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Economic Burden of Treatment-Resistant Depression: Insights from Real-World Data

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ABSTRACT

Background: Treatment-resistant depression (TRD) is a highly prevalent condition. It is generally referred to as the failure of at least two or more prior treatments with antidepressants or augmentation therapy with adequate dose and duration. TRD affects the individual's overall health and social life, in addition to the economic impact associated with the illness. Therefore, this review is focused on examining the financial burden of illness among patients with TRD across different countries and identifying the key drivers for the incremental costs and healthcare resource utilization (HRU).

Methods: A literature search was carried out in the PubMed database using relevant MeSH terms. This review included relevant studies published between 2019 & 2024.

Results: Overall, 22 studies were included in this review, with the majority based in the United States (n=15). The majority of the patients were females, ranging from 53.1% to 77%, and the mean age of patients with TRD ranged from 37.7±14.4 to 73.1±6.5 years. The mean annual all-cause healthcare cost per patient ranged from $3,190 to $40,040. The mean annual all-cause indirect costs per patient ranged from $4,199 to $6,342. Outpatient visits were the frequently utilized healthcare services, especially psychiatric visits and visits to general practitioners or family physicians. The incremental costs were primarily driven by worsening symptom severity, the presence of comorbidities, advancing age, and frequent visits to specialists.

Conclusion: Regardless of the factors influencing the cost burden, TRD generally accounts for higher healthcare use and costs compared to individuals with major depressive disorder or without any mental illness. This underscores the need for fostering newer interventions and implementation of multidisciplinary approaches to lessen the cost burden of this condition, in addition to managing it effectively.

Keywords: Treatment-resistant Depression, Economic burden, Healthcare resource utilization

Introduction

Depression is a prevalent psychological illness that impacts quality of life [1]. Failing to produce at least a moderate response to pharmacological treatments or achieving remission is referred to as treatment-resistant depression (TRD) [2]. A consensus definition for TRD is currently lacking. However, generally, TRD is defined as patients who failed at least two prior treatments with adequate dose and duration [3].

Prevalence rates for this condition have differed due to the varying definitions. In real-world practice, the prevalence of TRD ranges from 6% to 55%, while it is estimated to be over 30% in clinical research settings. Currently, about 30% of individuals with depression are recognized to meet the definition of TRD. According to international epidemiological estimates, more than 100 million individuals worldwide meet at least one definition of TRD [4].

TRD imposes a substantial burden on the individuals and the society [5]. The economic impact includes high healthcare costs, loss of productivity, and unemployment, with estimates suggesting that TRD accounts for a larger portion of the overall burden associated with major depressive disorder (MDD) [2,6,7]. Insights into different cost components and utilization of healthcare services among TRD patients are crucial to addressing the factors that impact the economic burden, as well as for tailoring interventions for better outcomes.

This literature review aimed to examine the financial burden of illness among patients with TRD and explore the key drivers of incremental costs and healthcare resource utilization (HRU). Recently published claims-based studies were integrated to provide in-depth insights on direct costs, indirect costs, and HRU across diverse populations of patients with TRD, gaining insights from real-world data.

Materials and Methods

A comprehensive search was performed focusing on the economic burden of TRD. The PubMed database was utilized to identify relevant articles. The literature search included a combination of MeSH terms or keywords such as “treatment-resistant depression,” “economic burden,” “healthcare resource utilization,” and “claims.” The literature search covered real-world studies analyzing costs and/or HRU based on claims databases or healthcare systems published in English between 2019 and 2024. Relevant studies were also hand-searched from reference lists of relevant articles.

Results

This review included a total of 22 studies, and Table 1 provides the characteristics of the studies included. The majority of the studies analyzed the direct costs (n=20), followed by HRU (n=19) and indirect costs (n=4). Most of the studies were conducted in the US (n=15), while the remaining studies were conducted in the UK (n=1), Sweden (n=1), Taiwan (n=1), South Korea (n=1), Spain (n=1), or Canada (n=1). Females were the predominant population with TRD in the overall cohort, majorly ranging from 53.1% to 77%, except in one study involving US veterans (18.1%). The mean age ± standard deviation (SD) of patients ranged from 37.7±14.4 to 73.1±6.5 years. Patients were primarily diagnosed with MDD, primary or secondary depression, unipolar MDD, or unipolar depression further classified as TRD. For comparisons, most studies included ≥1 control (TRD versus non-treatment-resistant depression [non-TRD] or non-treatment-resistant depression major depressive disorder [non-TRD MDD] and/or non-major depressive disorder [non-MDD]).

ECONOMIC BURDEN

Tables 2 to 4 present an overview of the cost components used to estimate total, direct, and indirect costs associated with TRD.

1.1. Total costs

The estimated mean total cost, including both direct and indirect costs per TRD patient, was €6,096 annually, according to a Spanish study [14]. Across the included studies, the mean healthcare cost per TRD patient for all causes ranged from $3,190 to $40,040 annually, including the use of home health services (HHS) [12,19,21,23,25–28]. The mean indirect cost per patient per year (PPPY) for all causes ranged from $4,199 to $6,342 among patients with TRD [19]. The estimated mean direct and indirect costs for all-cause among the included studies are depicted in Figure 1.

The presence of comorbidity increases the cost associated with complications, thereby contributing to increased total cost. The mean annual direct costs ranged from $16,674 to $22,541 per TRD patient with comorbidities [11,13,17], and the mean annual indirect costs ranged from $13,674 to $15,337 among TRD patients with comorbidities, including costs associated with complications [11,17].

1.2. Direct costs

Both patients with MDD and TRD incur higher medical costs with increasing severity; however, patients with TRD had a 1.2-fold increase in healthcare costs than MDD [9]. A US study reported that TRD patients with chronic non-cancer pain conditions (CNPC) incurred mean all-cause healthcare costs of $21,015 [13]. A Korean study found that TRD patients with psychiatric conditions had mean healthcare costs of KRW 3,089,106 [15]. Furthermore, a US study including TRD patients with anxiety disorder and/or substance use disorder (SUD) reported a healthcare cost of $16,674 [11]. Regardless of the disease stage, TRD patients incur higher costs, as evidenced in a study estimating a 3.5-fold increased mean all-cause healthcare costs of $19,626 attributable to patients with newly observed TRD episodes [22].

Many studies have assessed the incremental healthcare costs accounted for by TRD patients. According to one US study, TRD patients had an incremental cost of $3,000 more than those without TRD [24]. A US study including veterans with TRD estimated the all-cause healthcare cost (PPPY) to be $19,268, with incremental costs of $5,906 and $11,873 than non-TRD MDD and non-MDD patients, respectively [12]. Similarly, a US study involving an integrated delivery network (IDN) found that TRD patients had an incremental cost of $9,479 and $11,433 than non-TRD MDD and non-MDD, respectively [28]. A large US-based claims study reported that Medicare beneficiaries with TRD ($8,054.4) incurred higher all-cause annual incremental costs than commercial ($6,742.3) and Medicaid beneficiaries ($4,093.4) [18].

A UK study estimated the average healthcare costs per patient per month (PPPM) with TRD and found greater costs incurred during major depressive episodes (MDE, £992) than remission (£254) and recovery (£99) [16]. A two-year analysis in Canada also highlighted a greater mean healthcare cost of CA$20,998 for TRD patients, with incremental costs of CA$3,047 and CA$9,932 than non-TRD and non-MDD patients, respectively [20]. In a Taiwanese study, TRD patients had significantly higher all-cause annual healthcare costs (NT$91,370) than non-TRD patients (NT$51,650; $p < 0.001$) [10].

1.2.1. Outpatient care costs

Outpatient-related costs are one of the largest cost components contributing to the increased healthcare burden of TRD. In a Taiwanese study, patients with TRD had all-cause-related outpatient costs of NT$53,690 [10]. In a Spanish study, patients with TRD had greater costs towards primary care visits (€503.3) and specialist visits (€189) [14]. In a UK study, the average specialist visit costs PPPM were higher during MDE (£52) than remission (£30) and recovery (£30) [16].

In a Canadian study, TRD patients had higher mean costs for non-hospital-related outpatient visits (CA$1,088), specialty care (CA$1,079), and psychiatric visits (CA$1,016) [20]. In a US study, patients with TRD and CNPC had mean all-cause-related outpatient costs of $5,338 [13]. Another study in the US estimated the annual outpatient costs to be $16,978 for patients with physical conditions and TRD [17].

Some studies have assessed the outpatient costs across different user types or beneficiaries in the US. HHS users with TRD incurred higher mean outpatient costs for all-cause ($14,454 vs. $5,623 PPPY) and mental health-related ($2,431 vs. $2,108 PPPY) than non-HHS users with TRD [19]. The US veterans with TRD had all-cause outpatient costs of $12,560 PPPY [12]. The US IDN users [28] and Medicare beneficiaries [25] with TRD had higher mean all-cause ($11,277 and $7,143) and depression-related ($1,270 and $603) outpatient costs PPPY, respectively; and Medicaid beneficiaries with TRD had higher mean all-cause outpatient costs of $4,126 PPPY [27].

1.2.2. Inpatient care or hospitalization costs

Multiple medications increase the risk of adverse drug-drug interactions, which thereby increases hospitalizations and inpatient costs, in addition to suicide attempts and SUD among TRD patients leading to increased hospitalizations. A Spanish study estimated the mean cost per TRD patient for hospital stays to be €140.9 [14]. A US study reported the average hospitalization costs to be $5,529 for patients with newly observed TRD [22]. In a UK study, the mean hospitalization costs of PPPM were higher during MDE (£380) compared to remission (£42) and recovery (£12) [16]. A two-year analysis in Canada determined the average hospitalization costs to be CA$6,114, CA$2,756, and CA$2,500 for all-cause, MDD-related, and psychiatric-related, respectively [20]. In a Taiwanese study, the inpatient costs for all-cause and psychiatric-related were NT$32,660 and NT$7,810, respectively [10].

In the US, some studies have explored the mean all-cause inpatient costs of PPPY across

different beneficiaries and users with TRD. The estimates suggest $8,886 for Medicare beneficiaries [25], $3,688 for Medicaid beneficiaries [27], $7,897 for US IDN users [19], and $5,197 for US veterans [12]. Patients with CNPC and TRD had larger inpatient costs for all-cause ($7,603) and MDD-related ($543) [13]. Also, older adults with TRD had greater all-cause inpatient costs ($9,947) annually [23]. HHS users with TRD incurred greater mean all-cause inpatient costs PPPY ($15,387) than non-HHS users (2,085). Similarly, TRD patients using HHS incurred higher mean mental health-related inpatient costs PPPY ($4,700) than non-HHS users ($1,095) [19].

