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Treatment-Resistant Depression

Costs, Caregiving, and Gaps in Care

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EXECUTIVE SUMMARY

Treatment-resistant depression (TRD) refers to a subset of individuals diagnosed with major depressive disorder (MDD) whose symptoms persist despite multiple therapeutic interventions. The Centers for Disease Control and Prevention (CDC) reports that 13.1% of adolescents and adults in the United States—approximately 34 million people—experience depression[1]. TRD impacts roughly one in three patients with MDD. Among Medicare beneficiaries, TRD is associated with increased clinical complexity, elevated risk for crisis-driven care, and a sustained requirement for ongoing services. Although the clinical burden of MDD and TRD is widely acknowledged, their broader economic and caregiving implications are not consistently integrated in current literature syntheses.

Comprehensive assessments reveal that the overall annual economic impact of MDD—including direct healthcare expenditures, workplace productivity losses, household effects, and indirect costs such as absenteeism and unemployment—amounts to hundreds of billions of dollars. While many analyses predate 2020, recent modeled estimates indicate a societal burden exceeding $300 billion annually, primarily due to indirect costs related to lost productivity and household consequences.[2] These expenditures encompass not only direct medical costs associated with the treatment and management of depressive symptoms but also broader consequences resulting from functional impairment affecting employment, social participation, and caregiver responsibilities.

To prepare this report, both a literature review and data analysis were carried out to gain insight into existing research and the real-world impact by examining Medicare fee-for-service and Part D data from 2021 to 2023.

Literature review key findings:

- The annual national burden of TRD is estimated to range between $29 to $48 billion, representing approximately 27%–41% of the total MDD related costs (Zhdanava et al., 2021).
- Nationally, medication-related expenses attributable to MDD total approximately $92.7 billion annually, with nearly half (47.2%, or $43.8 billion) attributable specifically to TRD (Zhdanava et al., 2021). Individuals with TRD also account for 56.6% of the total healthcare burden and 32.3% of the unemployment burden associated with MDD, further illustrating the outsized economic impact of this subgroup (Zhdanava et al., 2021).

[1] Brody, DJ, Hughes, JP. (2025). Depression Prevalence in Adolescents and Adults: United States, August 2021-August 2023. National Center for Health Statistics Data Brief, 527, 1-11. DOI: https://dx.doi.org/10.15620/cdc/174579

[2] Greenberg, P. E., Fournier, A. A., Sisitsky, T., Pike, C. T., & Kessler, R. C. (2023). The economic burden of adults with major depressive disorder in the United States (2010 and 2018). Pharmacoeconomics, 41(1), 1–12. https://pubmed.ncbi.nlm.nih.gov/37518849/

- In the last decade, the United States has seen a significant increase in the number of family caregivers, with an average of 1 in 4 Americans identifying as caregivers, including an estimated 59 million Americans caring for an adult family member and 4 million Americans caring for a child with an illness or disability (American Association of Retired Persons, 2025).
- U.S. data indicates that caregiving for individuals with TRD is associated with greater time demands, productivity losses, and financial strain compared with caregiving for individuals with non-resistant depression or other health conditions (AARP & National Alliance for Caregiving, 2021).
- A national survey analyzing employed caregivers for people with TRD found these caregivers spent an average of 23.3 to 24 hours per week providing care—far more than those caring for individuals without TRD (Lerner et al., 2020).
- Even after factoring in demographic and work-related variables, caregivers of people with TRD faced much higher indirect costs, averaging about $11,121 each year, compared to $7,761 for non-TRD caregivers (Lerner et al., 2020).
- The annual direct costs for TRD caregiving were estimated at $29,805, whereas non-TRD caregiver households paid around $20,642, reflecting a larger burden of spending for TRD-related caregiver expenses like transportation, additional services, and supports (Lerner et al., 2020).
- Beyond the significant demands on caregivers' time and financial resources, research indicates that caring for family members with serious mental illness (SMI), such as MDD, TRD, and/or comorbidities, can result in caregiver depression. The Family Caregiver Alliance has described this issue as “one of today’s all-too silent health crises” and estimates that at least 20% of family caregivers are affected by this condition (National Council on Aging, 2024).

