, health maintenance organization [HMO], and preferred provider organization). Clinical characteristics were based on service claims during the 12 months before the index antidepressant fill. They included the Elixhauser comorbidity score to measure the number of treated comorbid medical conditions and outpatient diagnoses of substance use disorder (ICD-9-CM codes 291-292 and 303-305)²³; anxiety disorders (300.0, 300.2, 300.3, 304, and 308.3); other mental disorders (290-319, not already included); diabetes mellitus (250.00-250.33 and 250.40-250.93); congestive heart failure (398.91, 402.01, 402.11, 402.91, 404.01, 404.11, 404.91, and 428.0-428.9); ischemic heart disease (410-414); and chronic pulmonary disease (490-492.8, 493.00-493.92, 494-494.1, 495.0-505, and 506.4). Patients were also classified with respect to receiving inpatient and emergency department visits with any listed mental disorder diagnosis during the year before the index antidepressant prescription.

TABLE 1 Background and Clinical Characteristics of Medicaid Beneficiaries Treated for Depression with and Without TRD

Patient Characteristics (%)	Patients with TRD (n = 1,503)	Patients Without TRD (n = 4,298)	Unadjusted OR ^a (95% CI)	Adjusted OR ^{a,b} (95% CI)
Age, years				
18-34	38.7	53.4	1.00	1.00
35-44	20.7	18.9	1.51 (1.29-1.77)	1.52 (1.30-1.79)
45-54	27.7	17.1	2.23 (1.92-2.59)	2.18 (1.86-2.54)
55-64	12.9	10.6	1.68 (1.39-2.04)	1.61 (1.32-1.96)
Sex				
Female	71.0	76.2	1.00	1.00

Patient Characteristics (%)	Patients with TRD (n = 1,503)	Patients Without TRD (n = 4,298)	Unadjusted OR (95% CI)	Adjusted OR (95% CI)
Male	28.0	23.8	1.24 (1.09-1.42)	1.07 (0.94-1.23)
Race/ethnicity				
White	65.9	61.9	1.00	1.00
Black	26.1	29.4	0.83 (0.73-0.95)	0.80 (0.69-0.92)
Hispanic	1.3	2.3	0.54 (0.33-0.88)	0.55 (0.34-0.90)
Other	6.7	6.4	0.99 (0.78-1.25)	0.95 (0.74-1.21)
Health plan type				
Indemnity	62.6	56.2	1.00	1.00
HMO	28.0	24.7	0.73 (0.64-0.83)	0.83 (0.72-0.95)
POS	9.4	9.1	0.93 (0.75-1.14)	0.89 (0.72-1.10)
Elixhauser comorbidity score				
0	10.8	17.9	1.00	1.00
1	35.3	36.0	1.62 (1.33-1.97)	1.54 (1.26-1.87)
2	36.5	26.2	1.67 (1.36-2.05)	1.50 (1.22-1.85)
3+	27.4	19.8	2.29 (1.86-2.81)	1.82 (1.47-2.27)
Outpatient mental health services				
Substance use	16.2	13.6	1.23 (1.04-1.45)	1.07 (0.90-1.26)
Anxiety	11.1	11.8	1.07 (0.89-1.29)	1.03 (0.85-1.24)
Other mental health	20.0	19.4	1.03 (0.89-1.20)	1.16 (0.99-1.35)
Any mental health emergency services	6.6	6.1	1.09 (0.86-1.38)	1.15 (0.90-1.47)
Any mental health inpatient services	13.4	10.9	1.26 (1.06-1.51)	1.35 (1.12-1.61)
Selected medical comorbidities				

Patient Characteristics (%)	Patients with TRD (n = 1,503)	Patients Without TRD (n = 4,298)	Unadjusted OR (95% CI)	Adjusted OR (95% CI)
Diabetes mellitus	13.2	8.5	1.64 (1.36-1.96)	1.37 (1.13-1.66)
Congestive heart failure	1.8	1.3	1.39 (0.87-2.20)	1.08 (0.67-1.73)
Ischemic heart disease	3.7	2.8	1.36 (0.98-1.88)	0.92 (0.66-1.29)
Chronic pulmonary disease		14.6 11.1	1.36 (1.15-1.62)	1.23 (1.03-1.46)

^aResults from separate logistic regressions, one for each patient characteristic, with TRD as the dependent variable.

^bAdjusted for age, sex, race/ethnicity, health plan type, and year.

CI = confidence interval; HMO = health maintenance organization; OR = odds ratio; POS = point of service; TRD=treatment-resistant depression.