1.2.3. Emergency care costs

Emergency care costs, due to various factors, also contribute to increased healthcare costs. According to a Taiwanese study, the all-cause emergency care costs incurred by TRD patients for psychiatric reasons were NT$4,630 [10]. In a Spanish study, the mean emergency visit costs were estimated to be €63.1 [14]. In a Canadian study, the two-year mean emergency department (ED) visit costs for all causes were CA$899 [20].

In a US study, patients with TRD were reported to incur an average all-cause ED cost of $518 annually [24]. Notably, patients with newly observed TRD episodes incurred average emergency room (ER) visit costs of $1,109 [22]. Patients with CNPC and TRD had relatively higher mean all-cause and MDD-related ED costs of $1,789 and $188, respectively [13]. Among TRD patients, those using HHS had higher mean ED costs PPPY for all causes than those not using HHS ($1,991 vs. $821) [19]. Further, some studies in the US have evaluated the mean all-cause ED costs PPPY across different beneficiaries and user types, suggesting $1,161 for Medicare beneficiaries [25], $259 for Medicaid beneficiaries [27], and $1,090 for US IDN users [28].

1.2.4. Pharmacological and non-pharmacological treatment costs

The management of TRD involves multiple courses of AD treatment, which largely increases pharmacy costs. In the US, a study reported that those with new TRD episodes had all-cause pharmacy costs of $3,225 [22]. In another US study, patients with physical conditions and TRD incurred annual pharmacy costs of $5,562 [17]. Meanwhile, older adults with TRD incurred annual pharmacy costs of $5,467 yearly [23]. Other US-based studies have analyzed the mean all-cause pharmacy costs PPPY. The findings indicate $1,153 for US veterans [12], $3,899 for US IDN users [28], $4,251 for Medicaid beneficiaries [27], $4,633 for Medicare beneficiaries [25], and $5,605 versus $2,997 for HHS users with TRD versus non-HHS users with TRD [19]. Furthermore, a study in the US analyzed costs toward payers and patients and found that pharmacy costs to payers of $2,043 and $2,027 were greater than the prescription costs to patients of $406 and $350 during the first and second follow-up years, respectively [21].

Some studies have analyzed the costs of different medications and therapies associated with TRD. A Korean study described that patients with TRD adding atypical antipsychotics (AAP) incurred higher mean drug costs (KRW 264,787) compared to switching AD (KRW 93,182) or adding AD (KRW 141,966) [15]. In a UK study, the costs for drugs (£38), occupational therapy (£72), and cognitive behavioral therapy (CBT, £10) were frequently incurred during MDE by patients with TRD [16]. In a Spanish study, the mean cost per TRD patient for AD treatments was €340.9 [14]. In a Taiwanese study, psychiatric medication costs were majorly expended during outpatient care (NT$15,250) and inpatient care (NT$680) [10].

1.2.5. Other healthcare expenses

Apart from outpatient-, inpatient-, ED-, and treatment-related costs, patients with TRD also incur costs for other services, which contribute to a minor portion of the total cost. In a Spanish study, the mean cost per TRD patient for other healthcare services such as laboratory tests, conventional radiology, axial tomography, magnetic nuclear resonance, and other complementary evidence was €60.3, €11.7, €1.5, €3.2, and €5.1, respectively [14]. In a US study, the other costs for all-cause care were $4,314 annually, including skilled nursing facilities, home health agencies, durable medical equipment, and hospice services [23]. Patients with newly observed TRD episodes had mean costs of $100 for skilled nursing facilities, according to a US-based study [22].

1.3. Indirect costs

Indirect costs refer to the economic impact of the illness that is not directly related to the medical treatment expenses. These costs arise from the loss of productivity due to medical-related absenteeism and disability.

In a Spanish study, the average costs due to occupational productivity loss and permanent disability were €1,274 and €3,481.1, respectively. Significant cost differences were reported for TRD versus non-TRD regarding occupational productivity loss (€453) and

permanent disability (€1,080; both p < 0.001) [14]. Among TRD patients with anxiety disorders and/or SUD, the work loss-related costs ($13,674) largely differed from non-TRD MDD ($7,131) and non-MDD ($4,798) [11].

Among TRD patients with physical conditions, the mean all-cause work loss-related costs were $15,337 annually, of which $4,400 was attributed to medical-related absenteeism and $10,937 for disability. These patients annually incurred higher indirect costs of $10,323 and $8,676 related to all-cause than non-MDD and non-TRD MDD patients, respectively. Surprisingly, the annual mean physical condition-related work loss-related costs decreased by $167 and $67 in TRD, compared to non-TRD MDD and non-MDD, respectively [17].

In one US study, HHS users with TRD were reported to incur higher all-cause work loss-related costs PPPY ($6,342) compared to those HHS users with non-TRD MDD ($3,452) and non-MDD ($2,368). Disability primarily contributed to the work loss-related costs among these patients ($5,446). Similarly, non-HHS users with TRD ($4,199) incurred higher all-cause work loss-related costs PPPY than those non-HHS users with non-TRD MDD ($2,451) and non-MDD ($837). Disability was mainly attributed to the work loss-related costs among these patients as well ($3,382). The mental health-related work loss-related costs were also higher among HHS and non-HHS users [19].

HRU

The HRU among TRD patients such as hospitalizations, ED visits, outpatient visits, medication usage, and other healthcare services are represented in Table 5.

2.1. Outpatient-related visits

Approximately 99% of TRD patients had all-cause outpatient visits, including newly observed TRD episodes [10,20,22]. The most common outpatient visits were psychiatric visits and visits to GP or family medicine (GP/FM). In a Canadian study, TRD patients had more frequent GP/FM visits than non-TRD (all-cause: mean, 21 vs. 15) [20]. In a Taiwanese study, around 91.6% of patients with TRD visited psychiatrists annually [10].

Patients with TRD in the US (mean: 18 vs. 13.4) [24] and in Sweden (mean: 9.8 vs. 5.6 days) had more frequent outpatient visits than non-TRD patients [5]. According to a UK study, patients during MDE had more frequent monthly specialist visits (mean: 0.4 vs. 0.2 and 0.2) and primary care visits (mean: 0.3 vs. 0.2 and 0.1) than remission and recovery [16]. Furthermore, patients with TRD had increased outpatient-related rates than treatment-responsive depression (all-cause: Incidence Rate Ratio [IRR], 1.3-1.5; mental health-related: IRR, 1.5-1.9) [18].

Nearly 76.2% of patients with CNPC and TRD had ≥ one outpatient visit for all causes annually. These patients had nearly threefold higher rates of MDD-related outpatient visits [13]. Furthermore, the mean rates of all-cause-related outpatient visits were 23.8 for TRD patients with anxiety disorders and/or SUD [11] and 26.6 for physical conditions [17]. Those with psychiatric conditions and TRD had frequent outpatient visits while switching AD than adding AD or AAP (mean: 87.8 vs. 83 or 67.8) [15].

A large-scale HRU analysis found that ambulatory encounters, estimated at 97.8%, were related to all-cause cases among TRD patients [8]. In a two-year consecutive analysis, the number of outpatient visits by TRD patients was 11.5 and 7.4 during the first and second follow-up years, respectively [21]. Patients with TRD using Medicare or US IDN had outpatient visit rates PPPY of 1.2 or 1.5 times higher than non-TRD MDD and 1.6 or 2.7 times higher than non-MDD, respectively [25,28]. Likewise, Medicaid beneficiaries with TRD had 3.9 times higher outpatient visits PPPY than non-MDD [27].

2.2. Inpatient care, hospitalization, ED visits, and HHS utilization

The likelihood of hospitalization and ED visits was higher for those with TRD than those without TRD [18]. A two-year consecutive analysis found 8% and 7% of hospitalization encounters, while 26% and 22% of ED visits among patients with TRD during the first and second follow-up years, respectively [21]. A large-scale HRU analysis suggests a 1.4-fold higher odds of depression-related inpatient stays by TRD patients than by non-TRD MDD patients [8]. Older adults with TRD also had frequent inpatient visits and longer inpatient days [23].

Patients with CNPC and TRD had 3- and 2.2-fold higher rates of MDD-related inpatient and ED visits, respectively [13]. Patients with TRD and psychiatric conditions had frequent hospitalizations while switching AD (48%) than adding AD (42.8%) or AAP (43.3%). Conversely,

the inpatient days were higher when adding AAP than switching or adding AD (mean: 34.1 vs. 20.7 or 18.7) [15]. Furthermore, TRD patients with anxiety and/or SUD [11] or physical conditions [17] had increased inpatient admissions and ED visits.

In a Canadian study, TRD patients had higher rates of all-cause (67%) related ED visits [20]. A Taiwanese study including TRD patients also evidenced higher rates for all ER visits (40.5%), followed by similar rates (23.4%) of admissions and hospital days [10]. In a Swedish study, TRD patients had mean inpatient bed days of 3.9 [5]. In a UK study, TRD patients in MDE had more frequent hospitalizations monthly (1.4±4.2) than remission (0.2±1.2) and recovery (0.04±0.3) [16]. Patients with newly observed TRD episodes had increased all-cause hospitalization besides ≥1 ER visit [22]. In a US study, IDN users with TRD had 2- and 3.1-fold higher rates of inpatient visits than non-TRD MDD and non-MDD, respectively [28]. This study suggested that one in five TRD patients utilized HHS frequently, indicating this to be a common US healthcare pathway [19]. Furthermore, Medicaid-insured patients with TRD had 1.3-fold increased home care use than non-TRD MDD patients [27].

NON-HEALTH IMPACT: An overview of the lost workdays

Table 5 provides the summary of the lost workdays among patients with TRD, reflecting the non-health impact. In a Swedish study, TRD patients had higher lost workdays than non-TRD patients (mean: 132.3 vs. 58.7 days) [5]. Among patients with anxiety and/or SUD, TRD resulted in significant lost workdays than non-TRD MDD (54 vs. 32 days) and non-MDD (54 vs. 17 days; all $p < 0.01$) [11]. Patients with physical conditions and TRD had annual all-cause lost workdays of 57.5 days, with 3.7 days related to physical conditions. The majority of the lost workdays were related to disability (42.2 days), while medical-related absenteeism contributed to the least (15.3 days) [17].