Data analysis key findings:

- TRD patients are estimated to cost Medicare ~$46,000 per pt/yr, with the majority of costs being attributable to hospitalizations and prescribing costs.
- TRD patients cost Medicare about $8,000 more per patient in the 12 months following their TRD diagnosis than comparable patients with major depressive disorder who were well controlled
- That’s about $120M in annual excess spending for just incident patients. If we presumed that prevalent patients have similar excess cost burdens, the price tag would go higher. An outdated (2019) study by NIH matches our findings closely enough to make that a reasonable assumption.
- A small subset of our TRD patients, about 500 patients, received transcranial magnetic stimulation (TMS) for their TRD. These patients had a mean cost per pt/yr ranging from ~$66,000–$86,000.
- TRD patients undergoing TMS cost $30,000 excess cost compared to well controlled patients.

- A second small subset of our TRD patients, about 450, received electroconvulsive therapy (ECT) for their TRD. These patients had a $48,000 excess cost compared to well controlled patients.
- Neither TMS nor ECT provides a sustained treatment response, so those excess costs will be recurring costs for those patients.

The high rates and significant economic and caregiving demands of MDD and TRD highlight their importance as health concerns in the United States, calling for ongoing efforts to develop innovative, effective, and comprehensive care solutions. Scalable and long-lasting interventions that improve both symptoms and daily functioning could be especially suitable for tackling TRD. Non-pharmacological treatments, such as device-based neuromodulation, digital therapies, and technology-supported behavioral methods, may provide fresh advantages. Although additional research is needed to define the best use of these therapies for TRD, the current challenges indicate that new approaches focused on reducing symptoms, enhancing functionality, and easing economic and caregiver pressures could bring valuable benefits to individuals, families, and society, helping fill existing treatment gaps.

METHODOLOGY

To prepare this report, both a literature review and data analysis were carried out to gain insight into existing research and the real-world impact by examining Medicare fee-for-service and Part D data from 2021 to 2023.

A narrative literature review brought together recent findings about the burden of MDD and/or TRD, with a focus on economic and caregiver challenges. Searches for literature were performed using PubMed, PsycINFO, and grey literature sources including google scholar, government reports, surveillance data, policy reports, workforce industry reports, economic & labor market reports, and caregiving & social impact reports. The review applied inclusion criteria based on topical relevance to MDD and/or TRD, a geographic emphasis on the United States, publication date from 2020 onward, and authorship by credible institutions. Literature was excluded if it lacked direct relevance, did not focus on the United States, or failed to provide sufficient methodological detail or credible authentication. There were no restrictions on type of MDD, demographic population of focus, measure of economic burden, measure of caregiving burden, and frequency, type, or duration of failed therapies used by individuals with MDD and/or TRD. Following the search, titles and abstracts were screened against the study's predefined inclusion and exclusion criteria, followed by full text review of eligible literature. Given the heterogeneity in study designs and outcomes reporting, findings were synthesized narratively by thematic domain of economic burden and caregiving burden.

The report also analyzes Medicare fee-for-service claims and Part D data (2021–2023), comparing usage and spending between beneficiaries diagnosed with MDD who meet the claims-based definition of TRD and those who do not. MDD was identified using qualifying inpatient or repeated outpatient/physician claims with ICD-10 codes F33.1, F33.2, and F33.9, and TRD status was based on antidepressant treatment patterns during the year after the first qualifying MDD claim. Propensity matching was used to ensure that the outcomes were driven by the presence of TRD and not due to other patient characteristics. The analysis matched TRD and non-TRD beneficiaries 1:1 on baseline demographics, behavioral health comorbidities, and prior spending (14,965 beneficiaries per group after matching).

BACKGROUND AND INFORMATION FROM LITERATURE

In the context of TRD, care is often reactive, escalating only after repeated treatment failures. As a result, individuals with TRD frequently cycle through multiple therapies, clinical encounters, and care settings without achieving sustained symptom reduction and functional recovery. This episodic approach contributes to prolonged illness duration and sustained interaction with healthcare systems, driving individual suffering, direct medical costs, indirect productivity losses, and straining family and caregiver systems. Importantly, current models tend to prioritize symptom reduction as the primary outcome, often overlooking broader functional, economic, and caregiver-related consequences that define the true burden of TRD.

