

The Financial Implications of New Episodes of MDD for Treatment Resistant Versus Stable Depressed Individuals

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Summary

Objective: The primary aim of this study was to document the economic impact of increased direct medical costs associated with new treatment episodes of major depressive disorder (MDD). A second aim was to compare and contrast the magnitude of the cost drivers among MDD patients categorized as stable versus treatment resistant.

Method: Administrative claims data from the PHARMetrics database on adults with new MDD treatment episodes were stratified based upon anti-depressant use algorithms for defining treatment resistant and stable cohorts. A pre-post comparison of medical costs was completed for stable versus treatment resistant depression therapy to determine the aggregate and incremental costs, and the likelihood of cost increases following a new treatment episode.

Results: The mean increase in total direct medical costs using the less restrictive (more restrictive) algorithm was \$4,801 (\$8,047) for the treatment resistant cohort versus \$1,722 (\$2,249) for the stable cohort. From baseline, these increases were 104 percent (181 percent) for treatment resistant individuals and 44 percent (55 percent) for stable individuals. A post hoc analysis documented that non-depression related costs were significantly more likely to increase ($p < 0.001$) in the treatment resistant cohort (67 percent to 73 percent) versus the stable cohort (59 percent to 61 percent). The results were not sensitive to inclusion/exclusion of outlier values.

Conclusion: Increased direct medical costs of MDD are substantial following the onset of a new treatment and significantly higher among treatment resistant than among stable depressed patients. Direct medical cost for treatment resistance patients during new episodes of treatment are more than double their baseline cost.

Key Points

- Major Depressive Disorders are costly to manage and the magnitude of direct medical costs doubles among patients who are treatment resistant.
- Our estimates of the increases in direct medical costs associated with new treatment episodes are between \$4,801 and \$8,047 for treatment resistant patients and \$1,722 to \$2,249 for stable patients.
- Estimates of the prevalence and economic impact of treatment resistant depression are sensitive to the definition of treatment resistance.

Introduction

Depressive disorders are one of the most frequent reasons for primary care physician office visits, yet appropriate medication management of individuals with depression remains challenging despite significant breakthroughs in pharmacotherapy. Poor health outcomes are more likely for patients who have serious long-term illness and a diagnosis of depression.^{1,2} Therefore, appropriate management for

individuals with major depression is critical because depression often is episodic and recurrent, and may lead to a major depressive disorder (MDD) if not appropriately managed.³

Based on their antidepressant and other medical resource use, MDD patients can be defined as having a stable response to treatment or can be defined as treatment resistant. Patients are considered treatment resistant if they require modifications to

Exhibit 1. Demographics Data on Sample of Stable and Treatment Resistant Depressive Patients ^{4,5}

		Stable		Treatment Resistant	
		Method 1	Method 2	Method 1	Method 2
Age	Mean (STD)	41 (12)	41 (12)	41 (12)	42 (12)
Gender	Female N (%)	4,945 (65.04%)	6,755 (65.64%)	2,420 (67.86%)	610 (69.48%)
	Male N (%)	2,658 (34.96%)	3,536 (34.36%)	1,146 (32.14%)	268 (30.52%)
Insurance	Commercial N (%)	6,802 (89.46%)	9,196 (89.36%)	3,171 (88.92%)	777 (88.50%)
	Medicaid N (%)	429 (5.64%)	587 (5.70%)	229 (6.42%)	71 (8.09%)
	Medicare N (%)	68 (0.89%)	94 (0.91%)	30 (0.84%)	4 (0.46%)
	Self-Insured N (%)	270 (3.55%)	372 (3.61%)	122 (3.42%)	20 (2.28%)
	Missing/Unknown N (%)	34 (0.45%)	42 (0.41%)	14 (0.39%)	6 (0.68%)
Region	East N (%)	1,523 (20.03%)	2,161 (21.00%)	863 (24.20%)	225 (25.63%)
	Midwest N (%)	3,903 (51.33%)	5,197 (50.50%)	1,717 (48.15%)	423 (48.18%)
	South N (%)	1,535 (20.19%)	2,056 (19.98%)	661 (18.54%)	140 (15.95%)
	West N (%)	642 (8.44%)	877 (8.52%)	325 (9.11%)	90 (10.25%)

their drug therapies (e.g. switch, augmentation or dose adjustment), electroconvulsive therapy (ECT) or emergency treatment or inpatient hospitalization for a depression-related episode within one-year of treatment initiation.^{4,5} Treatment resistance depression (TRD), while not easily defined, is clinically characterized by misdiagnosis, poor patient compliance and inadequate therapy.⁶