HHS users and non-HHS users with TRD had mean all-cause lost workdays of 50.7 and 34.6, respectively. Disability contributed majorly by 36.7 and 25.5 days among HHS and non-HHS users, respectively. The mean mental health-related lost workdays were nearly equivalent between HHS users and non-HHS users (18.5±45.3 vs. 19.2±40.1 days), including medical-related absenteeism and disability [19].

Discussion

FACTORS THAT INFLUENCE INCREMENTAL COSTS AND HRU

Notably, increasing symptom severity is linked to incremental costs for TRD patients [9]. One US-based study evaluated the incremental all-cause healthcare costs to be $5,150 and $3,455 among patients with severe and moderate TRD, respectively, compared to mild TRD. The key drivers for the incremental costs were inpatient and outpatient costs [26].

Typically, TRD patients encounter longer hospital stays than non-TRD MDD patients [8]. Among older adults with TRD, risk factors such as patient demographics, geographical region, Charlson Comorbidity Index (CCI), and/or non-mental health comorbidities did not affect the initial hospitalization. However, TRD patients had a substantial risk of initial hospitalization and readmission within 30 days than non-TRD MDD patients [23]. Second-line treatments for TRD, such as adding AAP, increase the likelihood of hospitalizations by 1.3-fold, inpatient days by 2.6-fold, and costs by 1.2-fold. The key factors influencing medical costs were older age, higher CCI score, insomnia, and frequent specialist visits [15].

The comorbidities associated with incremental healthcare costs among TRD patients include CNPC, SUD, anxiety, and sleep disorders [13]. Those with TRD and physical conditions experience incremental costs likely due to comorbidities, with MDD possibly complicating the management of comorbidities or influencing the disease's progress. For instance, potential drug-drug interactions from certain ADs or combinational drugs can hinder the effective treatment of specific comorbidities. This imposes further safety monitoring, resulting in higher HRU and higher costs [17].

Across insurance types, Medicare beneficiaries with TRD incurred higher healthcare costs than commercial or Medicaid beneficiaries [25]. Commercial beneficiaries besides Medicare were also reported to incur higher HRU and costs [18]. The possible reasons for such disparities include beneficial plan designs, patient demographics, and clinical characteristics [18,25].

PERSPECTIVES ON REDUCING THE COST BURDEN AND HRU

Patients with TRD and comorbidities generally have difficulty managing those comorbidities. They also incur increased treatment costs. For this reason, Shah et al. suggested using healthcare delivery models through collaborative and multidisciplinary involvement to ameliorate the outcomes of comorbidities and lower the cost burden rather than standard care [13]. Szukis et al. also suggested multidisciplinary strategies

comprising primary care clinicians and mental health and social service providers to offer patient-centered and collaborative treatments [12].

Surprisingly, IDN users also incurred increased medical-related HRU and costs attributed to the burden of TRD, which pointed to the emergent need for efficacious treatment approaches for TRD patients, considering the extended treatments and wide-ranging variability with ADs [28]. Lynch et al. emphasized that insights into various symptom levels could facilitate individualizing treatments for better outcomes in the case of increasing severity imposing cost burden [9].

STRENGTH AND LIMITATIONS

The main strength of this review is its comprehensive design, covering the topic areas broadly and encapsulating each cost component associated with the burden of the illness. Secondly, this review reflects real-world data, which might be helpful in clinical practice in exploring alternative pathways to manage this condition effectively and reduce the healthcare burden.

There are some limitations in this review; for instance, the included studies have primarily investigated the healthcare costs among TRD patients, with only a few studies assessing the indirect costs. The intangible costs are not well established in the existing studies. Further studies discussing the non-health costs might be essential to a complete understanding of the economic impact on individuals and society.

Conclusion

Evidently, individuals worldwide suffer from the economic burden of TRD due to the increasing HRU, as well as work loss-related costs. The presence of comorbidities additionally increases the burden of TRD by affecting overall health and increasing HRU. Furthermore, the greater the symptom severity, the higher the HRU and costs were incurred. Although moderate or mild TRD imposes lower costs than severe TRD, the overall costs were superior for TRD over non-TRD. A wide perspective on the disease course and beneficial treatments integrating multidisciplinary strategies may help alleviate the burden of TRD.

Ethical Considerations

The Institutional Review Board of Government Medical College, Kannur, Kerala, granted ethical approval for this study. The approval reference number is IEC No.09/2023/GMCK, and it was issued on May 9, 2023.

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Authors' contributions

All authors contributed to obtaining final approval.

Conflict of interest

The authors declare that they have no known competing conflict of interests – be it financial or personal relationships that could have appeared to influence the work reported in this paper.

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Tables

Table 1. Characteristics of all the studies included in this review (n=22).

First author, Publication year; Country	Study design	Patient population	Sample size (N); Mean age (SD)/Median age (IQR) years; Female (%)	Data Source	Outcomes of interest		
					Direct costs	Indirect costs	HRU
Lundberg, 2023 [5]; Sweden	Population-based observational study	Patients with unipolar MDD classified as TRD	12,765; 43.5 (32.2-56.2); 63.4%	Data extracted from: Stockholm regional healthcare data warehouse EHR Swedish Social Insurance Agency	No	No	Yes
Adekkanattu, 2023 [8]; US	Retrospective cohort study	Patients with MDD classified as TRD	4,605; 54.1 (20.3); 65.3%	EHR from INSIGHT-CRN healthcare systems in New York City	No	No	Yes
Lynch, 2022 [9]; NA	Retrospective cohort study	Patients with TRD	24,534; 52.8; 72.8%	Integrated Healthcare system	Yes	No	No
Huang, 2022 [10]; Taiwan	Population-based study	Patients with unipolar depression classified as TRD	44,086; 49.5±15.7 63.8%	Taiwan National Health Insurance Research Database	Yes	No	Yes
Zhdanava, 2021 [11]; US	Retrospective study	Patients with MDD classified as TRD and with anxiety disorder and/or SUD	3,166; 39; 60.5%	Optum Health Care Solutions Inc. database	Yes	Yes	Yes
Szukis, 2021 [12]; US	Retrospective, matched-cohort study	Patients with MDD classified as TRD	10,449; 48.9; 18.1%	VHA claims database	Yes	No	Yes
Shah, 2021 [13]; US	Retrospective longitudinal study	Patients with MDD classified as TRD and with CNPC	2,147; 53.3 (16.6); 77%	Claims data from Optum Clinformatics DataMart	Yes	No	Yes
Pérez-Sola, 2021 [14]; Spain	Retrospective, observational study	Patients with MDD classified as TRD	3,559; 53.6 (17.2); 66.3%	EMR from BIG-PAC administrative database	Yes	Yes	No
Park, 2021 [15]; South Korea	Retrospective study	Patient with TRD and psychiatric conditions	15,887; 54.4±17.1; 59.8%	Korea Health Insurance Review and Assessment Service database containing claims from universal healthcare system	Yes	No	Yes
Denee, 2021 [16]; UK	Retrospective study	Patients with MDD classified as TRD	295; 43.3 (13.6); 60.3%	Medical records abstracted into eCRF system	Yes	No	Yes
Zhdanava, 2020 [17]; US	Retrospective, longitudinal matched cohort study	Patients with MDD classified as TRD and with physical conditions	2,317; 47.6 (12); 63.1%	Optum Health Care Solutions commercial insurance claims database	Yes	Yes	Yes
Shrestha, 2020 [18]; US	Retrospective cohort study	Patients with MDD classified as TRD	Commercial: 27,595; NA; 66.5% Medicaid: 5,556; NA; 75.5% Medicare: 1,856; NA; 61.4%	Truven MarketScan databases (commercial, Medicaid, and Medicare supplemental claims database)	Yes	No	Yes
Pilon, 2020 [19]; US	Retrospective, longitudinal study	Patients with MDD classified as TRD	HHS: 1,152; 45±12.2 62.2% / Non-HHS: 5,259; 39.5±13.3; 64.7%	Health claims data from Optum Health Care Solutions, Inc. database	Yes	Yes	Yes
McIntyre, 2020 [20]; Canada	Retrospective, longitudinal cohort study	Patients with MDD classified as TRD	277; 51.8 (15.9); 53.1%	Administrative health service records for publicly insured individuals in Ontario from multiple linked datasets held by the Institute for Clinical Evaluative Sciences	Yes	No	Yes
Li, 2020 [21]; US	Retrospective study	Patients with MDD classified as TRD	2,384; 39.2 (13); 62%	Insurance claims data from Optum Clinformatics Extended Data Mart	Yes	No	Yes
Cai, 2020 [22]; US	Retrospective cohort study	Patients with MDD classified as TRD	3,317; 37.7 (14.4); 61.3%	Health claims data from IBM MarketScan Commercial and Medicare Supplemental databases	Yes	No	Yes
Benson, 2020 [23]; US	Retrospective, longitudinal cohort study	Patients with MDD classified as TRD	178; 73.1 (6.5); 69.7%	5% random data from US Medicare database	Yes	No	Yes

Sussman, 2019 [24]; US	Retrospective cohort study	Patients with primary or secondary depression classified as TRD	800; 38.8 (14.1); 60.6%	Truven Health MarketScan databases (commercial claims, encounters database, Medicare Supplemental database)	Yes	No	Yes
Pilon, 2019a [25]; US	Retrospective, longitudinal-matched cohort study	Patients with MDD classified as TRD	3,224; 58.9 (14.6); 64%	Chronic Conditions Warehouse de-identified 100% Medicare database	Yes	No	Yes
Pilon, 2019b [26]; US	Retrospective, longitudinal cohort study	Patients with MDD classified as TRD	Mild: 455; 39.1 (13.3); 65.1% Moderate: 2,153; 40.4 (13.2); 63.4% Severe: 1,455; 41.1 (13.4); 64.9%	OptumHealth Care Solutions, Inc. database	Yes	No	Yes
Pilon, 2019c [27]; US	Retrospective, longitudinal-matched cohort study	Patients with MDD classified as TRD	14,170; 42.5 (12.3); 73.4%	Medicaid healthcare claims database	Yes	No	Yes
Pilon, 2019d [28]; US	Retrospective matched-cohort study	Patients with MDD classified as TRD	1,582; 45.6 (16.6); 66.5%	Optum Integrated Claims Electronic Health Records	Yes	No	Yes

Abbreviations: CNPC, Chronic Non-Cancer Pain Conditions; DD, Depressive Disorder; eCRF, Electronic Case Report Form; EHR, Electronic Health Records; EMR, Electronic Medical Records; HHS, Home Health Services; INSIGHT CRN, INSIGHT Clinical Research Network; IQR, Interquartile Range; MDD, Major Depressive Disorder; NA, Not Available; SD, Standard Deviation; TRD, Treatment-Resistant Depression; Unipolar MDD, Unipolar Major Depressive Disorder; VHA, Veterans Health Administration; %, percentage

Table 2. Summary of studies included reporting both direct and indirect costs in patients with TRD (n=4).

