Identification of a Claims Data "Signature" and Economic Consequences for Treatment-Resistant Depression

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Background: Major depressive disorder (MDD) is a debilitating condition with significant economic consequences. Conservative estimates indicate that between 10% and 20% of all individuals with MDD are treatment resistant. The objectives for this study were (1) to use current treatment strategies identified in the literature to evaluate the validity of studying treatment-resistant depression (TRD) using claims data and (2) to estimate cost differences between TRD-likely and TRD-unlikely patients identified by use of treatment patterns.

Method: The data source consisted of medical, pharmaceutical, and disability claims from a Fortune 100 manufacturer for 1996 through 1998 (N = 125,242 continuously enrolled beneficiaries between the ages of 18 and 64 years). The sample included individuals with medical or disability claims for MDD (N_{MDD} = 4186). A treatment pattern algorithm was applied to classify adult MDD patients into TRD-likely (N_{TRD} = 487) and TRD-unlikely groups. Resource utilization and costs were compared among TRD-likely and TRD-unlikely patients and a random sample of average beneficiaries (i.e., 10% of all beneficiaries) for 1998.

Results: Consistent with the epidemiologic literature, the algorithm classified 12% of the MDD sample as TRD-likely. Mean annual costs were $10,954 for TRD-likely patients, $5025 for TRD-unlikely patients, and $3006 for average beneficiaries. TRD-likely patients used almost twice as many medical services as did TRD-unlikely patients and incurred significantly greater indirect costs ($p < .0001$).

Conclusion: It is feasible to use an administrative dataset to develop a claim-based treatment algorithm to identify TRD-likely patients. Resource utilization by TRD-likely patients was substantial, not only for direct treatment of depression but also for treatment of comorbid medical conditions. Additionally, TRD imposed on employers substantial indirect costs resulting from high rates of depression-associated disability.

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Depression is a widespread, debilitating psychiatric illness with far-reaching personal and economic consequences.[1,2] An episode of major depressive disorder (MDD) is characterized by depressed mood or loss of interest in almost all activities for a period of 2 or more weeks. Individuals with MDD experience pervasive depressive symptoms (e.g., inability to concentrate, fatigue, sadness, hopelessness) that disrupt their ability to carry out usual activities of daily living.[3] The extent of the reported prevalence rate for major depression is as high as 17%,[4] with an average age at onset in the late 20s.[5] Research has indicated that depression is twice as likely to occur in women as in men, with a lifetime prevalence of 26% as compared with 12%, respectively.[5]

Given the prevalence of the disorder, it is understandable that MDD is responsible for a significant amount of both direct and indirect health care costs. MDD is a leading cause of disability worldwide with 50.8 million cases representing 11% of disabilities from all causes.[6] Greenberg and colleagues[2] estimated the annual economic burden of depression in the United States at approximately $44 billion in 1990. Of the total costs, $12.4 billion was attributed to direct costs, $23.8 billion was associated with indirect costs to employers and society due to absenteeism and decreased worker productivity, and $7.5 billion was associated with depression-related suicide.[2] Pharmacoeconomic studies have demonstrated that increased treatment effectiveness can lead to reductions in overall treatment costs,[7–9] with potentially significant decreases in both direct and indirect costs.[10]

Treatment-resistant depression (TRD) is a condition in which an individual with MDD fails to achieve or sustain remission despite adequate antidepressant therapy. Adequate antidepressant therapy is defined as receiving an appropriate medication, at the proper dosage, for a suitable length of time.[11] Conservative estimates indicate that between 10% and 20% of MDD patients remain symptomatic despite multiple trials of treatment,[12] demonstrating significant unmet need in the treatment of depression. Variations in the estimates of TRD prevalence depend on disease-state definitions used and methods for determining treatment response. Lack of standard diagnostic criteria and established diagnostic codes and the relative heterogeneity of the population impede retrospective studies of TRD by use of administrative data.[13]

There is a great deal of variability in the definition of treatment resistance and adequate treatment response. *Treatment resistance* implies that an individual has received what is generally considered an adequate treatment for depression and that the treatment has not effectively ameliorated the symptoms.[14] Within a clinical trial, patient- or clinician-rated instruments may be used to assess response to therapy, with predetermined scores for response, partial response, or nonresponse. A common definition of response is the rating of "much improved" on the Clinical Global Impressions scale.[15] However, many times, individuals rated as responders are not asymptomatic.[14] In other words, even though these patients are better, they are not well.

Management of individuals considered to be treatment resistant generally follows a "staged approach."[11,15,16] If a patient does not respond or exhibits a partial response to the initial antidepressant, treatment strategies typically begin with upward titration of the initial antidepressant followed, if necessary, by a switch to another antidepressant. If symptoms remain, subsequent treatment may include concomitant administration of multiple antidepressants, mood stabilizers, or atypical antipsychotics.[5,15] Late-stage treatment for TRD includes monoamine oxidase inhibitors (MAOIs) and electroconvulsive therapy (ECT). A logical extension of these criteria is to use them for identification of patients with treatment resistance in administrative databases in order to gain greater understanding of characteristics of the population and associated costs.

