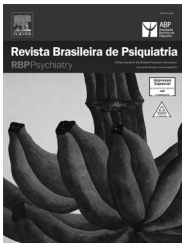
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ORIGINAL ARTICLE

Treatment-resistant depression increases health costs and resource utilization

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DESCRIPTORS:
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Abstract
Objective: Major Depressive Disorder (MDD) is a debilitating condition with a marked social impact. The impact of MDD and Treatment-Resistant Depression (TRD+) within the Brazilian health system is largely unknown. The goal of this study was to compare resource utilization and costs of care for treatment-resistant MDD relative to non-treatment-resistant depression (TRD-). *Methods*: We retrospectively analyzed the records of 212 patients who had been diagnosed with MDD according to the ICD-10 criteria. Specific criteria were used to identify patients with TRD+. Resource utilization was estimated, and the consumption of medication was annualized. We obtained information on medical visits, procedures, hospitalizations, emergency department visits and medication use related or not to MDD. *Results*: The sample consisted of 90 TRD+ and 122 TRD- patients. TRD+ patients used significantly more resources from the psychiatric service, but not from non-psychiatric clinics, compared to TRD- patients. Furthermore, TRD+ patients were significantly more likely to require hospitalizations. Overall, TRD+ patients imposed significantly higher (81.5%) annual costs compared to TRD- patients (R$ 5,520.85; US$ 3,075.34 vs. R$ 3,042.14; US$ 1,694.60). These findings demonstrate the burden of MDD, and especially of TRD+ patients, to the tertiary public health system. Our study should raise awareness of the impact of TRD+ and should be considered by policy makers when implementing public mental health initiatives.

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DESCRITORES:
Depressão;
Resistência ao tratamento;
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Custos de tratamento;
Custos hospitalares.

Depressão resistente ao tratamento aumenta os custos e utilização de recursos

Resumo
Objetivo: O Transtorno Depressivo Maior (TDM) é uma condição debilitante com um forte impacto social. O impacto do TDM e Depressão Resistente ao Tratamento (DRT+) no sistema de saúde brasileiro é praticamente desconhecido. Nosso objetivo é comparar a utilização de recursos e custos dos cuidados para o tratamento de DRT+ em relação ao TDM não resistente (DRT-). *Métodos*: Foram analisados retrospectivamente os prontuários de 212 pacientes diagnosticados com TDM segundo a CID-10. Critérios específicos foram utilizados para identificar pacientes com DRT+. A utilização dos recursos foi estimada e consumo de medicamentos foram anualizados. Foram obtidas informações sobre consultas, procedimentos, internações, atendimentos no serviço de emergência e uso de medicação relacionada ou não ao TDM. *Resultados*: A amostra foi composta de 90 pacientes DRT+ e 122 DRT-. Pacientes DRT+ utilizaram significativamente mais recursos do serviço de psiquiatria, mas não em clínicas não psiquiátricas, em relação a DRT-. Eles eram significativamente mais propensos a exigir internações. Pacientes DRT+ apresentaram um custo direto anual significativamente maior (81,5%) do que pacientes com depressão não resistente (R$ 5.520,85; US$ 3.075,34 contra R$ 3.042,14, US$ 1.694,60). Estes resultados demonstram o impacto do TDM, principalmente da DRT+ ao sistema de saúde público terciário. Nosso estudo deve aumentar a sensibilização para o impacto da DRT + e deve ser considerado pelos formuladores de políticas públicas na implementação de iniciativas de saúde mental.

Introduction

Major depressive disorder (MDD) is a chronic condition with a point-prevalence of approximately 4%[1] and a 1-year prevalence ranging from 7%-10%.[1-4] Approximately 17% of North Americans and Europeans have had at least one depressive episode in their lifetime.[2,3,5] MDD is a highly debilitating condition, imposing a considerable economic burden upon sufferers and upon society.[6] The economic burden of depression has been estimated in several studies worldwide. In fact, MDD is associated with higher costs than diseases such as asthma, osteoporosis, arterial hypertension and schizophrenia. The treatment-related costs (direct costs) of MDD to the United States in 1990 were approximately US$ 12.4 billion, whereas the costs due to the loss of productivity (indirect costs) were US$ 31.3 billion.[8] In addition, costs increased from US$ 77.4 billion in 2000 to US$ 83.1 billion in 2010 (inflation-adjusted US dollars).[9]