In the United States, MDD creates a significant economic impact costing $210.5 billion in 2010.[3] TRD contributes disproportionately, with costs between $29–$48 billion, representing 27%–41% of MDD-related expenses.[4] TRD leads to higher healthcare utilization, longer depressive episodes, increased prescription drug use, and greater productivity loss compared to individuals with non-TRD, MDD. TRD patients incur excess annual work-loss costs, specifically $8,676 more than non-TRD MDD and $10,323 more than those without MDD.[5] This accounts for a large share of medication and unemployment burdens. Key cost drivers include prescription drugs (37.6%) and inpatient services (30.8%), with nearly half of excess costs linked to comorbidities.[6] Furthermore, literature underscores the need for targeted interventions for TRD, as 30.9% of adults with MDD in the U.S. have TRD.[7]

Research on the impact of treatment-resistant depression (TRD) on caregivers is less extensive than studies on its economic burden, but the available research shows significant demands on

[3] Zhdanava M, Pilon D, Ghelerter I, Chow W, Joshi K, Lefebvre P, Sheehan JJ. The Prevalence and National Burden of Treatment-Resistant Depression and Major Depressive Disorder in the United States. *J Clin Psychiatry.* 82(2), 29169. doi: 10.4088/JCP.20m13699

[4] Ibid

[5] Ibid

[6] Shah D, Allen L, Zheng W, Madhavan SS, Wei W, LeMasters T J, Sambamoorthi U. Economic Burden of Treatment-Resistant Depression Among Adults with Chronic Non-Cancer Pain Conditions and Major Depressive Disorder in the US. *Pharmacoeconomics.* 39(6), 639-65. doi: 10.1007/s40273-021-01029-2. doi: 10.1007/s40273-021-01029-2

[7] McIntyre RS, Alsuwaidan M, Baune BT, Berk et al. Treatment-Resistant Depression: Definition, Prevalence, Detection, Management, and Investigational Interventions. *World Psychiatry*. 22(3): 394-412. doi: 10.1002/wps.21120

caregivers' time, productivity, and finances. TRD places considerable stress on families and informal caregivers, with an estimated 1 in 4 Americans acting as caregivers for adult and/or children with health challenges.[8] Of these, 29% are considered the "sandwich generation", supporting both older and younger family members.[9]

Caring for someone with TRD requires more time and leads to greater productivity losses and financial strain than caregiving for individuals with non-resistant depression or other conditions.[10] Caregivers of individuals with TRD provide 23–24 hours of care per week and face higher indirect costs (about $11,121 annually, compared to $7,761 for non-TRD caregivers), mainly due to lost productivity.[11] Direct caregiving expenses also run higher for TRD households at an annual estimate of $29,805 spent on transportation, services, and supports versus an annual estimate of $20,642 for non-TRD caregiving expenses.[12]

Beyond time and financial impacts, caring for relatives with serious mental illness can lead to decreased caregiver wellbeing, specifically depression which affects an estimated 20% of family caregivers.[13] Many rate their health as "fair or poor," highlighting the toll of caregiving.[14] Although specific studies on TRD caregivers are limited, broader research confirms that caregiving increases mental and physical health risks, financial stress, and lowers quality of life, stressing the need for better support and understanding for those affected by TRD.

Across the literature, individuals with TRD consistently experience greater healthcare utilization, longer illness duration, increased work loss, and higher overall costs compared with those with non-resistant MDD, while families and informal caregivers shoulder significant time, financial, and health-related strain. These findings reinforce that the burden of TRD extends well beyond clinical symptomatology and reflects systemic limitations in current care models. The results underscore how treatment approaches that remain largely episodic, medication-centric, and poorly integrated fail to address the functional, economic, and caregiver-related consequences that define real-world disease impact. Taken together, this evidence provides important context for understanding why TRD represents not only a clinical challenge, but also a broader public health and health system concern requiring more innovative and effective solutions.