Author, year	Country	Study design	Patient population	Sample size (N)		Direct and indirect costs
Zhdanava, 2021 [11]	US	Retrospective study	Patients with MDD classified as TRD and with anxiety disorder and/or SUD	3,166		Costs measured PPPY during the ≤24 months after index Direct costs in patients with TRD: Healthcare costs PPPY: $16,674 Indirect costs in patients with TRD: Work loss-related PPPY: $13,674
Pérez-Sola, 2021 [14]	Spain	Retrospective, observational study	Patients with MDD classified as TRD	3,559		Mean costs during the 18 months follow-up period: Mean direct and indirect costs per patient with TRD: €5,878.8 In the adjusted cost model (ANCOVA), the overall costs were higher in TRD patients than those without TRD: €6,096 vs. €3,846; difference: €2,250, p < 0.001
Zhdanava, 2020 [17]	US	Retrospective, longitudinal-matched cohort study	Patients with MDD classified as TRD and with physical conditions	2,317		Mean all-cause healthcare costs per year in TRD cohort accounted for $22,541 Only 278 patients' data was available for work loss related costs. The mean all-cause work loss related costs per year in TRD cohort: $15,337
Pilon, 2020 [19]	US	Retrospective, longitudinal study	Patients with MDD classified as TRD	6,411		Direct cost: Mean all-cause healthcare costs PPPY using HHS: $40,040 ($64,248) Mean all-cause healthcare costs PPPY not using HHS: $12,272 ($20,315) Indirect cost: Data of 336 patients using HHS and 1,572 patients not using HHS were available for indirect cost analysis Mean work loss-related costs PPPY using HHS: $6,342 ($14,818) Mean work loss-related costs PPPY not using HHS: $4,199 ($10,020)
				HHS: 1,152	Non-HHS: 5,259	

Abbreviations: ANCOVA, Analysis of Covariance; DD, Depressive Disorder; HHS, Home Health Services; MDD, Major Depressive Disorder; Non-TRD, Non-Treatment-Resistant Depression; Non-TRD MDD, Non-Treatment-Resistant Depression Major Depressive Disorder; PPPY, Per-Patient-Per-Year; SUD, Substance Use Disorder; TRD, Treatment-Resistant Depression

Table 3. Summary of studies included reporting direct healthcare-related costs among patients with TRD (n=20).

Author, year; Country	Study design	Patient population	Sample size (N)	Direct healthcare-related costs		
				Overall healthcare-related costs	Healthcare services-related costs (hospital-related and non-hospital-related healthcare services)	Treatments-related costs (pharmacological and non-pharmacological)
Lynch, 2022 [9]; NA	Retrospective cohort study	Patients with TRD	24,534	TRD incurred 1.2-fold higher average total healthcare costs than MDD Overall healthcare costs based on severity levels:	-	-

				Moderate TRD vs. severe TRD: $12,429 ($23,900) vs. $13,344 ($22,895); p < 0.001 Low TRD vs. severe TRD: $12,220 ($31,864) vs. $13,344 ($22,895); p < 0.001		
Huang, 2022 [10]; Taiwan	Population-based study	Patients with unipolar depression classified as TRD	44,086	Annual healthcare costs associated with TRD vs. non-TRD Overall all-cause costs: NT$91,370 (US$3,190) vs. NT$51,650 (US$1,840) Significant cost difference between TRD and non-TRD: p < 0.001	Annual healthcare costs associated with TRD (Significant cost difference: p < 0.001 for all inter-group comparisons [TRD vs. non-TRD]) Outpatient care: All-cause: NT$53,690 Psychiatric: NT$19,150 Emergency care: All-cause: NT$4,630 Psychiatric: NT$60 Inpatient care: All-cause: NT$32,660 Psychiatric: NT$7,810	Annual healthcare costs associated with TRD (Significant cost difference: p < 0.001 for all inter-group comparisons [TRD vs. non-TRD]) Outpatient care: Psychiatric medication: NT$15,250 Emergency care: Psychiatric medication: NT$3 Inpatient care: Psychiatric medication: NT$680
Zhdanava, 2021 [11]; US	Matched-cohort study	Patients with MDD classified as TRD and with anxiety disorder and/or SUD	3,166	Increased costs were associated with patients in TRD cohort compared to non-TRD MDD and non-MDD cohorts (p < 0.01): Healthcare costs in TRD: $16,674 Healthcare costs in non-TRD MDD: $10,945 Healthcare costs in non-MDD: $6,493	-	-
Szukis, 2021 [12]; US	Retrospective, matched-cohort study	Patients with MDD classified as TRD	10,449	Mean adjusted costs PPPY Overall all-cause healthcare costs in TRD: $19,268 Adjusted costs difference between TRD and non-TRD MDD: $5,906; p < 0.0001 Adjusted costs difference between TRD and non-MDD: $11,873; p < 0.0001	Mean adjusted costs PPPY: TRD vs. non-TRD MDD or non-MDD All-cause related: Inpatient costs: $5,195 vs. $3,001 or $1,150 Outpatient costs: $12,560 vs. $8,755 or $3,434	Mean adjusted costs PPPY: TRD vs. non-TRD MDD or non-MDD All-cause related: Pharmacy costs: $1,513 vs. $1,163 or $622
Shah, 2021 [13]; US	Retrospective longitudinal study	Patients with MDD classified as TRD and with CNPC	2,147	Mean unadjusted costs per year Overall all-cause healthcare costs: $21,015 ($42,504) Mean adjusted incremental costs (relative to non-TRD): Model 1: $3,388; p < 0.001 Model 2: $2,025; p < 0.001	Mean unadjusted costs per year All-cause related: Inpatient costs: $7,603 ($34,608) Outpatient costs: $5,338 ($14,972) ED costs: $1,789 ($5,100) MDD-related: Overall medical costs: $1,201 ($5,853) Inpatient costs: $543 ($4,557) Outpatient costs: $470 ($2,980) ED costs: $188 ($1,178)	Mean unadjusted costs per year All-cause related: Prescription drugs costs: $6,286 ($10,014)
Pérez-Sola, 2021 [14]; Spain	Retrospective, observational study	Patients with MDD classified as TRD	3,559	Mean cost per patient during the 18-month follow-up Direct health costs: €1,327.2 (€1,791.3)	Mean cost per patient during the 18-month follow-up Primary care visits: €503.3 (€396.7) Specialist visits: €189 (€401.7) Hospital stays: €140.9 (€1,190.3) ED visits: €63.1 (€128.7) Lab tests: €60.3 (€76.7) Conventional radiology: €11.7 (€39) Axial tomography: €1.5 (€12.6) Magnetic nuclear resonance: €3.2 (€26.7) Other complementary evidence: €5.1 (€92.3)	Mean cost per patient during the 18-month follow-up AD: €340.9 (€767.4) Electroconvulsive therapy: €8.2 (€90.9)

Park, 2021 [15]; South Korea	Retrospective study	Patient with TRD and psychiatric conditions	15,887	Medical costs in 3rd year Overall mean medical costs: KRW 3,098,106 ± 6,789,400 Overall mean psychiatry-related cost: KRW 439,289 ± 1,609,323	Medical costs in 3rd year Switching AD (n=8,270): Psychiatry-related cost: KRW 342,811 ± 1,371,521 Adding AD (n=6,025): Psychiatry-related cost: KRW 462,753 ± 1,511,229 Adding AAP (n=1,592): Psychiatry-related cost: KRW 902,256 ± 2,777,215	Drug costs in 3rd year Overall mean depression-related drug cost: KRW 127,312 ± 210,788 Switching AD (n=8,270): Depression-related drug cost: KRW 93,182 ± 163,735 Adding AD (n=6,025): Depression-related drug cost: KRW 141,966 ± 197,711 Adding AAP (n=1,592): Depression-related drug cost: KRW 264,787 ± 377,496
Denee, 2021 [16]; UK	Retrospective study	Patients with MDD classified as TRD	295	Mean costs PPPM During MDE: Overall HRU: £992 During remission: Overall HRU: £254 During recovery: Overall HRU: £99	Mean costs PPPM During MDE: Consultation and non-drugs: £570 Hospitalization: £380 Specialists visits: £52 Primary care visits: £10 During remission: Consultation and non-drugs: £118 Hospitalization: £42 Specialists visits: £30 Primary care visits: £7 During recovery: Consultation and non-drugs: £69 Hospitalization: £12 Specialists visits: £30 Primary care visits: £3	Mean costs PPPM: Frequently used During MDE: Drugs: £38 Occupational therapy: £72 CBT: £10 During remission: Drugs: £107 Occupational therapy: £29 CBT: £12 During recovery: Drugs: £28 Occupational therapy: £0 CBT: £4
Zhdanava, 2020 [17]; US	Retrospective, longitudinal-matched cohort study	Patients with MDD classified as TRD and with physical conditions	2,317	Mean annual costs during the follow-up period All-cause related: Overall healthcare costs: $22,541 Mean cost difference (TRD vs. non-TRD MDD): $5,091 Mean cost difference (TRD vs. non-MDD): $12,494	Mean annual costs during the follow-up period All-cause related: Outpatient costs: $16,978	Mean annual costs during the follow-up period All-cause related: Pharmacy costs: $5,562
Shrestha, 2020 [18]; US	Retrospective cohort study	Patients with MDD classified as TRD	Commercial: 27,595; Medicaid: 5,556; Medicare: 1,856	Incremental healthcare costs among TRD patients with MDD relative to treatment-responsive depression All-cause healthcare costs yearly: Commercial payer: $6,742.3 Medicaid payer: $4,093.4 Medicare payer: $8,054.4	Incremental healthcare costs among TRD patients with MDD relative to treatment-responsive depression Mental health-related costs yearly: Commercial payer: $3,428.1 Medicaid payer: $2,122.9 Medicare payer: $3,316.1	-
Pilon, 2020 [19]; US	Retrospective, longitudinal study	Patients with MDD classified as TRD	6,411 HHS: 1,152 Non-HHS: 5,259	Mean all-cause costs PPPY Using HHS Mean all-cause direct costs: $40,040 ($64,248) Not using HHS Mean all-cause direct costs: $12,272 ($20,315)	Mean all-cause costs PPPY (using HHS and not using HHS): Inpatient: $15,387 ($48,543) and $2,085 ($8,731) ED: $1,991 ($4,856) and $821 ($2,550) Outpatient: $14,454 ($24,335) and $5,623 ($11,589) HHS: $1,419 ($6,106) vs. $0 Mean mental health-related costs (using HHS and not using HHS): Inpatient: $4,700 ($30,547) and $1,095 ($4,809) ED: $353 ($1,264) and $215 ($911)	Mean all-cause costs PPPY Pharmacy costs (using HHS and not using HHS): All-cause: $5,605 ($9,802) and $2,997 ($7,209) Mental health-related: $1,462 ($2,582) and $1,164 ($1,892)