In the analysis of the first 12-month follow-up period, TRD was the key independent variable, and service use variables (Table 2) and direct cost variables (Table 3) were the dependent variables. A similar analytic structure was used for service variables (Table 4) and direct cost variables (Table 5) measured during the 12-month extension follow-up period. For the service use analyses, dependent variables included the presence of ≥ 1 inpatient admission or emergency department and outpatient visit during the first and second 12-month follow-up periods. For each type of service, separate variables measured all-cause, mental health-related (290-319), and depression-related (296.2, 296.3, 300.4, 311, 309.0, and 309.1) episodes. Among patients with service episodes, the numbers of inpatient days, emergency department visit days, and outpatient visit days, respectively, were also considered during the 2 follow-up periods. These variables were also considered as all-cause, mental health-related, and depression-related groups on the basis of any listed diagnoses.

TABLE 2 Service Use Outcomes of Medicaid Beneficiaries Treated for Depression with and Without TRD During Months 1 to 12

Service Types	Patients with TRD (n = 1,503)	Patients Without TRD (n = 4,298)	Unadjusted OR/ β^a (95% CI)	Adjusted OR/ $\beta^{a,b}$ (95% CI)
Any inpatient admission, %			OR	OR
All cause	31.0	21.6	1.63 (1.43-1.86)	1.58 (1.38-1.81)
Mental health related	12.7	7.6	1.77 (1.47-2.14)	1.97 (1.62-2.39)

Service Types	Patients with TRD (n = 1,503)	Patients Without TRD (n = 4,298)	Unadjusted OR/ β (95% CI)	Adjusted OR/ β (95% CI)
Depression related	10.1	6.1	1.73 (1.41-2.14)	1.95 (1.58-2.42)
Number of inpatient days, median			β	β
All cause	5.0	4.0	1.81 (0.09-3.53)	1.94 (0.22-3.67)
Mental health related	6.0	5.0	2.56 (0.87-4.25)	2.96 (1.27-4.65)
Depression related	6.0	5.0	1.83 (0.14-3.53)	2.17 (0.48-3.87)
Any ED visit (%)			OR	OR
All cause	50.0	44.0	1.17 (1.04-1.32)	1.28 (1.12-1.45)
Mental health related	28.1	5.8	1.53 (1.23-1.91)	1.65 (1.32-2.07)
Depression related	17.6	2.4	1.33 (0.94-1.88)	1.56 (1.10-2.23)
Number of ED visit days, median			β	β
All cause	2.0	2.0	0.90 (0.28-1.51)	0.99 (0.36-1.62)
Mental health related	1.0	1.0	0.07 (-0.11-0.25)	0.08 (-0.11-0.26)
Depression related	1.0	1.0	0.00 (-0.15-0.16)	0.02 (-0.15-0.19)
Any outpatient visit (%)			OR	OR
All cause	100.0	100.0	^c	^c
Mental health related	97.3	96.1	1.48 (1.04-2.10)	1.57 (1.10-2.25)
Depression related	93.9	92.5	1.26 (0.99-1.60)	1.29 (1.01-1.65)
Outpatient visit days, median			β	β
All cause	31.0	20.5	11.69 (9.45- 13.92)	10.24 (8.02- 12.46)
Mental health related	12.0	8.0	6.44 (4.67-8.20)	6.45 (4.68-8.22)
Depression related	9.0	5.0	4.47 (3.16-5.78)	4.17 (2.85-5.49)

^aOR results are from a series of logistic regressions with TRD status as independent variable of interest and each service type as the dependent variable. Beta coefficients are from a series of quantile regressions with TRD status as the independent variable of interest and median number days of each service type as the dependent variable.
^bAdjusted for age, sex, race/ethnicity, year, and health plan type.

^cNot calculable because all patients had outcome of interest.

β = beta coefficient; CI = confidence interval; ED = emergency department; OR = odds ratio; TRD = treatment-resistant depression.

TABLE 3 Mean Health Care Costs of Medicaid Beneficiaries Treated for Depression with and Without TRD During Months 1 to 12