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[8] Wynn P. Exclusive: AARP-NAC Report Finds 45% Increase in Americans Providing Care. July 24, 2025. American Association of Retired Persons. Available at: https://www.aarp.org/caregiving/basics/caregiving-in-us-survey-2025/.

[9] Ibid

[10] AARP & National Alliance for caregiving. Caregiving in the US 2025. July 24, 2025. Available at: https://www.aarp.org/pri/topics/ltss/family-caregiving/caregiving-in-the-us-2025/.

[11] Lerner D, Lavelle T, Adler D, Chow W, Chang H, Godar SC, Rogers WH. A Population-Based Survey of the Workplace Costs for Caregivers of Persons with Treatment-Resistant Depression Compared With Other Health Conditions. *J Occup Environl Med*. 62(9): 746-756. doi: 10.1097/JOM.0000000000001957

[12] Ibid

[13] National Council on Aging. Support for Caregivers of People with Mental Illness: A Practical Guide. March 21, 2024. Available at: https://www.ncoa.org/article/support-for-caregivers-of-people-with-mental-illness-a-practical-guide/.

[14] The John A. Hartford Foundation. National Alliance for Caregiving: Caregiving in the US 2025 Report and Data Hub. November 13, 2025. Available at: https://www.johnahartford.org/resources/view/national-alliance-for-caregiving-caregiving-in-the-us-2025-report.

KEY FINDINGS

The findings of the data analysis show a meaningful spending differential associated with TRD over the year following an MDD index date. Average total Medicare spending was $45,994 for beneficiaries with TRD compared with $37,873 for matched beneficiaries without TRD (about 21% higher). The gap is driven primarily by inpatient hospital care and physician services, suggesting that opportunities to reduce avoidable escalation and stabilize care through timely follow-up, coordinated behavioral health and medical management, and improved continuity may have the greatest potential impact.

Spending is especially elevated for the smaller subset of TRD beneficiaries who receive non-pharmaceutical interventions such as electroconvulsive therapy (ECT) or transcranial magnetic stimulation (TMS). Compared with matched non-TRD beneficiaries, TRD beneficiaries receiving ECT averaged $48,000 higher total spending in the year after index (127% higher), and those receiving TMS averaged $28,897 higher (76% higher). In both groups, the largest differences were driven by inpatient costs, highlighting these patients as a priority population for targeted outreach. Since both ECT and TMS are non-curative, the annual costs in this population will persist over time and these populations represent a significant opportunity for cost savings to the Medicare program.

- **Treatment resistant depression (TRD) is associated with materially higher total Medicare spending:** In the 12 months post-index, average total spending was $45,994 for TRD vs. $37,873 for non-TRD—about a 21% increase.
- **Spending increases are concentrated in inpatient and clinician-managed care:** TRD patients had higher inpatient ($13,983 vs. $8,867), physician ($10,564 vs. $8,627), and outpatient ($6,557 vs. $5,940) spending.
- **High-cost TRD subgroups receiving received Electro-convulsive therapy (ECT) or Transcranial Magnetic Stimulation (TMS) have much higher cost differentials:** Compared with non-TRD, ECT patients were $48,000 higher (127%) and TMS patients were $28,897 higher (76%) in total post-index spending, with the largest component attributable to inpatient cost differences (ECT +$37,022; TMS +$18,213).
- **While these findings focused on incident TRD patients specifically, the non-curative nature of TRD interventions means that similar cost differentials are likely to persist in the prevalent TRD population**

DATA SOURCES

We used 2021–2022 100% Medicare Standard Analytic File (SAFs) for inpatient,[15] outpatient,[16] and physician services[17] housed in the Centers for Medicare and Medicaid Services (CMS) Virtual Data Resource Center (VRDC) to identify patients who had major depressive disorder (MDD). The 2021–2022 Medicare 100% Part D (PDE) data were used and began a new course of therapy (antidepressants or antipsychotics). The 2021 Medicare Beneficiary Summary Files (MBSF) were used to obtain patient coverage, demographic characteristics such as age, gender, race, and age. Total payments in each setting were identified using 2021–2023 100% Inpatient, Outpatient, Carrier (physician services), skill nursing facility (SNF), home health agency (HHA), hospice SAFs; and spending on prescription drug was calculated using 2021–2023 Medicare 100% Part D data.