A systematic review of cost-of-illness studies for depression published worldwide indicated direct costs ranging from US$ 1,000 to US$ 2,500 per patient/year in 2003 inflation-adjusted US dollars; costs associated with morbidity ranging from US$ 2,000 to US$ 3,700; and finally, costs associated with mortality in the range of US$ 200 to US$ 400.[10] In 2004, the total annual cost of depression in Europe was estimated to be around € 118 billion, or € 253 per capita. Indirect costs were estimated at € 76 billion. Accordingly, depression is the most costly neuropsychiatric disorder in Europe, accounting for approximately 1% of the total European GDP (Gross National Product).[11]

Over half of the patients with a major depressive disorder episode eventually experience a second episode; 80% to 90% of those who had at least two episodes will have subsequent recurrences.[12] Despite available pharmacological and non-pharmacological treatments, as many as 30% of patients with MDD do not respond to their first antidepressant therapy.[12,13,14] Indeed only 20 to 40% of the treated MDD patients achieve full remission.[15] More conservative estimates report that 10 to 20% of the patients with MDD become resistant to multiples forms of therapy.[17,18] Patients with treatment-resistant depression (referred herein as TRD+) have a higher number of medical visits, increased rates of hospitalization, and higher use of psychotropic medications compared to patients with non-treatment resistant MDD (TRD-).[12,19,20,21] It is suggested that resistance to treatment is the main factor determining the economic burden of depression, rather than MDD severity.[22]

Epidemiological data on the prevalence of MDD and TRD+ are scarce in Brazil, and economic data are almost nonexistent. The Brazilian multicentric study of psychiatric morbidity estimated that the 1-month prevalence of depressive disorders ranged from 1.9% to 10.2% in different Brazilian regions.[23] A second study found a 1-month prevalence of 4.5%, 1-year prevalence of 7.1%, and lifetime prevalence of 16.8%.[24] The Longitudinal Investigation of Depression Outcomes (LIDO) study estimated the resource utilization costs of primary care subjects with depression in six international sites, including in Porto Alegre, Brazil.[25]

Accordingly, the objective of this study was to compare the resource utilization and the cost of treatment in TRD+ versus TRD- patients in a tertiary hospital. An additional objective was to estimate the proportion of patients with MDD who are TRD+ and to assess the demographic and clinical characteristics of the TRD+ and non-TRD patients. Such studies are critical to properly inform decisions regarding the allocation of resources and the formulation of public strategies to diagnose and treat mental disorders.

Method

Data source and sample

This retrospective 5-year study examined the medical records of patients seen from July 1997 to June 2002 at the Psychiatric Institute of the Clinics Hospital, School of Medicine, University of Sao Paulo, Brazil.

Our sample consisted of patients aged 18 years or older with MDD according to the ICD-10 (F32.0, F32.1, F32.2, F32.3, F32.8, F32.9, F33.0, F33.1, F33.2, F33.3, F33.4, or F33.8, F33.9). To be included in this analysis, patients had to be followed for at least 6 months in the hospital, as recommended by the World Health Organization (WHO).[26] Patients were excluded from the study if they had comorbid psychosis and/or if they were enrolled in a clinical trial during the study period.

The charts of eligible patients were reviewed, and demographic data, clinical characteristics, and resource utilization in the past five years were collected. Demographics included age, gender, marital status, occupational status and education level. Clinical characteristics included psychiatric and medical comorbidities and the duration of depression treatment. Missing demographic data were supplemented with information from the hospital statistics department database.