Cost Categories	Patients with TRD Mean (SD) n = 1,503	Patients Without TRD Mean (SD) n = 4,298	Unadjusted β^a (95% CI)	Adjusted $\beta^{a,b}$ (95% CI)
Total health care costs, \$				
Total	18,982 (35,276)	11,642 (29,203)	6,504 (4,862-8,146)	6,969 (6,087-7,851)
Mental health related	5,703 (9,771)	2,999 (7,171)	2,348 (1,911-2,784)	2,555 (2,121-2,990)
Depression related	3,112 (5,760)	1,910 (4,632)	1,065 (796-1,335)	1,083 (895-1,270)
Prescription pharmacy costs, \$				
Total	4,972 (8,096)	2,193 (5,211)	2,352 (1,991-2,712)	2,305 (2,083-2,528)
Psychotropic	1,573 (2,440)	332 (1,112)	989 (890-1,087)	970 (866-1,074)
Antidepressants	644 (989)	267 (535)	317 (274-360)	280 (239-321)
Inpatient care costs, \$				
Total	5,311 (27,582)	3,625 (24,713)	1,539 (193-2,885)	2,123 (787-3,458)
Mental health related	906 (4,801)	397 (2,427)	431 (230-631)	516 (293-740)
Depression related	645 (3,482)	315 (2,132)	283 (136-430)	350 (192-509)
Emergency department costs, \$				
Total	568 (1,952)	333 (1,028)	206 (119-294)	207 (128-286)
Mental health related	25 (176)	15 (120)	10 (2-17)	9 (2-16)
Depression related	6 (49)	4 (39)	2 (-1-4)	2 (0-5)

Cost Categories	Patients with TRD Mean (SD) n = 1,503	Patients Without TRD Mean (SD) n = 4,298	Unadjusted β (95% CI)	Adjusted β (95% CI)
Outpatient care costs, \$				
Total	7,322 (11,023)	5,013 (9,269)	2,084 (1,557-2,610)	2,026 (1,537-2,515)
Mental health related	2,717 (6,183)	1,990 (5,917)	665 (362-968)	829 (552-1,106)
Depression related	1,655 (3,704)	1,223 (3,849)	395 (201-589)	408 (240-575)
Other medical care costs, \$				
Total	810 (4,805)	478 (2,880)	293 (85-501)	209 (46-372)
Mental health related	481 (3,792)	266 (2,259)	188 (21-354)	140 (-2-283)
Depression related	162 (1,385)	101 (757)	54 (-10-118)	38 (-12-87)
<i>^aBeta coefficients and 95% CIs are based on 2-part log-link gamma regression models with 500 replications.</i>				
<i>^bAdjusted for age, sex, race/ethnicity, year, and health plan type.</i>				
<i>β = beta coefficient; CI = confidence interval; SD = standard deviation; TRD = treatment-resistant depression.</i>				

TABLE 4 Service Use Outcomes of Cohort Medicaid Beneficiaries Treated for Depression with and Without TRD During Months 13 to 24

Service Types	Patients with TRD (n = 1,503)	Patients Without TRD (n = 4,298)	Unadjusted OR/ β^a (95% CI)	Adjusted OR/ $\beta^{a,b}$ (95% CI)
Any inpatient admission, %			OR	OR
All cause	26.7	19.5	1.50 (1.31-1.72)	1.42 (1.23-1.63)
Mental health related	5.6	2.7	2.15 (1.61-2.87)	2.04 (1.52-2.73)
Depression related	3.7	1.7	2.18 (1.53-3.10)	2.13 (1.49-3.05)
Number of inpatient days, median			β	β
All cause	4.0	3.0	3.58 (0.71-6.45)	3.59 (0.64-6.53)
Mental health related	5.0	5.0	2.58 (-2.50-7.66)	3.39 (-2.07-8.84)

Service Types	Patients with TRD (n = 1,503)	Patients Without TRD (n = 4,298)	Unadjusted OR/ β (95% CI)	Adjusted OR/ β (95% CI)
Depression related	4.0	4.0	-0.42 (-2.97- 2.13)	-0.81 (-3.53- 1.91)
Any ED visit, %			OR	OR
All cause	47.7	44.8	1.12 (1.00-1.27)	1.19 (1.05-1.35)
Mental health related	5.7	4.3	1.33 (1.02-1.73)	1.32 (1.05-1.35)
Depression related	1.9	1.1	1.78 (1.12-2.84)	1.89 (1.18-3.05)
Number of ED visit days, median			β	β
All cause	2.0	2.0	1.11 (0.45-1.77)	1.17 (0.50-1.84)
Mental health related	1.0	1.0	0.04 (-0.15-0.23)	0.03 (-0.17-0.23)
Depression related	1.0	1.0	0.11 (-0.07-0.29)	0.11 (-0.08-0.30)
Any outpatient visit, %			OR	OR
All cause	97.0	94.7	1.81 (1.30-2.50)	1.80 (1.29-2.50)
Mental health related	79.0	61.2	2.39 (2.08-2.75)	2.26 (1.96-2.60)
Depression related	65.9	47.1	2.16 (1.91-2.45)	2.05 (1.81-2.32)
Outpatient visit days, median			β	β
All cause	22.0	14.0	10.17 (7.61- 12.72)	8.01 (5.47-10.54)
Mental health related	8.0	5.0	3.47 (1.20-5.74)	3.46 (1.18-5.75)
Depression related	6.0	4.0	2.70 (0.90-4.49)	2.39 (0.59-4.19)

^aOR results are from a series of logistic regressions with TRD status as independent variable of interest and each service type as the dependent variable. Beta coefficients are from a series of quantile regressions with TRD status as the independent variable of interest and median number days of each service type as the dependent variable.