SAMPLE SELECTION

Major depressive disorder (MDD) was identified using Medicare claims that included at least one inpatient encounter or a minimum of two hospital outpatient or carrier claims occurring on different days within the same calendar year. Eligible diagnoses were defined using ICD-10 codes F33.1, F33.2, and F33.9. For each beneficiary, the index date was assigned as the date of the first qualifying MDD claim during the study period.

Treatment-resistant depression (TRD) was defined based on treatment patterns in the 12 months following the index date. Beneficiaries who underwent two or more antidepressant therapy changes during this period were classified as having TRD. Stratified analyses distinguished patients with fewer than two failed therapies from those with four or more.

The analytic cohort was restricted to Medicare fee-for-service beneficiaries who were continuously enrolled for 12 months before and 12 months after the index date to ensure complete capture of clinical history and follow-up. Individuals residing outside the United States at any point during the study period were excluded. Beneficiaries with missing demographic, enrollment, or claims information required for matching or outcome assessment were also removed from the sample.

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[15] The Inpatient Standard Analytic File (SAF) contains fee-for-service (FFS) claims submitted by inpatient hospital providers for reimbursement of facility costs. These claim records represent covered stays (Medicare paid FFS bills.)

[1616] The Outpatient Standard Analytic File (SAF) contains FFS claims submitted by institutional outpatient providers. Examples of institutional outpatient providers include hospital outpatient departments, rural health clinics, renal dialysis facilities, outpatient rehabilitation facilities, comprehensive outpatient rehabilitation facilities, Federally Qualified Health Centers and community mental health centers.

[17] The Carrier Standard Analytic File (SAF) includes FFS claims submitted by professional providers, including physicians, physician assistants, clinical social workers, nurse practitioners. Claims for some organizational providers, such as free-standing facilities are also found in the Carrier Claims File. Examples include independent clinical laboratories, ambulance providers, free-standing ambulatory surgical centers and free-standing radiology centers.

PROPENSITY SCORE MATCHING

A 1:1 propensity score matching (PSM) method was used to control for confounding bias in the population.

- Covariates used in the matching were based on beneficiary's baseline year (2021) characteristics.
- Covariates used in the PSM algorithm include demographic characteristics, chronic conditions classified as risk factors for MDD, and Medicare payment information.
    - Age
    - Gender (Female/Male)
    - Race (White/Black/Hispanic/Other)
- Comorbidities were defined by the standard algorithm used by the Centers for Medicare and Medicaid Services[18]

    1. Substance Use Disorder
    2. Anxiety Disorder
    3. Bipolar Disorder
    4. Personality Disorders
    5. Schizophrenia

- Covariates standardized differences were estimated to determine the quality of matching.

RESULTS

The sample before matching included 110,269 non-TRD beneficiaries and 14,966 TRD beneficiaries. Prior to adjustment, the two groups differed meaningfully across several demographic and clinical characteristics. TRD patients were younger on average (64 vs. 68 years; standardized difference 0.29) and had higher prevalence of key psychiatric comorbidities, including anxiety disorder (77% vs. 53%; −0.52), bipolar disorder (23% vs. 12%; −0.30), personality disorders (15% vs. 6%; −0.29), and substance use disorder (37% vs. 24%; −0.28). Differences were also observed in race and gender distributions, with TRD patients more likely to be female and White. Spending in the 12 months prior to the index date showed modest imbalances, particularly in SNF spending (standardized difference −0.24) and physician and Part D prescription spending (0.13 and 0.12, respectively).

After applying 1:1 propensity score matching, both groups were reduced to 14,965 individuals, and covariate balance improved substantially. Standardized differences for all demographic and clinical variables fell to near zero, ranging from −0.02 to 0.04. Age, gender, race, dual-eligibility status, and all psychiatric comorbidities were closely aligned between groups.