Definition of treatment resistance

In this study, TRD+ was defined using the algorithm proposed by Corey-Lisle et al.[19] Accordingly, patients in this study were required to have at least one of the following between July 1997 and June 2002:

1. MDD treated with electroconvulsive therapy (ECT) or requiring the use of monoamine oxidase inhibitors (MAOI), or;
2. Patients who met both the criteria for the TRD scale and TRD matrix, as follows:
   a. TRD scale (TRD+ when score ≥ 5):
      - Augmentation with a mood stabilizer (score of 1) and/or with an antipsychotic (score of 1); scores ranging from 0 to 2.
      - Number of switches among antidepressants over a 5 year period, relative to the switching pattern of all MDD patients in the sample. Patients in the bottom quartile were scored as 0, with increasing scores until the top quartile (score of 3).
      - Number of antidepressant up-titrations over the 5 years relative to those of the whole MDD sample (by quartiles, scores ranging from 0 to 3).
   b. TRD matrix:
      - Three or more drug switches, or at least 2 switches and 2 antidepressant up-titrations across the 5 years of data collection.

MDD patients not meeting the criteria for TRD+ were considered non-resistant to treatment (TRD-).

Resource utilization and health care costs

Resource utilization and health care costs were estimated by measuring all of the health care products and services used by individuals with TRD+ and TRD- over a five-year period as per the hospital medical records. Because patients in the sample had varied follow-up times (from 6 months to 5 years), the amount of resources utilized by each patient was divided by their respective follow-up time. For each variable, we calculated the medium monthly consumption/use, which was then annualized. We obtained data on hospitalizations, emergency department visits, outpatient costs for medical visits and procedures in the psychiatric units as well as in other clinics of the hospital, and the costs of all prescribed medication (regardless of whether they were provided by the public healthcare system or purchased by patients), and therapeutic procedures. Costs were calculated in Brazilian Reais (R$) and US Dollars (US$) as of March 2010. We used the market value for each resource. Market value was used instead of the public health system database because the latter values are artificially low and misleading with respect to the true costs of procedures.

The cost of medical visits, procedures and laboratory or imaging tests were estimated by the Brazilian Medical Association – AMB (1992). This list establishes the payment coefficient rates (fixed) that are applied to each procedure to give the final value. The cost of each coefficient was periodically readjusted to account for inflation and to avoid distortions. At the time of the estimation, coefficients were rated as R$ 0.29. When procedures were not found in this list, we estimated the costs using the list of the School of Medicine Foundation from 2010 or the 2003 values corrected by the National Consumer Price Index (IPCA).

For medications, costs were calculated using the Brazilian Pharmaceutical Guide (March 2010) or the 2003 values corrected by the National Consumer Price Index (IPCA).

Dental procedures were estimated using the Brazilian Dentistry Association list of procedures. Because nurse visits were not listed in the AMB list of procedures, they were valued as a proportion of the cost of a medical visit considering the hourly wage rates paid by the São Paulo State Secretary of Health to physicians and nurses. Other professional visits and activities not reimbursed by health plans were not included in the calculations. Disposable materials were also not included in our calculation, as medical records do not list them.

Sample size calculation and statistical analyses

Because one of our aims was to compare groups of TRD+ and TRD- MDD, we estimated the minimum sample size for TRD+ as 36 patients to detect cost differences of 0.5 standard deviations (SD) between both groups. Significance levels of 5% and a power of 90% were considered. The most conservative estimate for TRD proportion (15%) was used[17] to calculate the total sample size of 240 patients.

We identified 865 patients who were seen in June 2002 and treated for at least 6 months. Patients were selected by systematic sampling of medical charts with a random starting point (first name of patient list in alphabetical order) and sampling interval = 4, generating 217 potential participants. Because our preliminary chart review indicated that a large proportion of subjects did not meet the eligibility criteria, we repeated the above described procedure. A total of 559 patients were selected, and 212 were considered eligible.

We used summary tables and descriptive statistics to describe demographic and clinical features. Groups were compared using the Chi-square test (proportions) for

categorical variables, the parametric Student t-test for normally distributed continuous variables or the non-parametric Mann-Whitney test for non-normally distributed continuous variables. Normality was assessed with the Kolmogorov-Smirnov test, and the homogeneity of variance was tested with Levene's test.

This study was approved by the Ethics Committees of the Clinics Hospital and the Faculdade de Saúde Pública - Universidade de São Paulo. All forms and databases were de-identified; patients were identified in the database by their initials and a sequential number to protect their confidentiality.