^bAdjusted for age, sex, race/ethnicity, year, and health plan type.

β = beta coefficient; CI = confidence interval; ED = emergency department; OR = odds ratio; TRD = treatment-resistant depression.

TABLE 5 Mean Health Care Costs for Medicaid Beneficiaries Treated for Depression with and Without TRD During Months 13 to 24

Cost Categories	Patients with TRD Mean (SD) n = 1,503	Patients Without TRD Mean (SD) n = 4,298	Unadjusted β^a (95% CI)	Adjusted $\beta^{a,b}$ (95% CI)
Total health care costs, \$				
Total	17,997 (34,146)	10,325 (28,224)	6,749 (5,268-8,230)	5,923 (4,409-7,437)
Mental health related	4,122 (8,657)	1,869 (6,643)	1,957 (1,586-2,327)	2,015 (1,607-2,423)
Depression related	1,969 (4,203)	943 (3,314)	899 (725-1,072)	760 (595-925)
Prescription pharmacy costs, \$				
Total	4,986 (9,529)	2,247 (6,881)	2,330 (1,883-2,777)	2,031 (1,673-2,389)
Psychotropic	1,475 (2,941)	343 (1,311)	899 (780-1,018)	829 (710-949)
Antidepressants	536 (1,017)	197 (574)	283 (241-326)	233 (191-276)
Inpatient care costs, \$				
Total	5,637 (27,493)	3,293 (22,547)	2,072 (855-3,288)	1,762 (411-3,113)
Mental health related	391 (4,125)	172 (1,890)	185 (10-359)	156 (16-295)
Depression related	201 (1,511)	105 (1,545)	83 (10-155)	70 (-5-144)
Emergency department costs, \$				
Total	519 (1,869)	364 (1,247)	141 (50-232)	119 (37-201)
Mental health related	15 (97)	11 (101)	3 (-2-9)	3 (-2-8)
Depression related	3 (34)	2 (31)	1 (-1-2)	1 (-1-3)
Outpatient care costs, \$				
Total	6,126 (10,907)	3,989 (9,075)	1,923 (1,436-2,409)	1,565 (1,115-2,016)

Cost Categories	Patients with TRD Mean (SD) n = 1,503	Patients Without TRD Mean (SD) n = 4,298	Unadjusted β (95% CI)	Adjusted β (95% CI)
Mental health related	1,835 (5,389)	1,126 (5,120)	653 (412-894)	672 (445-900)
Depression related	1,057 (3,169)	576 (2,674)	429 (291-566)	354 (235-473)
Other medical care costs, \$				
Total	728 (4,214)	434 (3,137)	260 (71-449)	255 (110-400)
Mental health related	407 (3,252)	217 (2,649)	165 (19-312)	162 (44-280)
Depression related	172 (1,148)	63 (586)	90 (41-139)	88 (35-141)

^aBeta coefficients and 95% CIs are based on 2-part log-link gamma regression models with 500 replications.

^bAdjusted for age, sex, race/ethnicity, year, and health plan type.

β = beta coefficient; CI = confidence interval; SD = standard deviation; TRD = treatment-resistant depression.

Total health care costs were defined as gross payments to a provider after applying pricing guidelines, such as fee schedules and discounts, and before applying deductibles, copayments, and coordination of benefits policies.

Total health care costs were defined for each study patient during the first and second follow-up periods.

Following the classification for services, costs were partitioned by service into inpatient, emergency, and outpatient and by clinical focus into total, mental health related, and depression related on the basis of any listed ICD-9-CM codes. In addition, separate categories were created for prescription pharmacy costs and a residual group of other medical care costs.

Statistical Analysis

Baseline demographic and clinical service use characteristics of patients with and without TRD were first compared using unadjusted and adjusted (age, sex, race, health plan type, and study year) logistic models.