[18] Chronic Conditions Data Warehouse. Other Chronic Health, Mental Health, and Potentially Disabling Conditions. Available at: https://www2.ccwdata.org/web/guest/condition-categories-other.

Pre-index spending measures also showed strong balance, with standardized differences reduced to 0.04 or lower across all spending categories. **Table 1** reflects a well-balanced matched cohort suitable for comparative analyses of outcomes and spending patterns between TRD and non-TRD patients.

Table 1. Standardized Difference Before and After Propensity Score Matching

	Before Matching			After Matching		
	Non-TRD N=110,269	**TRD N=14,966**	**Std. Difference**	**Non-TRD N=14,965**	**TRD N=14,965**	**Std. Difference**
Patients Characteristics in 2021						
Age	68	64	−0.29	64	64	0.00
Gender						
Female	69%	74%	−0.11	75%	74%	0.01
Dual Status						
Dual	42%	44%	−0.04	44%	44%	−0.01
Race						
White	83%	87%	−0.12	88%	87%	0.00
Black	8%	5%	0.15	5%	5%	−0.01
Hispanic	3%	3%	0.02	3%	3%	0.00
Comorbidity						
Substance Use Disorder	24%	37%	−0.28	37%	37%	−0.01
Anxiety Disorder	53%	77%	−0.52	77%	77%	0.01

	Before Matching			After Matching		
	Non-TRD N=110,269	**TRD N=14,966**	**Std. Difference**	**Non-TRD N=14,965**	**TRD N=14,965**	**Std. Difference**
Bipolar Disorder	12%	23%	−0.30	23%	23%	−0.01
Personality Disorders	6%	15%	−0.29	14%	15%	−0.02
Schizophrenia	5%	7%	−0.09	7%	7%	−0.02
Spending 12 Months Before the Index Date						
Inpatient	$10,135	$11,188	0.04	$10,995	$11,187	0.01
SNF	$5,349	$2,131	−0.24	$2,016	$2,103	0.01
HHA	$13	$13	0.00	$16	$13	−0.01
Hospice	$343	$102	−0.08	$89	$102	0.00
Outpatient	$4,762	$5,650	0.07	$5,715	$5,649	−0.01
Physicians	$7,331	$8,857	0.13	$8,385	$8,857	0.04
Part D Prescription	$7,152	$9,807	0.12	$9,461	$9,806	0.02

Figure 1 and **Table 2** display the average spending for TRD and non-TRD patients in the following setting: 1) inpatient; 2) SNF; 3) HHA; 4) hospice; 5) outpatient; 6) physicians; 7) part D prescription.

Average spending in the 12 months after the MDD index date was consistently higher for patients with TRD compared with matched non-TRD patients across most care settings. TRD patients incurred substantially greater inpatient spending ($13,983 vs. $8,867) and higher outpatient costs ($6,557 vs. $5,940), reflecting more intensive and frequent use of acute and ambulatory services. Physician spending also showed a notable increase among TRD patients ($10,564 vs. $8,627), suggesting greater reliance on clinician visits and ongoing management. Spending in post-acute settings such as SNF, HHA, and hospice was similar or slightly lower for TRD patients. Part D prescription spending was modestly higher for TRD patients ($11,754 vs. $11,009), consistent with more complex medication regimens. When summed across all categories, total Medicare spending reached $45,994 per TRD patient compared with $37,873 for non-TRD patients—an overall increase of roughly 21% over the first year following the MDD index date.

We also evaluated average spending for the subsets of TRD patients who received Electro-convulsive therapy (ECT) or Transcranial Magnetic Stimulation (TMS). These are two types of non-pharmaceutical interventions for TRD. TRD patients with these interventions were significantly more costly than non-TRD patients. Patients receiving ECT were $48,000 more costly than non-TRD patients, while patients receiving TMS were $28,897 more costly than non-TRD patients in the 12 months post-index event. These differences were most pronounced in the inpatient hospital setting where ECT patients were $37,022 more costly than non-TRD patients and TMS patients were $18,213 more costly than non-TRD patients. Overall, ECT patients were 127% more costly and TMS patients were 76% more costly.