Results

Sample characteristics

Our sample consisted of 212 patients with MDD; 90 (42.5%) met the criteria for TRD-. Table 1 summarizes the demographics and clinical characteristics per patient group. TRD+ and TRD- patients were not significantly different regarding gender (p = 0.42), age (p = 0.14), race (p = 0.08), education (p = 0.94), marital status (p = 0.68) and employment status (p = 0.83). Overall, most patients were women (79.2%), older than 40 (79.2%), with at least some high school education (58.5%), married (50.5%), and working at the time of the study (42.0%).

The mean treatment time for TRD+ patients was 6 years, which was significantly longer when compared with TRD- patients (4 years, p < 0.001). Psychiatric comorbidity was similar between groups (0.38 vs. 0.30, NS). In fact, depression was the only psychiatric diagnosis in nearly 70% of the patients, regardless of MDD status. The most frequent non-psychiatric comorbidities were hypertension (15.1%), diabetes (9.4%) and hypothyroidism (7.6%), with no differences between TRD+ and TRD- patients.

Resource utilization

Table 2 lists the resource utilization by patients with TRD+ and TRD-. In the psychiatric clinic, the mean number of annual psychiatric outpatient visits was not

Table 1 Demographic and clinical characteristics

	TRD+ (N = 90)	TRD- (N = 122)	p-value
Demographics			
Age, Mean (SE)	53.8 (1.52)	52.8 (1.48)	0.14
% Women	76.7	81.1	0.42
% Working	40.0	43.5	0.83
% Married	52.2	46.7	0.68
Clinical Characteristics			
Treatment duration (years), Mean (SE)	6.0 (0.43)	4.0 (0.35)	< 0.001
Psychiatric Comorbidities, Mean number/patient (SE)	0.38 (0.07)	0.30 (0.05)	0.57
Mild mental retardation (F70)	1.1%	1.6%	
Dementia in other diseases classified elsewhere (F02)	2.2%	1.6%	
Obsessive-compulsive Disorder (F42)	2.2%	1.6%	
Persistent mood disorders (F34)	3.3%	0.8%	
Phobic anxiety disorders (F40)	2.2%	2.5%	
Eating disorders (F50)	2.2%	4.9%	
Specific personality Disorders (F60)	5.6%	1.6%	
Disorders due to psychoactive substance use (F10-F19)	8.9%	1.6%	
Other Anxiety Disorders (F41)	5.6%	6.6%	
Non-Psychiatric Comorbidities, Mean number/patient (SE)	0.87 (0.11)	0.84 (0.12)	0.67
Migraine	1.1%	2.5%	
Acute Myocardial Infarction	3.3%	0.8%	
Dyslipidemia	1.1%	3.3%	
Other soft tissue disorders	6.7%	0.0%	
Gastritis and duodenitis	2.2%	4.1%	
Obesity	3.3%	5.7%	
Hypothyroidism	11.1%	7.4%	0.36
Diabetes	7.8%	9.8%	0.81
Hypertension	12.2%	17.2%	0.30

TRD: treatment-resistant depression; MDD: major depressive disorder; SE: standard error.