Two notable clinical trials provide further evidence of the risk of treatment resistance. Corey-Lisle et al performed a secondary analysis based upon the ARTIST trial that compared three therapeutic treatments for symptoms of depression.⁷ Their follow-up study documented that 46 percent of patients who completed a 6-month follow-up were “nonresponders” despite the fact that many of these individuals were classified as adequately treated with an adequate dose of medication for an adequate duration.⁸ Rush et al. compared acute and long-term treatment outcomes for MDD based upon the National Institute of Mental Health study for treatment

resistant depression STAR*D trial.⁹ For the follow-up study, only 67 percent of MDD patients achieved remission after four treatment steps.¹⁰ The small proportion of patients who achieve complete remission underscores the need to further examine MDD treatment, outcomes, and costs, with particular attention to whether patient therapy reflects that the patient was stable or treatment resistant.

Studies document that depression alone imposes tremendous economic burdens on employers and insurers.¹¹ One can expect even greater health care expenditures as a result of TRD. Crown et al. examined clinical characteristics, health care utilization, and direct medical cost of TRD patients using the MEDSTAT medical claims database.¹² Their analysis yielded higher depression-related outpatient costs among both patients who were hospitalized for TRD as well as those who were treated purely in an outpatient setting.¹² They also found that general medical costs and pharmaceutical costs were higher in the treatment-resistance group.¹² TRD

Exhibit 2. Costs for Stable and Treatment Resistant Depression Surrounding New Treatment Episodes^{4,5}

	Pre Period Costs				Post Period Costs			
	Stable		Treatment Resistant		Stable		Treatment Resistant	
	Method 1	Method 2	Method 1	Method 2	Method 1	Method 2	Method 1	Method 2
Inpatient	\$1,491	\$1,582	\$1,779	\$1,596	\$1,688*	\$2,004*	\$3,096*	\$3,701*
Outpatient Medical	\$1,952*	\$2,029	\$2,276*	\$2,361	\$2,886*	\$3,144*	\$4,475*	\$6,314*
Anti-depressant Drugs	\$0	\$0	\$0	\$0	\$315*	\$376*	\$657*	\$992*
Other Drugs	\$457*	\$485	\$541*	\$477	\$732*	\$820*	\$1,168*	\$1,474*
Total Costs	\$3,900*	\$4,096	\$4,596*	\$4,434	\$5,621*	\$6,344*	\$9,396*	\$12,481*

* Indicates values between Stable and Treatment Resistant are significant at $p < 0.05$

Exhibit 3. Likelihood of Increases in Total (Depression and Non-Depression Related) Direct Medical Costs for Stable and Treatment Resistant Depression Surrounding New Treatment Episodes^{4,5}

Change in Cost (post vs. pre)	Method 1			Method 2		
	Stable N (%)	Treatment Resistant N (%)	P value (test of proportion)	Stable N (%)	Treatment Resistant N (%)	P value (test of proportion)
Increase	5,436 (71.50%)	2,819 (71.50%)	<0.001	7,530 (73.04%)	742 (84.13%)	<0.001
No change or decrease	2,167 (28.50%)	747 (20.95%)		2,780 (26.96%)	140 (15.87%)	

patients were twice as likely to be hospitalized and incurred greater depression related cost.¹² The mean total medical costs among TRD compared to non-treatment resistant depressed patients were six times as great (\$42,344 vs. \$6,512) ($p < .001$), while total depression-related costs were 19 times great among TRD versus those in the comparison group (\$28,001 vs. \$1,455) ($p < .001$).¹²

The objective of this current retrospective study is to perform an analysis of a claims database to explore the variation in direct medical costs following a new treatment episode for stable versus treatment resistant MDD patients. Our analysis provides more recent estimates of cost of TRD than previously reported results.