Among patients with and without TRD, we then determined the percentage of each categorical service use outcome and, among those of service use, the median number of service days. Logistic regression models were used to examine associations between TRD status during the first follow-up period, and the categorical service use variables and quantile regressions were used for the median service day outcomes in each follow-up period. Mean health care costs and associated standard deviations (SDs) within each cost category were then calculated separately for patients with and without TRD. We conducted unadjusted and adjusted regression models using Stata twopm (StataCorp, College Station, TX) to examine the effect of TRD on treatment costs.²⁴ Because some

patients had no treatment costs, we used 2-part models for all analyses, which are commonly used when a large proportion of the population has no costs, and those with costs have a skewed distribution of costs.²⁵

The first part of the model used a logistic regression to predict any cost during the study period, while the second part used a generalized linear model with a gamma distribution and log link to predict costs among those with non-zero costs during this period. The predicted costs for each patient were derived by multiplying predicted costs from each part of the model. For ease of interpretation, we present the predictive margins to quantify the average cost difference between TRD and non-TRD groups. *P* values for this difference were obtained using a nonparametric bootstrap with 500 iterations. A sensitivity analysis was performed by comparing direct health care costs with further adjustment for medical comorbidity burden with the Elixhauser comorbidity score.

Results

Background and Clinical Characteristics of TRD

Of the 5,801 patients who met study eligibility criteria, approximately one quarter (25.9%; *n* = 1,503) of the pharmacologically treated patients with MDD met criteria for TRD during the first 12 months after their index antidepressant prescription fills. Among the study sample, the crude or unadjusted odds of TRD were 1.24 times higher for males than females. As compared with depressed patients without TRD, those with TRD were also proportionately more likely to be older, white, and in indemnity rather than HMO health plans. During the year before the index antidepressant prescription, patients who met criteria for TRD were also more likely than patients without TRD to have been diagnosed with a substance use disorder, a chronic pulmonary disease, and diabetes. The TRD cohort was also more likely than the non-TRD cohort to have received inpatient mental health treatment and to have an elevated Elixhauser comorbidity score during the year before the index pharmacological regimen. After controlling for background characteristics, the associations of age, race, health plan type, diabetes, comorbidity, and inpatient mental health services during the pre-baseline period with TRD status remained significant ([Table 1](#)).

Service Use Outcomes During Post-index Months 1 to 12

During the first follow-up year, patients who met criteria for TRD were significantly more likely than patients without TRD to receive inpatient care for any reason (31.0% vs. 21.6%), as well as for a mental health condition (12.7% vs. 7.6%) and for depression (10.1% vs. 6.1%; all *P* values < 0.001; [Table 2](#)). Among those who received inpatient mental health care, the median length of stay was longer for patients with TRD than for those without TRD. These relationships remained significant after controlling for background patient characteristics ([Table 2](#)). During the first 12 months after the index antidepressant medication prescription, all-cause and mental health-

related emergency department visits were also significantly more common among patients with TRD than among those without TRD in the unadjusted and adjusted analyses. Among patients with mental health-related emergency department visits, patients with TRD, compared with those without TRD, also had a significantly larger median number of such visit days. All patients with and without TRD had outpatient visits during the first follow-up year. However, compared with patients without TRD, patients with TRD had a significantly larger median number of outpatient visits (Table 2).

Health Care Cost Outcomes During Post-index Months 1 to 12

Consistent with the service use patterns, mean total health care costs were significantly higher for patients with TRD (\$18,982 [SD ± \$35,276]) than for those without TRD (\$11,642 [SD ± \$29,203]) during the first year after their index antidepressant prescriptions. Cost differences between the patient groups remained significant after controlling for background patient characteristics (beta coefficient [β] = \$6,969, 95% confidence interval [CI] = \$6,087-\$7,851; Table 3) and in a sensitivity analysis that also adjusted for the Elixhauser score (β = \$6,765, 95% CI = \$5,864-\$7,666).

Similar group differences in mean costs were observed for outpatient care and for total, psychotropic, and antidepressant pharmacy costs during the first year of follow-up. Mean mental health-related and depression-related inpatient care costs, as well as total emergency department costs, were also significantly higher for patients with TRD than for patients without TRD during this period (Table 3).

Service Use Outcomes During Post-index Months 13 to 24

Over the second 12-month period of follow-up, several of the group differences in service use were maintained. Specifically, patients with TRD continued to be significantly more likely than patients without TRD to receive inpatient care for any cause (26.7% vs. 19.5%; $P < 0.001$), as well as for mental health-related (5.6% vs. 2.7%; $P < 0.001$) and depression-related diagnoses (3.7% vs. 1.7%; $P < 0.001$; Table 4). Among patients with any emergency department visits and within each of the 3 categories of outpatient visits, patients with TRD also continued to have a significantly higher median number of days of service use than patients without TRD. Although not evident in the first follow-up year because of ceiling effects, patients with TRD were also significantly more likely than patients without TRD to have any outpatient visit, as well as mental health-related and depression-related outpatient visits, during the second follow-up year (Table 4).