						Outpatient: $2,431 ($6,369) and $2,108 ($8,323) HHS: $128 ($910) and $0	
McIntyre, 2020 [20]; Canada	Retrospective, longitudinal cohort study	Patients with MDD classified as TRD	277		Mean costs for 2 years Overall healthcare costs: CA$20,998 (CA$33,228) Costs difference between TRD and non-TRD: CA$3,047 Costs difference between TRD and non-MDD: CA$9,932	Mean costs for 2 years Hospital-related costs Hospitalization: CA$6,114 (CA$19,010) MDD-related hospitalization: CA$2,756 ($12,459) Psychiatric-related hospitalization: CA$2,500 (CA$12,448) ED visits: CA$899 (CA$1,588) ED visits related to MDD: CA$124 (CA$369) Outside hospital-related costs Other outpatient visits: CA$1,088 (CA$1,705) Specialty care: CA$1,079 (CA$4,087) Psychiatric visits: CA$1,016 (CA$2,706) GP visits: CA$249 (CA$872)	-
Li, 2020 [21]; US	Retrospective study	Patients with MDD classified as TRD	2,384		At 1st year of follow-up: Overall healthcare costs: $12,726 Adjusted mean difference (TRD vs. non-TRD): $3,846 At 2nd year of follow-up: Overall healthcare costs: $11,591 Adjusted mean difference (TRD vs. non-TRD): $2,412	At 1st year of follow-up: Costs to payer Medical costs: $9,075 Adjusted mean difference (TRD vs. Non-TRD): $2,950 Costs to patients Medical costs: $1,373 Adjusted mean difference (TRD vs. Non-TRD): $444 At 2nd year of follow-up: Costs to payer Medical costs: $8,393 Adjusted mean difference (TRD vs. Non-TRD): $1,772 Costs to patients Medical costs: $1,207 Adjusted mean difference (TRD vs. Non-TRD): $245	At 1st year of follow-up: Costs to payer Pharmacy costs: $2,043 Adjusted mean difference (TRD vs. Non-TRD): $535 Costs to patient Prescription costs: $406 Adjusted mean difference (TRD vs. Non-TRD): $88 At 2nd year of follow-up: Costs to payer Pharmacy costs: $2,027 Adjusted mean difference (TRD vs. Non-TRD): $362 Costs to patient Prescription costs: $350 Adjusted mean difference (TRD vs. Non-TRD): $49
Cai, 2020 [22]; US	Retrospective cohort study	Patients with MDD classified as TRD	3,317		Average costs of newly observed TRD episodes Overall all-cause healthcare costs: $19,626	Average costs of newly observed TRD episodes All-cause related: Overall medical costs: $16,401 Hospitalization: $5,529 ER visit: $1,109 Office visit: $1,433 Outpatient encounter: $8,230 Skilled nursing facility: $100	Average costs of newly observed TRD episodes All-cause related: Pharmacy costs: $3,225
Benson, 2020 [23]; US	Retrospective, longitudinal cohort study	Patients with MDD classified as TRD	178		GLM-adjusted annual all-cause costs Overall costs: TRD: $24,543 Non-TRD MDD; $16,059 Non-MDD: $8,058	GLM-adjusted annual all-cause costs Inpatient costs: $9,947 Outpatient costs: $3,082 ER costs: $330 Outpatient office costs: $5,158 Other costs: $4,314	GLM-adjusted annual all-cause costs Pharmacy costs: $5,467
Sussman, 2019 [24]; US	Retrospective cohort study	Patients with primary or secondary depression classified as TRD	800		Mean costs per year (TRD vs. non-TRD) All-cause related healthcare costs: $9,890 vs. $6,848; p < 0.001 Depression-related healthcare costs: $2,740 vs. $1,322; p < 0.001	Mean costs per year (TRD vs. non-TRD) All-cause related: ED costs: $518 vs. $408; p < 0.05 Outpatient costs: $3,603 vs. $2,585; p < 0.05	Mean costs per year (TRD vs. non-TRD) All-cause related: Pharmacy costs: $2,613 vs. $1,837; p < 0.05
Pilon, 2019a [25]; US	Retrospective, longitudinal-matched cohort study	Patients with MDD classified as TRD	3,224		Mean healthcare costs PPPY Overall costs: $25,059 ($36,832)	Mean healthcare costs PPPY All-cause related: Overall medical costs: $20,425 ($33,463) Inpatient costs: $8,886 ($20,930)	Mean healthcare costs PPPY All-cause related pharmacy costs: $4,633 ($10,843) Depression-related (AD pharmacy costs): $290 ($561);

				Cost difference between TRD and non-TRD MDD: $3,377; p < 0.001 Cost difference between TRD and non-MDD: $3,675; p < 0.001	ED costs: $1,161 ($2,491) Outpatient costs: $7,143 ($11,410) Depression-related: Medical costs: $4,815 ($11,303) Inpatient costs: $3,210 ($9,142) ED costs: $237 ($1,143) Outpatient costs: $603 (($1,716)	p < 0.001 compared to non-TRD MDD or non-MDD
Pilon, 2019b [26]; US	Retrospective, longitudinal cohort study	Patients with MDD classified as TRD	6,411	Mean healthcare costs PPPY Severe TRD (n=1,455) Overall all-cause costs: $18,911; p < 0.001 Severe vs. mild: adjusted cost difference $5,150; p < 0.001 Moderate TRD (n=2,153) Overall costs: $16,885 Moderate vs. mild: adjusted cost difference $3,455; p < 0.001 Mild TRD (n=455) Overall costs: $12,123	Mean healthcare costs PPPY Severe TRD (n=1,455) Behavioural health-related costs: $7,498 Non-behavioural health-related costs: $11,413 Moderate TRD (n=2,153) Behavioural health-related costs: $5,344 Non-behavioural health-related costs: $11,541 Mild TRD (n=455) Behavioural health-related costs: $3,680 Non-behavioural health-related costs: $8,443	-
Pilon, 2019c [27]; US	Retrospective, longitudinal-matched cohort study	Patients with MDD classified as TRD	14,170	Mean healthcare costs PPPY All-cause related: Overall costs: $16,654 ($25,388) Adjusted cost difference between TRD and non-TRD MDD: $4,382; p < 0.001 Adjusted cost difference between TRD and non-MDD: $8,294; p < 0.001	Mean healthcare costs PPPY (compared to non-TRD MDD or non-MDD: all p < 0.001) All-cause related: Medical costs: $12,403 ($21,130) Inpatient costs: $3,688 ($13,128) ED costs: $259 ($655) Outpatient costs: $4,126 ($6,717) Mental-health institute costs: $220 ($1,322) Long-term care cost: $599 ($8,089)	Mean healthcare costs PPPY (compared to non-TRD MDD or non-MDD: all p < 0.001) All-cause related: Pharmacy costs: $4,251 ($9,876)
Pilon, 2019d [28]; US	Retrospective matched-cohort study	Patients with MDD classified as TRD	1,582	Mean healthcare costs PPPY Overall all-cause related costs: $25,807 ($42,549) Adjusted cost difference between TRD and non-TRD MDD: $9,479; p < 0.001 Adjusted cost difference between TRD and non-MDD: $11,433; p < 0.001	Mean healthcare costs PPPY (compared to non-TRD MDD or non-MDD: all p < 0.001) All-cause related: Medical costs: $21,908 ($39,844) Inpatient costs: $7,897 ($25,551) ED costs: $1,090 ($5,742) Outpatient costs: $11,277 ($21,406) Depression-related: Medical costs: $1,270 ($3,162) Inpatient costs: $380 ($2,072) ED costs: $27 ($350) Outpatient costs: $816 ($2,084)	Mean healthcare costs PPPY (compared to non-TRD MDD or non-MDD: all p < 0.001) All-cause related pharmacy costs: $3,899 ($8,024) Depression-related (AD pharmacy costs): $540 ($781)

Abbreviations: AD, Antidepressant; AAP, Atypical Antipsychotics; CA$, Canadian Dollar; CBT, Cognitive Behavioral Therapy; CNPC, Chronic Non-Cancer Pain Conditions; DD, Depressive Disorder; ED, Emergency Department; ER, Emergency Room; GLM, Generalized Linear Model; GP, General Practitioner; HHS, Home Health Services; HRU, Healthcare Resource Utilization; KRW, Korean Won; MDD, Major Depressive Disorder; MDE, Major Depressive Episode; NA, Not Available; Non-TRD, Non-Treatment-Resistant Depression; Non-TRD MDD, Non-Treatment-Resistant Depression Major Depressive Disorder; NT$, New Taiwan Dollar; PPPM, Per-Patient-Per-Month; PPPY, Per-Patient-Per-Year; SUD, Substance Use Disorder; TRD, Treatment-Resistant Depression; vs., versus

Table 4. Summary of studies included reporting indirect costs among patients with TRD (n=4).