Table 2 Annual resource utilization

	TRD+	TRD-	p-value
Psychiatry, outpatient			
Medical Visits			
Mean (SE)	10.56 (0.53)	9.74 (0.44)	
Median	9.50	8.70	0.12
Psychotherapy			
Mean (SE)	0.05 (0.04)	0.28 (0.20)	
Median	0.00	0.00	**
Diagnostic Tests			
Mean (SE)	8.71(1.03)	7.02 (1.18)	
Median	6.40	0.40	< 0.001
ECT			
Mean (SE)	1.15 (0.47)	-	-
Median	0	-	-
Medications			
Mean (SE)	1.73 (0.11)	1.49 (0.12)	0.01
Median			
Other Clinics, outpatient			
Medical Visits, Mean (SE)	0.30 (0.11)	0.35 (0.11)	0.84
Diagnostic Tests, Mean (SE)	0.70 (0.40)	0.79 (0.26)	0.26
Procedures, Mean	-	0.00	-
Medications, Mean (SE)	0.44 (0.07)	0.42 (0.09)	0.01
Emergency Department			
Medical Visits, Mean (SE)	0.01 (0.001)	0.02 (0.001)	**
Diagnostic Tests	-	0.00	-
Procedures	-	0.00	-
Medications	-	0.00	-
Inpatient Stay			
Hospitalizations, Mean (SE)	0.09 (0.02)	0.05 (0.02)	0.009
Inpatient Days, Mean (SE)	3.53 (0.12)	1.72 (0.08)	0.22
Length of Stay* (days), Mean (SE)	37.6 (7.3)	51.4 (24.2)	0.32
Medical Visits, Mean (SE)	2.79 (0.09)	0.77 (0.03)	0.16
Other Visits, Mean (SE)	0.15 (0.06)	0.24 (0.19)	-
Nurse Care, Mean (SE)	10.32 (3.10)	1.35 (0.71)	0.50
Diagnostic Tests, Mean (SE)	1.82 (0.05)	0.66 (0.03)	**
Procedures, Mean (SE)	0.52 (0.03)	0.01 (0.001)	**
Medications, Mean (SE)	0.52 (0.01)	0.22 (0.01)	0.01

** Not applicable due to small sample size; * Admitted patients only; **TRD+**: Treatment-Resistant Depression; **TRD-**: Not Treatment Resistant Depression; **SE**: Standard Error.

significantly different between the two groups (TRD+ = 10.59, TRD- = 9.74, p = 0.12). However, more laboratory tests (median 6.4 vs. 0.4, p < 0.0001) were requested for those with TRD+ compared to those with TRD-. Because procedures (e.g., electroconvulsive therapy and polysomnography) were only performed in the TRD+ group, group comparison was not possible. Electroconvulsive therapy was performed in 14 patients, for a total of 103.81 sessions per year.

Regarding the pharmacological treatment of depression, over 90% of individuals with TRD- used from one to five different medications during the 5 years of assessment. In those with TRD+, more than half of the patients used more than 10 medications during the same time period (p < 0001).

Regarding resource utilization in specialty clinics other than psychiatry, no significant differences were found among groups with regard to the number of medical visits

and laboratory tests. Regarding non-psychiatric medication, the only drugs prescribed significantly more in the TRD+ group were drugs to treat gastrointestinal tract disorders (Table 1).

The yearly hospitalization rate was higher in the TRD+ group compared to TRD- (9% vs. 5%, p = 0.009); the mean number of inpatient days per year was also higher in the TRD+ group (3.53 vs. 1.72, p = 0.009). Although not statistically significant, the mean number of hospitalization days in a subsample of patients who were admitted to hospital was surprisingly shorter in the TRD+ group when compared to the TRD- patients (37.6 days vs. 51.4 days, respectively, p = 0.32). Furthermore, we found no significant differences in the number of tests and procedures, or with the medication utilized during the inpatient stay, when comparing both groups.

Health care costs

Table 3 summarizes the health care costs for TRD+ and TRD- subjects. TRD+ was significantly more expensive than that of TRD- subjects in all settings but at the emergency department. Accordingly, the total individual costs of annual treatment for TRD+ was 81.5% more expensive than the TRD- group [R$ 5,520.85 (US$ 3,075.34) vs. R$ 3,042.14 (US$ 1,694.60, respectively).

Overall, outpatient psychiatric care accounted for the vast majority of costs in both groups (60% in TRD+ vs. 72% in TRD-), followed by inpatient care (23% in TRD+ vs. 17% in TRD-) (Figure 1). Approximately 85% of the total costs for treating MDD patients were derived from medication use (67% for TRD+ and 72% for TRD-) and inpatient per diem charges (15% for TRD+ and 13% for TRD-) (Figure 2).