Health Care Cost Outcomes During Post-index Months 13 to 24

Several of the group differences in health care costs were also maintained during the second year of follow-up. Unadjusted mean total health care costs were significantly higher for patients with TRD (\$17,997 [SD ± \$34,146])

than without TRD (\$10,325 [SD ± \$28,224]) during this period and remained significantly higher after adjustment for age, sex, race/ethnicity, year, and health plan type ($\beta = \$5,923$, 95% CI = \$4,409-\$7,437; [Table 5](#)). In a sensitivity analysis that also adjusted for the Elixhauser score, the mean total health care cost difference was little changed ($\beta = \$5,898$, 95% CI = \$4,315-\$7,482). In relation to patients without TRD, patients with TRD also continued to have significantly higher mean mental health-related and depression-related health care costs during the second year, as well as higher total, psychotropic, and antidepressant prescription pharmacy costs. In addition, the mean total outpatient, mental health-related, and depression-related health care costs of patients with TRD were significantly higher than those of patients without TRD during the second 12 months of follow-up ([Table 5](#)).

Discussion

Within the adult nonelderly Medicaid population, TRD is a common condition that is associated with persistently elevated health care costs. Consistent with research based on commercially insured patients,^{6,8,16,17} approximately one quarter of adult depressed patients in the Medicaid program met the TRD criteria over the first year of a depression treatment episode. During this period, their overall health care costs were approximately two-thirds higher than the costs of depressed patients who did not meet the TRD criteria. This cost difference, which was distributed across inpatient, outpatient, emergency, and pharmacy services, persisted during the second year of follow-up. The clinical profile of patients with TRD in the Medicaid program, which included disproportionately older adults and those with general medical comorbid disorders, is consistent with clinical research on the course of depressive disorders. In clinical studies, older patient age and medical comorbidities have been linked to poor outcomes of depression.^{26,27} In practice, these patients are more likely to receive treatment in general medical than in specialty mental health settings.²⁸ In view of the increased risk for TRD in these patients, dedicated efforts may be required to strengthen care coordination to increase their access to specialized mental health services. With greater emphasis on integration of mental and physical health services and transitions toward behavioral health homes,²⁹ there are also new opportunities in several health care systems for providing specialized mental health treatment of depression to older adult patients with medical comorbidities. Models that coordinate the care of depression and chronic medical illnesses have been shown to improve clinical outcomes of both conditions.³⁰

In this Medicaid-insured sample with TRD, outpatient costs accounted for the largest share of health care costs, followed by inpatient, pharmacy, and emergency department service costs. This pattern differs from previous reports of TRD in commercially insured populations in which pharmacy and inpatient costs accounted for a proportionately larger share of costs than outpatient care costs.^{8,17} Although further analyses are needed to probe the basis of these patterns, it is possible that the high background prevalence of persistent serious health conditions in the Medicaid sample³¹ contributes to the proportionately greater contribution of outpatient care to

their cost profile³² and that Medicaid formulary restrictions designed to restrict access to specified high-cost medications contributes to their relatively lower pharmacy costs.

Inpatient care costs were substantially higher among patients with TRD than among patients without TRD. Most of these costs were not directly related to claims-based diagnoses of depression or other mental health conditions. Prospective research strongly suggests bidirectional etiologic relationships between depression and several common general medical conditions, including diabetes mellitus,³¹ ischemic heart disease,³² and chronic pulmonary disease.³³ Because depression tends to decrease adherence to a wide range of medication treatment regimens,³⁴ persistent depression can also adversely affect the clinical course of general medical conditions. Improving the management of depression, especially TRD, may offer opportunities to capture cost-offsets associated with integrated mental health and general medical care.³⁵

Little is known about the clinical course of TRD. Previous claims-based studies have focused on 1-year periods or episode lengths defined by the pattern of depression treatment.^{6,7,8,11,17} We found that differences between depressed patients with TRD and those without TRD in health care costs and services, including depression-related outpatient and inpatient services, persisted during the first year following the year in which TRD developed. A clinical implication of these enduring service demands of TRD patients is that they may commonly require longer-term depression treatment. Although the American Psychiatric Association's practice guideline for MDD recommends that in order to reduce the risk of relapse, patients who have been successfully treated with antidepressants should be continued for 4-9 months beyond the acute phase of treatment,²² longer episodes of maintenance depression treatment may be indicated for patients with TRD.