Author, year	Country	Study design	Patient population	Sample size (N)	Indirect costs
Zhdanava, 2021 [11]	US	Retrospective study	Patients with MDD classified as TRD and with anxiety disorder and/or SUD	3,166	Indirect costs PPPY for ≤24 months post index date: Work loss data (n=310 in all cohorts [TRD, non-TRD MDD and non-MDD]) Work loss-associated costs (TRD vs. non-TRD MDD): $13,674 vs. $7,131; p < 0.01 Work loss-associated costs (TRD vs. non-MDD): $13,674 vs. $4,798; p < 0.01
Pérez-Sola, 2021 [14]	Spain	Retrospective, observational study	Patients with MDD classified as TRD	3,559	Indirect costs during the 18-month follow-up: An adjusted cost model (ANCOVA)

Author, year	Country	Study design	Patient population	Sample size (N)	Indirect costs
					Costs related to lost occupational productivity (TRD vs. non-TRD): €1,274 vs. €821 Mean difference between TRD and non-TRD: €453; p < 0.001 Costs related to permanent disability (TRD vs. non-TRD): €3,481 vs. €2,401 Mean difference between TRD and non-TRD: €1,080; p < 0.001
Zhdanava, 2020 [17]	US	Retrospective, longitudinal-matched cohort study	Patients with MDD classified as TRD and with physical conditions	2,317	Indirect costs during the one-year follow-up: Mean annual all-cause work loss costs: Overall costs: $15,337 Mean difference between TRD and non-TRD MDD: $8,676 Mean difference between TRD and non-MDD: $10,323 Medical-related absenteeism: $4,400 Disability: $10,937 Mean annual physical condition-related work loss costs: Overall costs: $884 Mean difference between TRD and non-TRD MDD: -$167 Mean difference between TRD and non-MDD: -$67 Medical-related absenteeism: $684 Disability: $200
Pilon, 2020 [19]	US	Retrospective, longitudinal study	Patients with MDD classified as TRD	6,411	Indirect costs PPPY during the 2-year follow-up post index date: Data available for analysis: Patients using HHS: TRD (n=336) vs. non-TRD MDD (n=1,259) and non-MDD (n=3,093) Patients not using HHS: TRD (n=1,572) vs. non-TRD MDD (n=9,016) and non-MDD (n=46,177) Using HHS Mean all-cause related: Overall work loss-related costs: $6,342 vs. $3,452 and $2,368 Medical-related absenteeism: $895 vs. $915 and $915 Disability costs: $5,446 vs. $2,537 and $1,453 Mental health-related: Overall work loss-related costs: $2,761 vs. $829 and $66 Medical-related absenteeism: $312 vs. $280 and $38 Disability costs: $2,448 vs. $550 and $28 Not using HHS Mean all-cause related: Overall work loss-related costs: $4,199 vs. $2,451 and $837 Medical-related absenteeism: $817 vs. $755 and $454 Disability costs: $3,382 vs. $1,696 and $383 Mental health-related: Overall work loss-related costs: $2,359 vs. $1,177 and $42 Medical-related absenteeism: $435 vs. $348 and $26 Disability costs: $1,924 vs. $829 and $16

Abbreviations: ANCOVA, Analysis of Covariance; HHS, Home Health Services; MDD, Major Depressive Disorder; Non-TRD, Non-Treatment-Resistant Depression; Non-TRD MDD, Non-Treatment-Resistant Depression Major Depressive Disorder; PPPY, Per-Patient-Per-Year; SUD, Substance Use Disorder; TRD, Treatment-Resistant Depression; vs. versus

Table 5. Summary of studies included reporting HRU and lost workdays among patients with TRD (n=20).

Author, year; Country	Study design	Patient population	Sample size (N)	Outcomes	
				Healthcare resource utilization (HRU)	Lost workdays
Lundberg, 2023 [5]; Sweden	Population-based observational study	Patients with unipolar MDD classified as TRD	12,765	HRU calculated 12 months post index (TRD episodes, n=12,793 vs. non-TRD episodes, n=62,817) Outpatient physician visits: mean, 9.8 days (95% CI: 9.7-9.9) vs. 5.6 days (95% CI: 5.5-5.7) Inpatient bed-days: mean, 3.9 days (95% CI: 3.6-4.1) vs. 1.3 days (95% CI: 1.2-1.4)	Data calculated 12 months post index (TRD episodes, n=12,793 vs. non-TRD episodes, n=62,817) Lost workdays: mean, 132.3 days (95% CI: 129.5-135.1) vs. 58.7 days (95% CI: 56.8-60.6)
Adekkanattu, 2023 [8]; US	Retrospective cohort study	Patients with MDD classified as TRD	4,605	HRU encounters: TRD vs. non-TRD MDD during the 12 months follow-up Overall visits: 1,034,884 vs. 608,390 Ambulatory visits: All-cause related: 1,012,615 (97.8%) vs. 594,003 (97.6%); OR=1.1, 95% CI: 1.1-1.1; p < 0.005	-

Author, year; Country	Study design	Patient population	Sample size (N)	Outcomes	
				Healthcare resource utilization (HRU)	Lost workdays
				Depression: 34,818 vs. 16,588; OR=1.2, 95% CI: 1.2-1.3; p < 0.005 ED visits: All-cause related: 11,573 vs. 7,876; OR=0.9, 95% CI: 0.8-0.9; p < 0.005 Depression: 429 vs. 196; OR=1.5, 95% CI: 1.3-1.8; p < 0.005 Inpatient stays: All-cause related: 6,808 vs. 4,352; OR=0.9, 95% CI: 0.9-1; p < 0.005 Depression: 1,565 vs. 1,030; OR=1.4, 95% CI: 1.3-1.6; p < 0.005	
Huang, 2022 [10]; Taiwan	Population-based study	Patients with unipolar depression classified as TRD	44,086	Overall all-cause related HRU per year Outpatient care: Outpatient visits: 99.9% Inpatient care: Admissions: 23.4% Hospital days: 23.4% Emergency care: ER visits: 40.5% Overall psychiatric-related HRU per year Outpatient care: Outpatient visits: 91.6% Inpatient care: Admissions: 5.5% Hospital days: 5.5% Emergency care: ER visits: 1.5%	-
Zhdanava, 2021 [11]; US	Retrospective study	Patients with MDD classified as TRD and with anxiety disorder and/or SUD	3,166	TRD cohort had increased HRU, compared to non-TRD MDD or non-MDD cohorts: Inpatient admission: 0.3 vs. 0.2 or 0.1; p < 0.01 Outpatient visits: 23.8 vs. 16.8 or 11.6; p < 0.01 ED visits: 0.9 vs. 0.7 or 0.6; p < 0.01	Work loss data (n=310) in all cohorts [TRD, non-TRD MDD and non-MDD]) Work loss days (TRD vs. non-TRD MDD): 54 days vs. 32 days; p < 0.01 Work loss days (TRD vs. non-MDD): 54 days vs. 17 days; p < 0.01
Szukis, 2021 [12]; US	Retrospective, matched-cohort study	Patients with MDD classified as TRD	10,449	All-cause related adjusted HRU PPPY during the follow-up period. TRD vs. non-TRD MDD: Inpatient days: IRR=2.3, 95% CI: 2.0-2.6; p < 0.0001 Inpatient visits: IRR=1.7, 95% CI: 1.6-1.8; p < 0.0001 Outpatient visits: IRR=1.5, 95% CI: 1.4-1.5; p < 0.0001	-

Author, year; Country	Study design	Patient population	Sample size (N)	Outcomes	
				Healthcare resource utilization (HRU)	Lost workdays
				Pharmacy visits: IRR=1.5, 95% CI: 1.5-1.5; p < 0.0001 TRD vs. non-MDD: Inpatient days: IRR=12.0, 95% CI: 10.6-13.7; p < 0.0001 Inpatient visits: IRR=5.0, 95% CI: 4.5-5.6; p < 0.0001 Outpatient visits: IRR=3.8, 95% CI: 3.7-3.9; p < 0.0001 Pharmacy visits: IRR=3.3, 95% CI: 3.3-3.4; p < 0.0001	
Shah, 2021 [13]; US	Retrospective longitudinal study	Patients with MDD classified as TRD and with CNPC	2,147	Mean unadjusted HRU All-cause related (% with 1 or more visits): Inpatient visits: 22.4% Outpatient visits: 76.2% ED visits: 39.9% All-cause related (mean number of visits): Inpatient visits: 0.5 (1.3) Outpatient visits: 8.0 (15.8) ED visits: 1.0 (2.4) MDD-related (% with 1 or more visits): Inpatient visits: 3.6% Outpatient visits: 7.8% ED visits: 2.3% MDD-related (mean number of visits): Inpatient visits: 0.1 (0.3) Outpatient visits: 3.9 (6.9) ED visits: 0.03 (0.23)	-
Park, 2021 [15]; South Korea	Retrospective study	Patient with TRD and psychiatric conditions	15,887	Overall HRU for two years: Switching AD vs. adding AD vs. adding AAP Hospitalization: 48% vs. 42.8% vs. 43.3%; p < 0.001 Inpatient days: mean, 20.7 (75.8) vs. 18.7 (78.5) vs. 34.1 (115.6); p < 0.001 Outpatient visits: mean, 87.8 (66.6) vs. 83 (64.6) vs. 67.8 (54.3); p < 0.001 ER visits: mean, 0.2 (1.2) vs. 0.2 (1) vs. 0.2 (0.8)	-
Denee, 2021 [16]; UK	Retrospective study	Patients with MDD classified as TRD	295	Mean number of encounters per month by health status MDE: Primary care visits: 0.3 (0.5) Primary care visits for depression: 0.3 (0.5) GP visits: 0.3 (0.5) Nurse visits: 0.03 (0.2) Specialist visits: 0.4 (0.2) Hospitalizations: 1.4 (4.2) Remission:	-