Methods

We identified 22,338 patients from PHARMetrics, a nationally representative, patient-centric, longitudinal database of nearly 50 million patients from more than 85 health plans. The study period was January

01, 2003 through June 30, 2005. Age and gender variables were provided; however, information on patient race was not available. All identified patients were quality controlled and HIPAA compliant. All research was performed following HIPAA policy and used only de-identified data with no personal health information (PHI). This research was exempt from review by the University's Institutional Review Board.

A pre-post comparison of medical costs for stable versus treatment resistant patients to determine the magnitude and likelihood of cost increases following a new treatment episode. The index date of the study was the date of diagnosis of new episode of MDD. To qualify as a new episode, the patient could not have any depression-related diagnosis or pharmacotherapy during the prior 365 days. In cases where the fill date for an antidepressant occurred within 30 days prior to the date of diagnosis, the index date was reassigned to the antidepressant fill date. This analytical approach compared individual

Exhibit 4. Likelihood of Increases in Non-Depression Related Direct Medical Costs for Stable and Treatment Resistant Depression Surrounding New Treatment Episodes^{4,5}

Change in Cost (post vs. pre)	Method 1			Method 2		
	Stable N (%)	Treatment Resistant N (%)	P value (test of proportion)	Stable N (%)	Treatment Resistant N (%)	P value (test of proportion)
Increase	4,523 (59.49%)	2,386 (66.91%)	<0.001	6,281 (60.92%)	640 (72.56%)	<0.001
No change or decrease	3,080 (40.51%)	1,180 (33.09%)		4,029 (39.08%)	242 (27.44%)	

Exhibit 5. Definition of Non-Stable Depression Using Two Methods^{4,5}

Algorithm One (Russell 2004)

At least **two** changes (switching/augmentation*) **or**
 One *change* + depression-related hospitalization
 (Primary or secondary diagnosis) **or**
 One *change* + ECT (CPT code 90870, 90871) **or**
 One *change* + suicide attempt (ICD 30090, E950x, E959x)

Definitions

*Augmentation = the addition of a second agent to an existing antidepressant
 ECT = Electroconvulsive Therapy
 CPT = Current Procedural Terminology
 MAOIs = Monoamine Oxidase Inhibitors

Algorithm Two (Corey-Lisle 2002)

ECT or MAOIs **or**
 Three switches + 5 points on the TRD Scale **or**
 Two switches + 2 upward titrations + 5 points on the TRD Scale

Treatment –Resistant Depression Scale (TRD)

1 point for one augmentation (2 maximum allowed)
 0-3 points depending on the quartile of *switches*
 (3 being on the highest quartile)
 0-3 points depending on the quartile of *upward titration*
 (3 being on the highest quartile)

health care expenditures following the initiation of a new treatment with that same individual's expenditures in the year prior. Each patient served as his/her own control avoiding problems with a comparison of mean values.