Table 3 Mean annual cost of treatment for TRD+ and TRD-, overall and by care category (costs for March 2010)

	TRD+		TRD- (R$)		MDD (R$)	
	R$	US$	R$	US$	R$	US$
Psychiatric Clinic						
Medical Visits	245.95	137.00	226.16	125.98	234.56	130.66
Other Visits	3.45	1.92	17.08	9.51	11.29	6.29
Nurse Care	0.39	0.22	0.09	0.05	0.22	0.12
Diagnostic Tests	174.78	97.36	133.44	74.33	150.99	84.11
Procedures	236.33	131.65	0.00	0.00	100.33	55.89
Medications	2,637.93	1,469.44	1,798.53	1,001.85	2,154.88	1,200.36
Subtotal	3,298.83	1,837.58	2,175.30	1,211.73	2,652.27	1,477.42
Other Clinics						
Medical Visits	6.96	3.88	7.94	4.42	7.52	4.19
Diagnostic Tests	12.11	6.75	15.21	8.47	13.89	7.74
Procedures	0.00	0.00	0.07	0.04	0.04	0.02
Medications	910.64	507.26	321.99	179.36	571.89	318.57
Subtotal	929.71	517.89	345.21	192.30	593.34	330.51
Emergency Department						
Medical Visits	0.29	0.16	0.41	0,23	0.36	0.20
Diagnostic Tests	0.00	0.00	0.38	0.21	0.22	0.12
Procedures	0.00	0.00	0.00	0.00	0.00	0.00
Medications	0.00	0.00	0.14	0.08	0.08	0.04
Subtotal	0.29	0.16	0.93	0.52	0.66	0.37
Hospitalizations						
Days	849.26	473.07	406.50	226.44	594.47	331.14
Medical Visits	64.77	36.08	17.91	9.98	37.80	21.06
Other Visits	3.35	1.87	13.51	7.53	7.32	4.08
Nurse Care	90.59	50.46	11.85	6.60	45.28	25.22
Diagnostic Tests	38.01	21.17	12.60	7.02	23.39	13.03
Procedures	108.14	60.24	2.99	1.67	47.63	26.53
Medications	137.90	76.82	55.34	30.83	90.39	50.35
Subtotal	1,292.02	719.71	520.70	290.05	846.28	471.41

R$ = Values in Brazilian Real; US$ = American Dollars; TRD+: Treatment Resistant Depression; TRD-: Non-Treatment-Resistant Depression.

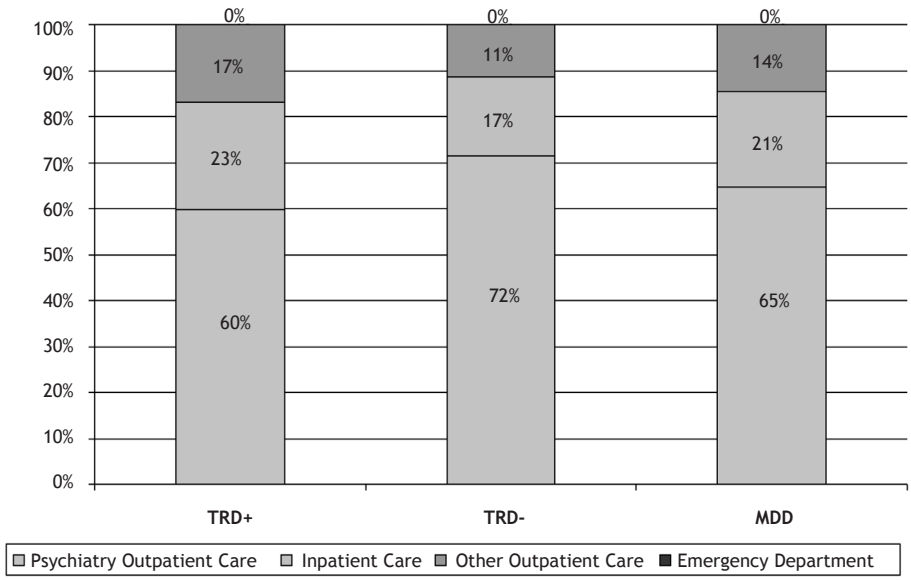


Figure 1 Health Care System distribution costs.