Author, year; Country	Study design	Patient population	Sample size (N)	Outcomes	
				Healthcare resource utilization (HRU)	Lost workdays
				Primary care visits: 0.2 (0.5) Primary care visits for depression: 0.2 (0.3) GP visits: 0.2 (0.4) Nurse visits: 0.05 (0.2) Specialist visits: 0.2 (0.2) Hospitalizations: 0.2 (1.2) Recovery: Primary care visits: 0.1 (0.2) Primary care visits for depression: 0.04 (0.1) GP visits: 0.1 (0.3) Nurse visits: 0.1 (0.2) Specialist visits: 0.2 (0.3) Hospitalizations: 0.04 (0.3)	
Zhdanava, 2020 [17]; US	Retrospective, longitudinal matched cohort study	Patients with MDD classified as TRD and with physical conditions	2,317	Mean HRU per year in TRD (n=278) All-cause related (TRD vs. non-TRD MDD or non-MDD) Inpatient admissions: IRR=1.5 or 3.4; p < 0.001 for both Inpatient days: IRR=1.3; p = 0.062 or 3.6; p < 0.001 ED visits: IRR=1.3; p < 0.017 or 2.3; p < 0.001 Outpatient visits: IRR=1.5 or 2.3; p < 0.001 for both Physical condition-related (TRD vs. non-TRD MDD or non-MDD) Inpatient admissions: IRR=1.2; p = 0.113 or 2.4; p < 0.001 Inpatient days: IRR=1.1; p = 0.611 or 2.5; p < 0.001 ED visits: IRR=1.4; p = 0.001 or 2.1; p < 0.001 Outpatient visits: IRR=1.2; p = 0.001 or 1.4; p < 0.001	Mean work loss days per year in TRD (n=278) All-cause related: Total work loss days: 57.5 Medical-related absenteeism: 15.3 Disability: 42.2 Physical condition-related: Total work loss days: 3.7 Medical-related absenteeism: 2.5 Disability: 1.2
Shrestha, 2020 [18]; US	Retrospective cohort study	Patients with MDD classified as TRD	Commercial: 27,595; Medicaid: 5,556; Medicare: 1,856	The odds of hospitalization were higher with TRD than treatment-responsive depression: All-cause related: OR=1.3-1.8; p < 0.001 Mental health-related: OR=1.5-2.2; p < 0.001 The odds of ED visits were significantly higher with TRD than treatment-responsive depression: All-cause: OR=1.4-1.5; p < 0.001 Mental health-related: OR=1.5-2.1; p < 0.001 The IRRs of outpatient visits were greater with TRD than treatment-responsive depression:	-

Author, year; Country	Study design	Patient population	Sample size (N)	Outcomes	
				Healthcare resource utilization (HRU)	Lost workdays
				All-cause: IRR=1.3-1.5; p < 0.001 Mental health-related: IRR=1.5-1.9; p < 0.001 Incremental HRU by payer type for TRD (Commercial, Medicaid, and Medicare) All-cause HRU: Hospitalization: OR/IRR: 1.8, 1.3, and 1.6 ED visits: OR/IRR: 1.5, 1.4, and 1.4 Outpatient visits: OR/IRR: 1.5, 1.4, and 1.3 Mental health-related HRU: Hospitalization: OR/IRR: 2.2 vs. 1.5 vs. 2.2 ED visits: OR/IRR: 1.9 vs. 1.5 vs. 2.1 Outpatient visits: OR/IRR: 1.9 vs. 1.5 vs. 1.9	
Pilon, 2020 [19]; US	Retrospective, longitudinal study	Patients with MDD classified as TRD	6,411 HHS: 1,152 No HHS: 5,259	Mean HRU PPPY across patients using HHS and not using HHS All-cause related Inpatient visits: 0.9 (1.9) and 0.3 (1.0) No. of inpatient days: 4.7 (13.9) and 1.3 (4.2) ED visits: 1.7 (3.0) and 0.9 (1.8) Outpatient visits: 35.2 (22.8) and 23.6 (17.4) Mental health-related Inpatient visits: 0.3 (1.1) and 0.2 (0.9) No. of inpatient days: 2.2 (10.2) and 1.0 (3.8) ED visits: 0.3 (1.2) and 0.2 (0.8) Outpatient visits: 13 (14.3) and 13.7 (14.7) HHS-related HRU in TRD vs. non TRD MDD or non-MDD All-cause related: 4.6 (11) vs. 3.9 (8.7) or 3.4 (8.1) Mental health-related: 0.2 (1.1) vs. 0.2 (1.4) or 0.1 (1.4)	Work loss data was available for 336 patients using HHS and 1572 patients not using HHS All-cause related Total work loss days: 50.7 (62.7) vs. 34.6 (55.2) Medical-related absenteeism days: 14.1 (13.5) vs. 9.1 (9.2) Disability days: 36.7 (65.1) vs. 25.5 (56.7) Mental health-related: Total work loss days: 18.5 (45.3) vs. 19.2 (40.1) Medical-related absenteeism days: 4.6 (8.4) vs. 5 (6.9) Disability days 14 (44.7) vs. 14.2 (40.2)
McIntyre, 2020 [20]; Canada	Retrospective, longitudinal cohort study	Patients with MDD classified as TRD	277	HRU during the 2-year follow-up: TRD compared to non-TRD (n=1,108) and non-MDD (n=1,108) All-cause related % of visits: Outpatient visits: 99% vs. 99% and 94% ED visits: 67% vs. 57% and 43% Mental health-related visits: 14% vs. 6% and 0% GP/FM visits: 98% vs. 96% and 89% Psychiatry visits: 72 % vs. 36% and 4% Average no. of visits: Outpatient visits: 38.2 vs. 24.2 and 14.4	-

Author, year; Country	Study design	Patient population	Sample size (N)	Outcomes	
				Healthcare resource utilization (HRU)	Lost workdays
				ED visits: 2.7 vs. 2.0 and 1.1 Mental health-related visits: 0.3 vs. 0.1 and 0 GP/FM visits: 21 vs. 15 and 10 Psychiatry visits: 10 vs. 3 and 0 Depression-related % of visits: ED visits: 14% vs. 3% and 0% Mental health-related visits: 12% vs. 2% and 0% GP/FM visits: 52% vs. 43% and 0% Psychiatry visits: 48% vs. 24% and 0% Average no. of visits: ED visits: 0.2 vs. 0.1 and 0 Mental health-related visits: 0.2 vs. 0.02 and 0 GP/FM visits: 3.1 vs. 1.6 and 0 Psychiatry visits: 5.9 vs. 2 and 0	
Li, 2020 [21]; US	Retrospective study	Patients with MDD classified as TRD	2,384	HRU accounted per year (TRD vs. non-TRD) ED visits in 1st year: 26% vs. 19%; OR=1.4, 95% CI: 1.2-1.6 ED visits in 2nd year: 22% vs. 18%; OR=1.3, 95% CI: 1.1-1.4 Inpatient hospitalization in 1st year: 8% vs. 5%; OR=1.7, 95% CI: 1.5-2.1 Inpatient hospitalization in 2nd year: 7% vs. 5%; OR=1.4, 95% CI: 1.2-1.7 No. of hospital stay days in 1st year: 8.8 vs. 5.9 No. of hospital stay days in 2nd year: 9.6 vs. 6.2 No. of outpatient visits in 1st year: 11.5 vs. 8.5 No. of outpatient visits in 2nd year: 7.4 vs. 5.6	-
Cai, 2020 [22]; US	Retrospective cohort study	Patients with MDD classified as TRD	3,317	All-cause HRU of TRD episodes vs. non-TRD MDD Hospitalization: 24.3% vs. 14% ER visit (at least 1 visit): 32.6% vs. 13.4% Physician office visit: 97.6% vs. 87.7% Outpatient services: 99.1% vs. 90.8%	-
Benson, 2020 [23]; US	Retrospective, longitudinal cohort study	Patients with MDD classified as TRD	178	All-cause HRU among TRD vs. non-TRD MDD or non-MDD Inpatients visits PPPY: 0.3 vs. 0.2 or 0.1; $p < 0.05$ for all comparisons ER visits PPPY: 0.7 vs. 0.4 or 0.3; $p < 0.05$ for all comparisons Inpatient stay days: 3.0 vs. 0.7 or 0.2 % Patients using pharmacotherapy during the 12-month follow-up:	-

Author, year; Country	Study design	Patient population	Sample size (N)	Outcomes	
				Healthcare resource utilization (HRU)	Lost workdays
				1 AD: 13.8% vs. 71.9% vs. 16.1% 2 ADs: 26.1% vs. 20.6% vs. 3% 3 ADs: 29.7% vs. 3.4% vs. 0% ≥4 ADs: 10.3% vs. 0.1% vs. 0% Antipsychotics: 34.3% vs. 3.6% vs. 0.4% Anticonvulsants: 16.8% vs. 10.2% vs. 7.1%	
Sussman, 2019 [24]; US	Retrospective cohort study	Patients with primary or secondary depression classified as TRD	800	HRU per year during the 12-month follow-up period (comparison of matched cohorts: TRD vs. non-TRD) All-cause related: Hospitalizations: 0.1 (0.4) vs. 0.1 (0.4); p = 0.418 ED visits: 0.3 (0.9) vs. 0.2 (0.8); p = 0.047 Outpatient visits: 18 (17) vs. 13.4 (13.9); p < 0.001 Prescriptions: 29.9 (25.0) vs. 24 (22.3); p < 0.001 Depression-related: Hospitalizations: 0.04 (0.2) vs. 0.02 (0.2); p = 0.031 ED visits: 0.04 (0.2) vs. 0.02 (0.2); p = 0.013 Outpatient visits: 6.5 (10.9) vs. 3.2 (7.3); p < 0.001 Prescriptions: 10.1 (7.0) vs. 6.5 (5.9); p < 0.001	-
Pilon, 2019a [25]; US	Retrospective, longitudinal-matched cohort study	Patients with MDD classified as TRD	3,224	All-cause HRU PPPY TRD cohort vs. non-TRD MDD: Inpatient visits: 0.7 vs. 0.5; IRR=1.3, 95% CI: 1.2-1.5; p < 0.001 Inpatient days: 4.2 vs. 3.1; IRR=1.4, 95% CI: 1.2-1.5; p < 0.001 ED visits: 1.3 vs. 1.1; IRR=1.3, 95% CI: 1.2-1.3; p < 0.001 Outpatient visits: 21.4 vs. 17.6; IRR=1.2, 95% CI: 1.2-1.3; p < 0.001 TRD cohort vs. non-MDD: Inpatient visits: 0.7 vs. 0.3; IRR=1.9, 95% CI: 1.2-2.1; p < 0.001 Inpatient days: 4.2 vs. 1.9; IRR=1.9, 95% CI: 1.7-2.2; p < 0.001 ED visits: 1.3 vs. 0.6; IRR=2.2, 95% CI: 2-2.3; p < 0.001 Outpatient visits: 21.4 vs. 12.3; IRR=1.6, 95% CI: 1.6-1.7; p < 0.001	-
Pilon, 2019b [26]; US	Retrospective, longitudinal cohort study	Patients with MDD classified as TRD	6,411	HRU PPPY stratified by severity level: Severe (n=1,455), moderate (n=2,153) and mild (n=455) All-cause related Moderate vs. mild: Inpatient visits: 0.6 vs. 0.4; IRR=1.5, 95% CI: 1.1-1.8; p = 0.002	-