The clinical literature suggests that TRD runs a variable course, with many patients having enduring depressive symptoms.³⁶⁻³⁸ In a study of patients with moderately advanced unipolar or bipolar TRD, only 7.8% of patients reported symptomatic remission during the week preceding their 2-year follow-up assessment.³⁶ Another study that followed adults with treatment-resistant unipolar or bipolar depression for an average of 3 years found that patients experienced depressive symptoms during nearly two thirds (61%) of the follow-up months.³⁷ A third long-term follow-up study reported that approximately half (48%) of patients with persistent affective disorders achieved symptomatic remission for the 6-month period preceding their 5-year assessments.³⁸ The frequent persistent nature of depressive symptoms in patients with TRD likely contributes to their long-term health care costs.

Limitations

This study has several potential limitations. First, diagnoses were based on clinical judgments of treating clinicians and were not subject to expert validation through structured assessments. Depression and other mental disorders may be underreported in claims data because of social stigma and financial incentives to bill

for the management of general medical disorders, although we have no reason to believe that underreporting operated differentially across study groups.

Second, a lack of clinical measures for depressive symptoms in the claims database prevents direct assessment of treatment response and resistance. Without prospective clinical data, it is also not possible to distinguish switches in treatments for MDD that were related to treatment nonadherence, ineffectiveness, and intolerability. However, our overall rate of TRD (25.9%) is similar to the rate reported from a large clinical sample of depressed patients who remained depressed after 2 treatment trials (21.9%).³⁹

Third, the analyses were limited to nonelderly adult Medicaid patients without Medicare coverage, so the results may not generalize to older patients, those with dual eligibility, or other patient populations. Fourth, the cost estimates were not adjusted for inflation.

Fifth, diagnoses within claims data do not permit precise attribution of mental health-related and depression-related service costs. For example, even subthreshold depressive symptoms have been associated with increased medical care costs of adults with diabetes.⁴⁰ Finally, it is not known whether the persistence of increased service use and health care costs observed during the second year would continue over longer periods of observation.

Conclusions

Within the U.S. Medicaid program, patients with MDD who have evidence of TRD have substantially higher health care costs than their counterparts who do not meet criteria for TRD. This general finding may be particularly important to third-party payers and managers of health care benefits who bear financial responsibility for health care costs or oversee service delivery to this patient population. The persistence of health care cost differences over the year following development of TRD suggests that depression treatment resistance is often an enduring clinical characteristic. In addition to demonstrating the practical utility of retrospective Medicaid claims to identify patterns and costs associated with treatment resistance, these results underscore the challenge of developing interventions and management strategies to meet the complex and enduring clinical needs of this large and vulnerable patient population.

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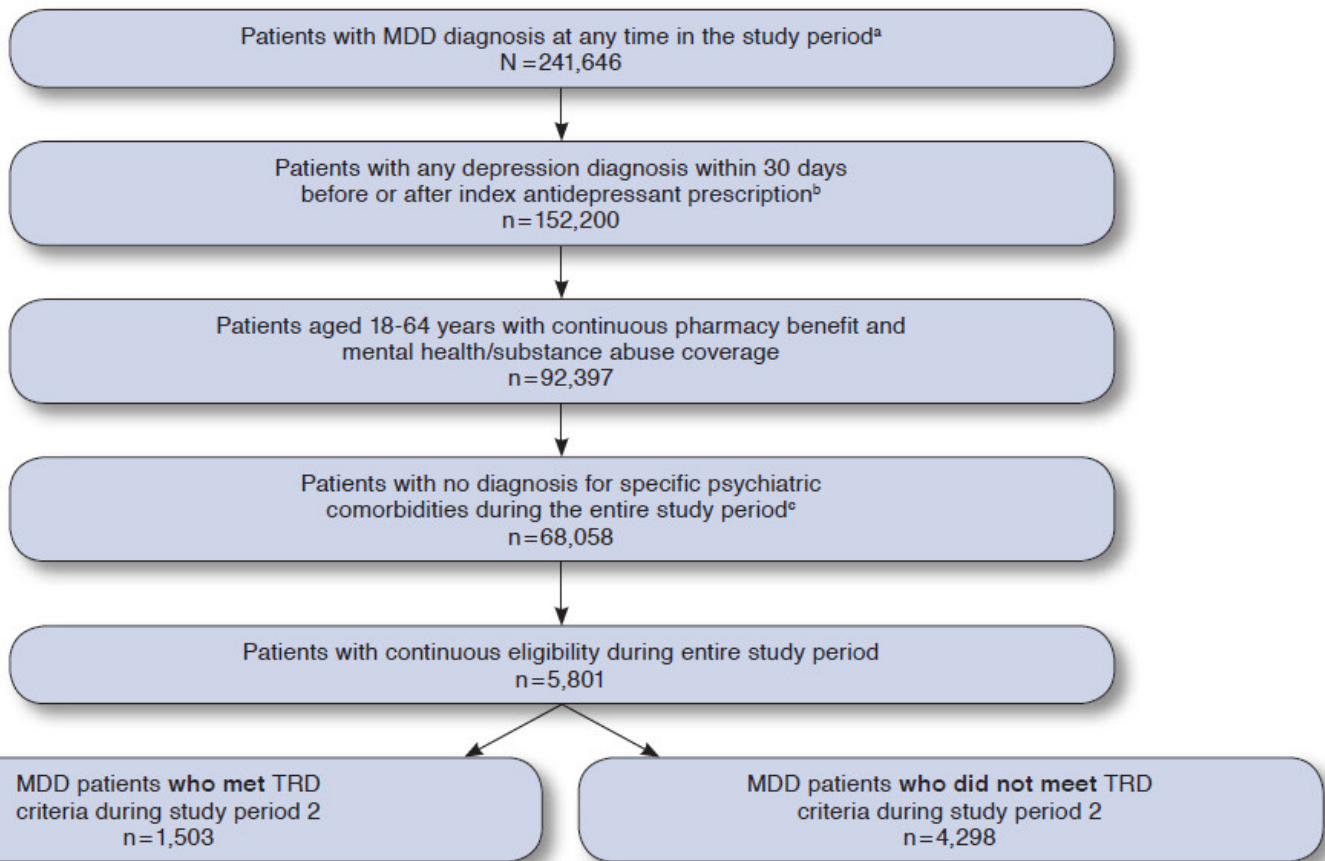
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APPENDIX A *Sample Selection*