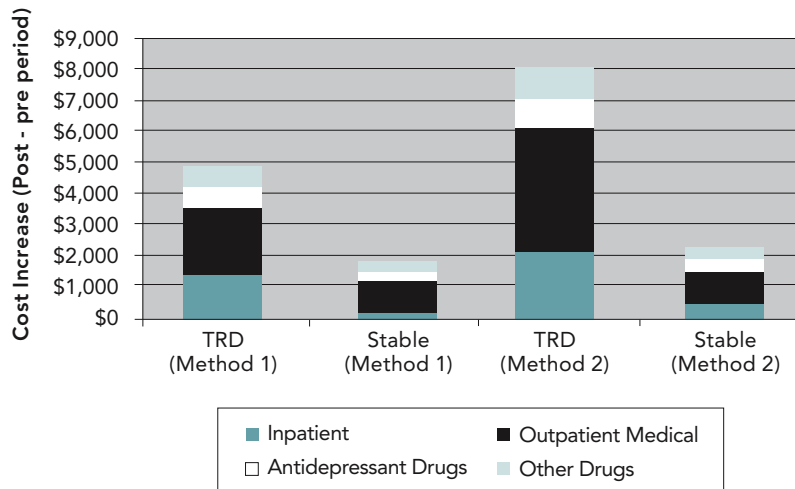
Patients were included if they were aged 18 or older with ICD-9 codes of 2962x, 2963x, 2980x, 3004x, 3091x, 311xx, based on HEDIS 2005, as reported by AHRQ;¹³ met the diagnosis criteria for a new episode, and were continuously enrolled from baseline through the one year follow-up period. Patients were excluded if they had ICD-9 codes of dementia (290xx to 295xx), paranoid (297xx), other psychoses (298xx to 299xx), Alzheimer's disease (331.0), Parkinson's disease (332.x), retardation (317xx to 319xx), senility w/o psychosis (797xx) at baseline or during the follow-up period.⁴ Patients also were excluded if there was a gap between the index date and first anti-depressant fill date greater than or equal to 30 days; if they were without at least four weeks of anti-depressants at appropriate doses, or if they had outlier cost values (0.1 percent at either end).

The cost components of interest were those associated with depression-related treatment, such as anti-depressant and other drug costs, as well as other medical costs associated with inpatient care. The cost algorithms were designed to compare the magnitude of cost increases among those categorized as stable versus treatment resistant based upon two published anti-depressant use algorithms (see Exhibit 5). The first algorithm is based upon the work of Russell.⁴ An alternative algorithm follows the work of Corey-Lisle⁵ and the design of a TRD scale. The TRD scale has a range of values from zero to eight and is based on a matrix of therapy augmentations, switches and titrations. While ECT and MAOIs alone identify a patient as TRD-likely, the matrix of items in the TRD scale, in combination with multiple switches or in combination with upward titration, solidifies the current definition of TRD.

Results

The economic impact of new MDD treatment and the major cost drivers of direct medical expenditures

Exhibit 6. Increases in costs following new treatment initiation



were compared based upon two published anti-depressant use algorithms of Russell and Corey-Lisle.⁴⁵ Exhibit 1 presents the demographic information for the 11,169 MDD individuals who met the inclusion and exclusion criteria and were categorized as being stable or treatment resistant according to the two algorithms. The percentage of patients categorized as treatment resistant was 32 percent using Method 1 (less restrictive) and 8 percent using Method 2 (more restrictive).

Exhibit 2 reflects the differences in costs for MDD patients. Total medical costs following a new onset of anti-depressant treatment for treatment resistant individuals were \$9,396 using Method 1 (\$12,481 for Method 2), while similar costs for stable individuals are \$5,622 using Method 1 (\$6,344 for Method 2). The mean increase in total direct medical costs was \$4,801 using Method 1 (\$8,047 for Method 2) for the treatment resistant cohort versus \$1,722 using Method 1 (\$2,249 for Method 2) for the stable cohort, which represents increases from baseline of 104 percent using Method 1 (181 percent for Method 2) for treatment resistant individuals and 44 percent using Method 1 (55 percent for Method 2) for stable individuals. The major components of these cost increases using the two algorithms were as follows: outpatient care \$2,199 (\$3,952) vs. \$934 (\$1,115); inpatient care \$1,317 (\$2,106) vs. \$197 (\$423); and anti-depressant medications of \$657 (\$992) vs. \$315 (\$376) for treatment resistant and stable cohorts, respectively ($p < 0.001$). Exhibit 6 presents the differences in the post-period costs to the pre-period costs for both cohorts.

As shown in Exhibit 3, the likelihood of increases

in total medical costs was statistically greater ($p < 0.001$) for treatment resistant patients (79 percent for Method 1; 84 percent for Method 2) than for stable patients (72 percent for Method 1; 73 percent for Method 2). A post hoc analysis, shown in Exhibit 4, highlights the fact that among the treatment resistant patients, there were a greater proportion of patients who experienced an increase in direct medical costs that were not directly related to depression. In addition, Non-depression related costs were significantly more likely to increase ($p < 0.001$) in the treatment resistant cohort (67 percent for Method 1; 73 percent for Method 2) in the stable cohort (59 percent for Method 1; 61 percent for Method 2). These results were insensitive to the inclusion or exclusion of outlier values.