Author, year; Country	Study design	Patient population	Sample size (N)	Outcomes	
				Healthcare resource utilization (HRU)	Lost workdays
				Inpatient days: 2.8 vs. 1.7; IRR=1.7, 95% CI: 1.2-2.2; p = 0.001 ED visits: 1.6 vs. 1.3; IRR=1.2, 95% CI: 1.0-1.4; p = 0.04 Outpatient visits: 46.3 vs. 42.6; IRR=1.1, 95% CI: 1.0-1.2; p = 0.017 Severe vs. mild: Inpatient visits: 0.9 vs. 0.4; IRR=2.5, 95% CI: 2-3.2; p < 0.001 Inpatient days: 4.1 vs. 1.7; IRR=2.6, 95% CI: 1.9-3.6; p < 0.001 ED visits: 2.0 vs. 1.3; IRR=1.5, 95% CI: 1.3-1.8; p < 0.001 Outpatient visits: 46.9 vs. 42.6; IRR=1.1, 95% CI: 1.0-1.2; p = 0.005 Behavioural health-related Moderate vs. mild Inpatient visits: 0.3 vs. 0.2; IRR=1.5, 95% CI: 1.1-2.1; p = 0.011 Inpatient days: 1.6 vs. 0.9; IRR=1.7, 95% CI: 1.1-2.6; p = 0.016 ED visits: 0.3 vs. 0.2; IRR=1.2, 95% CI: 0.9-1.6; p = 0.207 Outpatient visits: 24.6 vs. 22.2; IRR=1.0, 95% CI: 0.7-1.4; p = 0.983 Severe vs. mild Inpatient visits: 0.6 vs. 0.2; IRR=3.7, 95% CI: 2.7-5.2; p < 0.001 Inpatient days: 3.1 vs. 0.9; IRR=3.5, 95% CI: 2.3-5.4; p < 0.001 ED visits: 0.5 vs. 0.2; IRR=2.0, 95% CI: 1.5-2.7; p < 0.001 Outpatient visits: 26.1 vs. 22.2; IRR=1.3, 95% CI: 1.1-1.4; p < 0.001	
Pilon, 2019c [27]; US	Retrospective, longitudinal-matched cohort study	Patients with MDD classified as TRD	14,170	All-cause HRU calculated during the follow-up (from index date up to 2 years after index date) TRD vs. non-TRD MDD (p < 0.05 for all): Inpatient visits: IRR=1.4, 95% CI: 1.4-1.5 Inpatient days: IRR=1.5, 95% CI: 1.4-1.5 ED visits: IRR=1.3, 95% CI: 1.3-1.4 Outpatient visits: IRR=1.4, 95% CI: 1.3-1.4 Home care: IRR=1.3, 95% CI: 1.2-1.4 Mental-health institution admissions: IRR=1.8, 95% CI: 1.7-2 Long-term care admissions: IRR=1.2, 95% CI: 1.0-1.5 TRD vs. non-MDD (p < 0.05 for all): Inpatient visits: IRR=3.4, 95% CI: 3.3-3.5	-

Author, year; Country	Study design	Patient population	Sample size (N)	Outcomes	
				Healthcare resource utilization (HRU)	Lost workdays
				Inpatient days: IRR=2.9, 95% CI: 2.9-3 ED visits: IRR=3.6, 95% CI: 3.5-3.6 Outpatient visits: IRR=3.9, 95% CI: 3.8-3.9 Home care: IRR=1.2, 95% CI: 1.2-1.2 Mental-health institution admissions: IRR=28.8, 95% CI: 26.5-31.3 Long-term care admissions: IRR=2.4, 95% CI: 2.1-2.7	
Pilon, 2019d [28]; US	Retrospective matched-cohort study	Patients with MDD classified as TRD	1,582	HRU PPPY calculated during the follow-up (from index date up to 2 years after index date) TRD vs. non-TRD MDD: Inpatient visits: 0.4 vs. 0.2; IRR=2.0, 95% CI: 1.7-2.4; p < 0.001 Inpatient days: 3.2 vs. 1.0; IRR=3, 95% CI: 2.3-3.8; p < 0.001 ED visits: 0.8 vs. 0.6; IRR=1.4, 95% CI: 1.1-1.7; p = 0.001 Outpatient visits: 22 vs. 14.1; IRR=1.5, 95% CI: 1.4-1.6; p < 0.001 TRD vs. non-MDD: Inpatient visits: 0.4 vs. 0.1; IRR=3.1, 95% CI: 2.5-3.7; p < 0.001 Inpatient days: 3.2 vs. 0.8; IRR=2.4, 95% CI: 1.9-3.2; p < 0.001 ED visits: 0.8 vs. 0.4; IRR=1.9, 95% CI: 1.5-2.3; p < 0.001 Outpatient visits: 22 vs. 8.2; IRR=2.7, 95% CI: 2.5-2.8; p < 0.001	-

Abbreviations: AD, Antidepressant; AAP, Atypical Antipsychotics; CNPC, Chronic Non-Cancer Pain Conditions; ED, Emergency Department; ER, Emergency Room; GP, General Practitioner; GP/FM: General Practitioner/Family Medicine; HHS, Home Health Services; HRU, Healthcare Resource Utilization; IRR, Incidence Rate Ratio; MDD, Major Depressive Disorder; MDE, Major Depressive Episode; Non-TRD, Non-Treatment-Resistant Depression; Non-TRD MDD, Non-Treatment-Resistant Depression Major Depressive; OR, Odds Ratio; PPPY, Per-Patient-Per-Year; SUD, Substance Use Disorder; TRD, Treatment-Resistant Depression; vs. versus; 95% CI: 95% Confidence Interval; %, percentage

Figures

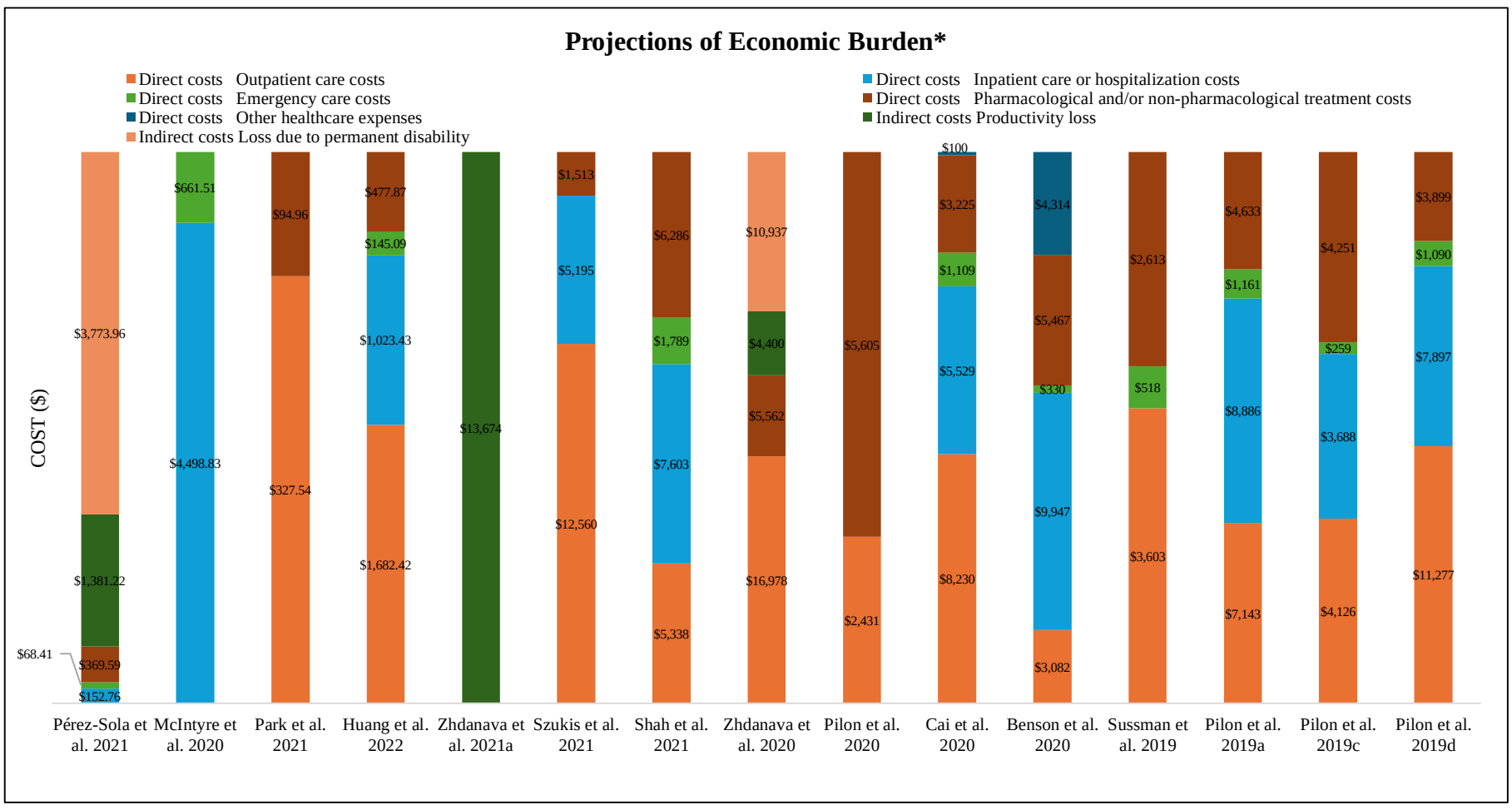

Figure 1. Estimated mean direct and indirect costs related to all-cause for patients with TRD in the included

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