Figure 1. Average Total Payments by Setting in 2022 Between Patients with and without Treatment-resistant Depression

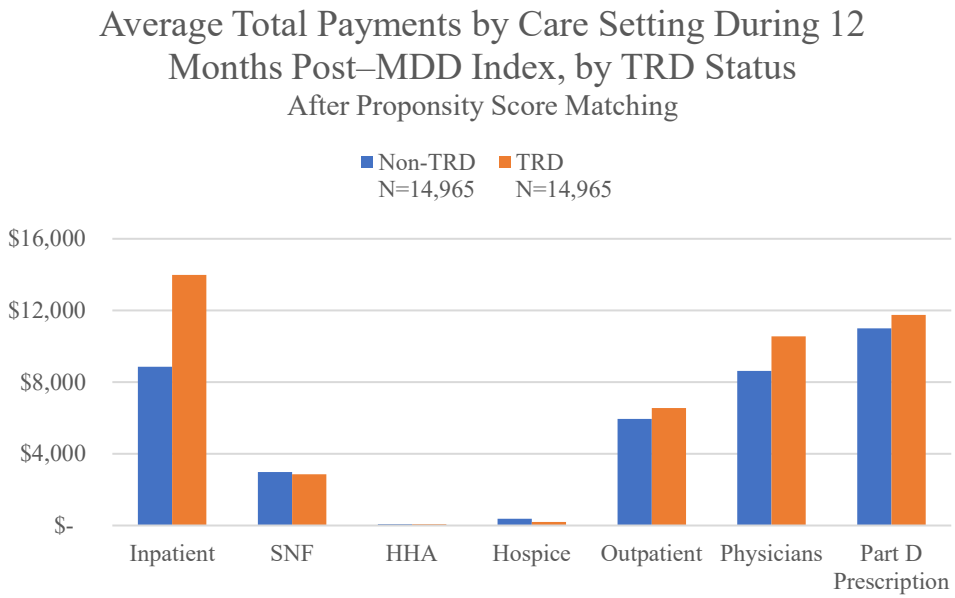

Table 2. Average Total Payments by Setting in 2022 Between Patients With and Without Treatment-resistant Depression

Spending in 12 Months Following MDD Index Date	After Matching	
	Non-TRD N=14,965	**TRD N=14,965**
Inpatient	$8,867	$13,983
SNF	$2,985	$2,866
HHA	$72	$65
Hospice	$372	$205
Outpatient	$5,940	$6,557
Physicians	$8,627	$10,564
Part D Prescription	$11,009	$11,754
Total	*$37,873*	*$45,994*

Table 3. Average Total Payments by Setting in 2022 Between Patients without Treatment-Resistant Depression and Those with TRD Who Received ECT or TMS

Spending in 12 Months Following MDD Index Date	After Matching		
	Non-TRD N=14,965	**TRD N=14,965**	**TRD w/ TSM N=543**
Inpatient	$8,867	$13,983	$27.080
SNF	$2,985	$2,866	$3,676
HHA	$72	$65	$95
Hospice	$372	$205	$14
Outpatient	$5,940	$6,557	$10,475
Physicians	$8,627	$10,564	$13,380
Part D Prescription	$11,009	$11,754	$12,049
Total	*$37,873*	*$45,994*	*$66,769*

CONCLUSION

The magnitude and persistence of TRD-related burden highlighted in this review underscore the need to broaden the therapeutic toolkit beyond current models of care, which are often limited to traditional pharmacological therapies. Interventions that are scalable, durable, and capable of addressing both symptoms and functional outcomes may be particularly well suited to address the challenges posed by TRD. Non-pharmacological therapies, including device-based neuromodulation, digital therapeutics, and technology-assisted behavioral interventions may offer potential, novel advantages. While further research is needed to establish the optimal role of different non-pharmacological therapies within TRD treatment pathways, the current burden suggests that innovation aimed at reducing symptomology, improving functionality, and alleviating economic and caregiver burdens may yield meaningful benefits at the individual, family, and societal levels, and address the current gap that exists.

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