Discussion

Major depressive disorder (MDD) is the leading cause of disability in the U.S.¹⁴ Nationally representative data indicate that the prevalence of clinically significant lifetime MDD affects 16.2 percent of adults in the U.S., or between 32.6 to 35.1 million people, and the mean duration of an impairment lasts approximately 16 weeks.¹⁵ In comparison, heart disease affects approximately 1 in 3 adults in the U.S.¹⁶ and is responsible for about 29 percent or almost 700,000 deaths each year.¹⁷ In terms of the economic burden of disease for U.S. employers, the annual cost of illness per employee ranks heart related condition, such as hypertension (\$392) and heart disease (\$368) as the top two illnesses, followed by mental illness (\$348) and arthritis (\$327).¹⁸ These findings correlate to the World Health Organiza-

tion's assessment that MDD is expected to rank second worldwide by the year 2020, after heart disease, as a leading cause of disability.¹⁴

This study examined the direct medical costs of new treatment for patients with major depressive disorder (MDD) who undergo multiple changes in antidepressant treatment within one year of treatment initiation. Both treatment resistant and stable patients were included in the study. The total direct medical costs were two to four times higher among the TRD versus the non-TRD individuals. These treatment resistant patients used more inpatient care services as well as more outpatient medical resources than the stable patients. Our findings are similar to the work of Crown et al in his study of hospitalized patients identified with TRD. Increased resource utilization for both hospitalizations and outpatient visits were identified for the treatment resistant patients. Crown found that TRD hospitalized patients incur a six-fold higher cost difference in their total mean medical costs than the non-TRD patients (\$42,344 vs. \$6,512) ($p < .001$). TRD patients have approximately 12 percent more outpatient visits ($p < .02$) and receive a mean of 2.2 prescriptions versus a mean of 1.4 prescriptions in the cohort of relatively Stable patients.¹²

Russell et al found similar findings with his analysis of 7,737 patients from the MarketScan fee for service (FFS) database. The study patients were identified with TRD, i.e., those who received between two to eight medications changes or had a depression-related hospitalization during the study period. Russell found that both inpatient and outpatient health care expenditures are greater among individuals who are not stabilized on therapy.⁴ In addition, Russell noted that physical illness and mental depression appear to be synergistic in nature and thus, as MDD increases, costs for both general medical care (66 percent to 76 percent) and depression-related illness (24 percent to 33 percent) show an increasing trend that impacts patients who were either non-responsive to therapy or in periods of treatment resistance.⁴

Croghan et al.,¹⁹ in their study of medical and pharmaceutical claims, found that depression-related costs make up only 28 percent of the total medical expenditures for patients who exhibit comorbid chronic disease, such as those associated with musculoskeletal pain, rheumatoid disorders and cutaneous disorders. It is significant that the non-depression-related cost increases were more common among treatment resistant patients, since non-depressive illnesses account for more than 70 percent of the total charges for individuals treated for depression in primary care and that these physical illnesses are influenced by depression.¹⁹

The results of our current database study of medical claims can be compared to a study published by Corey-Lisle and colleagues, who focused on TRD among MDD patients. Their results report that 12 percent of MDD patients are TRD-likely and that annual total medical are \$5,025 for TRD-unlikely; \$10,954 for TRD-likely; and \$3,006 for a matched cohort of individual without depressive disorders.⁵ These results also are consistent with the STAR*D trial, which concluded that a greater burden of illness is characteristic of those who require more treatment steps (i.e. those who took longer to achieve remission or never received remission).¹⁰ Our current research also concurs with earlier studies that examine non-depression costs among patients with depression. When patients are treatment resistant and require multiple changes to their therapies, they risk further deterioration in their physical health, which could lead to increased non-depression health care costs.