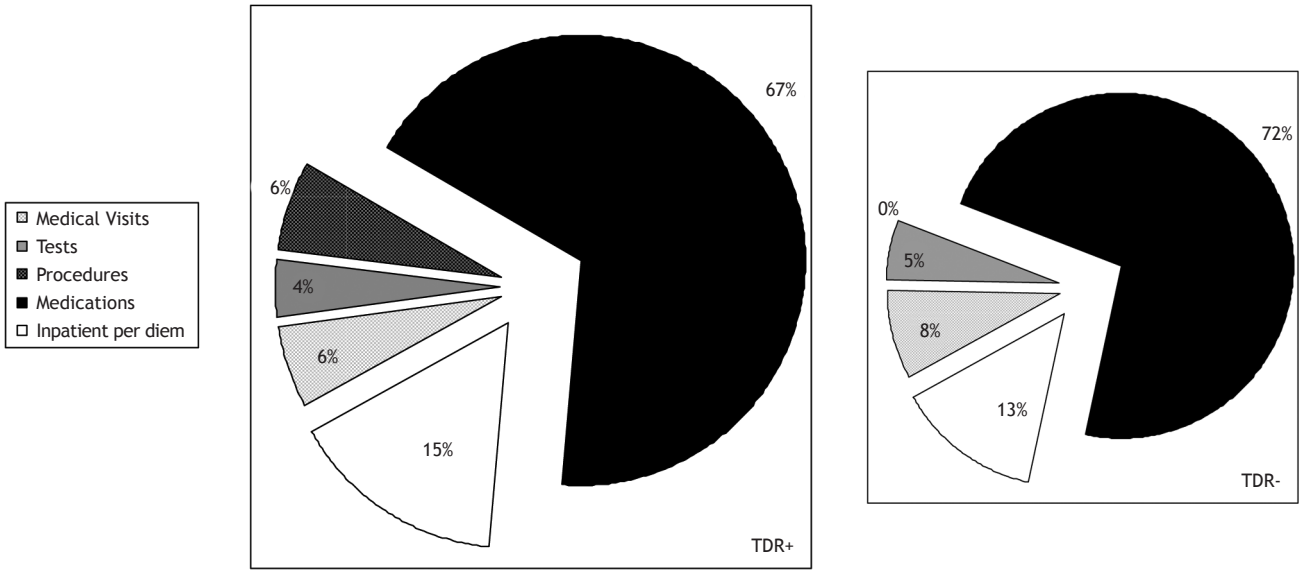


Figure 2 Cost analysis for TRD+ and TRD- groups.

Discussion

Results from this study are consistent with the literature in that TRD+ is a common condition and treatment for TRD+ patients is associated with significantly higher costs when compared to TRD- patients.[19-22] Due to the nature of the psychiatric institution in which these data were collected (i.e., a tertiary center), the high prevalence of TRD+ was expected. When analyzing our data, we observed that a significant proportion of subjects were being prescribed suboptimal doses of medication. It has been reported that, for reasons that are not fully understood, patients seen in academic institutions often receive suboptimal medication doses.[15] Nonetheless, this fact is not seen exclusively in tertiary care settings. Studies conducted in managed care settings[13,27] suggest that only 11% of patients in need

of antidepressant therapies receive the proper dose and duration of treatment. This issue may have contributed to the inflated TRD+ prevalence observed in this sample because our study used an algorithm to categorize patients into the TRD+ or TRD- groups based on medication records rather than actual face-to-face psychiatric assessment. Groups were similar regarding sociodemographic characteristics, as well as psychiatric and non-psychiatric comorbidities. Clinical factors found to be associated with treatment resistance in other studies, such as comorbid anxiety disorders,[28] were not significantly different in both sub-groups, possibly due to the small sample size.

Individuals with TRD+ utilize more resources and are substantially more costly to the health system compared to individuals with TRD-. This result was expected because TRD+ is defined as a series of conditions related to failure in the previous use of resources that results in an increased use of resources. Medication costs were responsible for 70% of the total costs in our sample, whereas the per diem hospitalization cost was responsible for 15%. Other costs are smaller.