^aICD-9-CM codes for MDD are 296.2x and 296.3x.

^bAny depressive disorder ICD-9-CM codes: 296.2x, 296.3x, 300.4x, 309.0x, 309.1x, and 311.xx.

^cSpecific psychiatric comorbidities ICD-9-CM codes: 298.xx (psychosis), 295.xx (schizophrenia), 296.0x, 296.1x, 296.4x, 296.5x, 296.6x, 296.7x, 296.8x (bipolar disorder/manic depression), and 290.xx, 294.1x (dementia).

ICD-9-CM= International Classification of Diseases, Ninth Revision, Clinical Modification; MDD= major depressive disorder; TRD= treatment-resistant depression.

APPENDIX B List of Antidepressant Medications, Minimum Adequate Doses, and Augmentation Medications

Antidepressant Medication	Minimum Daily Adequate Dose ^a	Augmentation Medications
SSRIs		Anticonvulsant medication
Citalopram	20 mg	Carbamazepine
Escitalopram	10 mg	Gabapentin
Fluoxetine	20 mg	Lamotrigine
Paroxetine	20 mg	Phenytoin
Paroxetine, extended release	12.5 mg	Tiagabine
Sertraline	50 mg	Topiramate
Vilazodone	10 mg	Anxiolytic medication

Antidepressant Medication	Minimum Daily Adequate Dose	Augmentation Medications
DNRI		Buspirone
Bupropion	150 mg	Antipsychotic medication
SNRIs		Aripiprazole
Desvenlafaxine	50 mg	Olanzapine
Duloxetine	60 mg	Paliperidone
Levomilnacipran	20 mg	Quetiapine
Milnacipran	12.5 mg	Risperidone
Venlafaxine	37.5 mg	Ziprasidone
Serotonin modulators		Lithium medication
Nefazodone	50 mg	Lithium
Trazodone	150 mg	Psychostimulant
Vortioxetine	10 mg	Dextroamphetamine
Norepinephrine-serotonin modulator		Methamphetamine
Mirtazapine	15 mg	Methylphenidate
Tricyclic and tetracyclic antidepressants		Modafinil
Amitriptyline	25 mg	Pemoline
Amoxapine	25 mg	Thyroid hormone medication
Doxepin	25 mg	Liothyronine
Desipramine	25 mg	
Imipramine	25 mg	
Maprotiline	75 mg	
Nortriptyline	25 mg	
Protriptyline	10 mg	
Trimipramine	25 mg	
MAOIs		
Isocarboxazid	10 mg	
Moclobemide	150 mg	
Phenelzine	15 mg	
Selegiline transdermal	6 mg	

Antidepressant Medication	Minimum Daily Adequate Dose	Augmentation Medications
Tranylcypromine	10 mg	
Other selected medication		
Olanzapine-fluoxetine	25 mg	

^aMinimum adequate doses based on APA practice guidelines or FDA package inserts.²²

APA = American Psychiatric Association; DNRI = dopamine-norepinephrine reuptake inhibitor; FDA = U.S. Food and Drug Administration; MAOI = monoamine oxidase inhibitor; SNRI = serotonin-norepinephrine reuptake inhibitor; SSRI = selective serotonin reuptake inhibitor.

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