While not the focus of this current study, there is evidence that MDD is associated with high indirect costs, too. Research by Greenberg et al suggests that the economic implications of TRD among employees at a Fortune 100 company was not only associated with higher direct medical costs for inpatient and outpatient care, but also was associated with statistically significantly greater indirect costs, such as disability and absenteeism.²⁰ These findings imply that increases in the total cost (direct + indirect costs) between treatment resistant and stable depression patients may be even greater than reported estimates based solely upon direct costs.

Evidence from our multivariate regression analysis suggests that there are certain characteristics of MDD patients that can lead to a greater likelihood of increased health care expenditures following a new MDD treatment. These include treatment resistant vs. stable (Adjusted OR 1.51 (CI = 1.38, 1.67), $p < 0.0001$); males vs. female, (Adjusted OR 1.20 (CI = 1.09, 1.31), $p < 0.0001$); and those patients who have a commercial insurance plan vs. other coverage (Adjusted OR 1.19 (CI = 1.04, 1.36), $p = 0.0098$). Age, however, was not a significant predictor of a greater likelihood of cost increases following a new MDD treatment.

It is well understood that as physical health deteriorates, patients require additional health resources. For patients with chronic medical conditions, co-morbid depression tends to magnify physical illness symptoms.^{21, 22, 11} In addition, the addition of DSM-IV Major Depressive Disorder (MDD) on top of other chronic medical conditions can significantly increase health care utilization and costs. For example, Katon and colleagues report higher costs among elderly patients with depression.

Adults aged 60 and older under the care of a Seattle Washington staff-model health maintenance organization were mailed the PRIME-MD 2-item depression screen.²³ After controlling for chronic illness severity, health care resources and costs were higher among patients with co-morbid depression compared to those patients with chronic medical conditions without depression. In this study, both the non-depressed and depressed individuals incurred inpatient and outpatient costs; however, the non-mental health costs for the co-morbid patients demonstrated an increasing trend in all outpatient categories. When both depression-related and non-depression related total outpatients costs were observed, patients with co-morbid depression had, on average, costs that ranged from \$1,045 to \$1,700, i.e. 47 percent to 51 percent higher than those without depression. Other evidence comes from a cross sectional study of the general Canadian population that compared chronically ill patients and the impact of MDD on functional disability.²⁴ In this study, adjusted for socioeconomic characteristics and illnesses, patterns were noted across common illnesses, such as COPD, diabetes, and arthritis, which indicate that functional disability may be exacerbated by MDD.

There are certain limitations inherent within our study, due to the observational nature of the data. First, the categorization of stable versus treatment resistant was not validated by a clinician; however, the categorization schemes are based on two published algorithms. Similarly, the diagnosis of MDD is based on diagnosis codes rather than a clinical assessment. Another limitation is that medical history is not taken into account, such as comorbidities and responses to previous depression episode. There are heterogeneities in the pre period costs, which suggest determinants other than those currently studied, may play a role. Our results suggest that treatment resistant patients represent somewhere between one in three and one in 10 individuals with depression, highlighting the sensitivity of prevalence to clinical definition. Finally, the costs reflect only those paid by the insurer and, therefore, ignore the direct and indirect costs to the patients.

Further research is needed to determine the magnitude of the incremental costs associated with TRD and whether these additional costs can be reduced with enhanced clinical and pharmacologic management of depression, and thus clarify the association between typical medication practices and economic outcomes. Nonetheless, the use of this nationally representative administrative claims dataset provides additional evidence on the burden of treatment resistant versus stable depression.

Conclusions

The costs associated with new MDD are significantly higher among individuals with treatment resistant depression. Our results suggest that TRD adds between \$3,079 and \$5,799 in 2005 U.S. dollars to annual direct medical cost and treatment episodes. Costs rise to more than double the baseline health care cost of these patients. The magnitude of the incremental costs associated with TRD versus stable depression is sensitive to the definition of TRD; however, the costs are higher for treatment resistant patients than stable patients, regardless of the definition for stable versus TRD. There is a parallel greater likelihood of an increase in direct medical costs that are not directly related to depression among treatment resistant MDD patients. Finally, factors other than whether the patient is stabilized on antidepressant therapy contribute to the likelihood of increased costs following new treatment episodes; these include, but are not necessarily limited to gender and the type of insurance coverage. **JMCM**

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