When comparing the two groups, we found no differences regarding the number of medical visits or laboratory tests conducted in non-psychiatric clinics, nor did we find any differences in the treatment for disorders other than MDD. These findings differ from other studies that reported that an increased severity of depression translates into higher health-care utilization and costs for comorbid conditions[18,28] and that the improvement in the symptoms of depression is associated with lower resource utilization for non-depression-related reasons.[29-32]

Indeed, in our data, the costs of comorbidities accounted for only 14% of the total costs. Other studies reported that up to 70% of the costs of managing depression were due to the treatment of comorbidities.[34] This discrepancy may be explained by the fact that patients referred to the tertiary care often have the treatment of their comorbidities taken care of at the primary or secondary level. Because these treatments occur outside of the teaching hospital setting, our study did not capture these costs.

The mean annual cost for the symptoms of depression was R$ 4,092.55 (US$ 2,279.72), which is greater than the costs of other chronic disorders in Brazil (reference). The annual costs of osteoporosis (2001) were R$ 748.81 per patient.[35] For schizophrenia (1998), they were R$ 1,256.00.[36]

Medication was the most significant driver of healthcare cost, accounting for 70% of the total cost. This figure is in contrast with that observed in other studies that report that 6% to 29% is associated with drug costs.[10,11] In other studies, the most relevant cost drivers of direct costs are usually hospitalization (average 42% versus 21% in our study) or outpatient care.[10,11,33] This lower hospitalization cost, compared with the literature, is not due to lower hospitalization rates or shorter lengths of stay. In our study, the average number of annual inpatient days was similar to those found in US studies using claim databases for TRD+ and TRD- patients[19,20] and higher than that observed in primary care patients with depression in Porto Alegre, Brazil.[37] The length of stay of hospitalized patients was similar (42.8 days in the MDD sample) when compared to the average length of stay in Brazilian psychiatric hospitals (40 days, source: MS/SAS/DECAS/CGSIAH/2000).To explain this discrepancy, we highlight that the list payment values of the Brazilian Medical Association is clearly outdated and insufficient to even minimally cover current hospital costs. In contrast, because medication is listed according to the market price, its cost is more likely to reflect the current market environment. The fact that we were unable to account for the costs of non-medical staff or certain procedures (e.g., social worker care, staff meetings to discuss treatment, use of disposable material) may have contributed to an increase in the medication costs in this study.

Certain limitations should be considered in interpreting these findings.

- This study reflects healthcare utilization pattern within a tertiary care hospital that is likely not representative of public mental healthcare services in Brazil. Furthermore, being a teaching hospital, multiple medical residents were likely responsible for patient care over the time encompassed by this study. This fact is of critical importance because this turnover may have led to insufficient knowledge about the patient's history; it may be that changes in medication are sometimes not totally necessary. It is possible, in this case, that this TRD+ group could include patients with "pseudo-resistance", a finding reported in other teaching hospitals.[15]
- The sample size calculation estimated that 240 patients were needed for the study. The final sample consisted of 212 patients. However, because we had a higher proportion of TRD+ patients than initially expected (42.5% versus 15%), we do not believe that this fact had a significant impact on our results. However, the moderate sample size did not allow us to detect differences with regard to some variables such as resource utilization in other clinics and the emergency department.
- As all antidepressant switches and up-titrations were counted in the TRD scale and the TRD matrix regardless of the adequacy of antidepressant dosage and treatment duration, the proportion of TRD+ was likely overestimated.
- Due to its retrospective nature, we were unable to capture indirect costs in this study. The results of "cost of illness" studies in depression are variable, but indirect costs always account for the greater share of the total cost.[8-11] It has also been reported that TRD+ patients have significantly higher indirect costs than TRD- patients.[19-20] Although significantly higher, the costs of TRD+ compared to TRD- were not as substantial in our study as has been reported elsewhere, where TRD+ was reported to cost up to 6-times more than TRD-.[29,32,38]

Conclusion

We assessed the costs of MDD in a tertiary reference hospital. Our study should raise awareness of the impact of TRD+ and should be considered by policy makers when implementing public mental health initiatives. Despite inherent limitations, this study demonstrates that MDD, and specifically TRD+, is associated with high treatment costs. Considering that indirect costs were not captured in this study, we urge future studies to account for these costs to further measure the economic impact of depression on the healthcare system.

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