The purpose of this retrospective, descriptive study was to develop an algorithm for identifying patients who were TRD-likely using established treatment patterns and then to apply it in an administrative claims database to obtain 1-year cost differentials between TRD-likely and TRD-unlikely patients. To the extent that improvement in depressive symptoms leads to decreases in both direct and indirect expenditures, significant cost differences would be expected between TRD-likely and TRD-unlikely patients.

METHOD

Data

The study examined claims data for 1996 through 1998 from a national Fortune 100 manufacturing company providing comprehensive health insurance to a predominantly unionized workforce. The database included 333,055 beneficiaries enrolled in any of the 3 years. 97,356 persons aged 65 years or older were excluded because their medical claims were potentially incomplete due to payments made under the Medicare system. 61,926 patients aged 17 or younger were also excluded because this study focused on the adult population. The remaining population was 173,773. For inclusion in the analytic sample, patients were also required to be eligible for benefits in 1996, 1997, and 1998 to allow an adequate, continuous observation period of treatment patterns; approximately 28% of the population were excluded because they did not have benefit coverage for all 3 years. The resulting sampling frame for the analysis included 125,242 persons (including employees [i.e., primary beneficiaries] as well as spouses and dependents) covered by the corporation's health care plan.

Claims included actual payments for inpatient care, outpatient care, and prescription drugs from managed fee-for-service plans. Data on patients in health maintenance organization (HMO) plans (who account for approximately 20% of all enrollees) were not available and were therefore excluded from this study. Additionally, short- and long-term disability claims were available for employees enrolled in this program (who account for approximately 90% of this workforce). Demographic data for each beneficiary consisted of year of birth, gender, job classification (if employee), and type of health care plan.

For benchmarking purposes, claims data for individuals with MDD were contrasted with data from the overall beneficiary population. The contrast group consisted of a random 10% sample of all beneficiaries from the entire claims dataset including individuals with depression diagnosis, using the same age and enrollment inclusion criteria. This approach allows statements regarding comparisons between TRD patients and the "average beneficiary" which is relevant for payers. In addition to epidemiologic comparisons and analyses of direct costs, disability costs were estimated for the subset of employed beneficiaries.

Employer administrative files provide information concerning all claims for each beneficiary, including the date of service and diagnostic code for the complaint. The International Classification of Diseases, 9th Revision (ICD-9), Current Procedural Terminology (CPT) and National Drug Codes (NDC) allow comparisons of diagnosis, treatment patterns, utilization of medical services, and pharmaceutical use across beneficiaries with specific conditions of interest.

Statistical Methods

T tests and chi-square tests were used to analyze differences (at the 95% significance level) in demographic characteristics between the TRD-likely and TRD-unlikely patient and employee samples. In the case of equal variances of the 2 samples that are being compared, we used the pooled method to calculate the degrees of freedom. In the case of unequal variances, the Satterthwaite approximation to the degrees of freedom was employed. T tests were used for comparisons of mean age, and chi-square tests were used to compare gender and status. In evaluating utilization and costs, we analyzed 3 samples for both patients and employees: beneficiaries who were (1) TRD-likely, (2) TRD-unlikely, or (3) in a 10% random sample of the employer population (i.e., the average beneficiary). T tests and chi-square tests were used to evaluate the pairwise differences among the 3 samples in the number of claims (utilization groupings by place of service) and for various cost types. The Bonferroni adjustment was applied to account for multiple comparisons ($\alpha = .05/(3 \times$ number of tests with related outcome variables [i.e., number of claims by place of service and costs by type]). Cost outliers were examined for both the TRD-likely and TRD-unlikely samples. We considered direct medical (e.g., office, hospital inpatient, hospital outpatient, pharmacy) and indirect (disability and absenteeism) costs. All reported cost and diagnosis values appeared legitimate. Consequently, we retained all observations for the analysis.

Sample

Male and female patients, aged 18 to 65 years, with a medical or disability claim for MDD (ICD-9 codes 296.2, 296.3, 300.4, 309.0, 309.2, or 311) in 1996 were identified in the claims database. The criteria for inclusion in the MDD sample were expanded from major depression (e.g., ICD-9 codes 296.2 and 296.3) to include less conclusive diagnoses (e.g., ICD-9 codes 300.4 and 311). These diagnoses were included because of discrepancies between clinical presentation and coded diagnoses documented in the depression literature.[16,17] Patients were excluded from the analysis if they had at least 1 claim for psychosis, schizophrenia, bipolar disorder, manic depression, or dementia at any time during the study period (i.e., 1996–1998; excluded N = 773). No patients were excluded for alcohol or substance abuse, but patients with alcohol or drug psychoses were excluded from the study. There were 4186 patients with at least 1 disability or medical claim for MDD meeting the inclusion criteria.

Treatment Pattern Algorithm

Current depression treatment guidelines[5] and published treatment strategies[15,16] recommend an adequate trial of antidepressant medication as an initial primary treatment for MDD. An adequate trial of an antidepressant agent is generally considered to be 4 to 8 weeks and includes titration to a therapeutic dose depending on the development of side effects, the patient's age, and the presence of comorbidities.[5] If a moderate improvement is not accomplished, patients are generally switched to another antidepressant.

The availability of new classes of antidepressants offers the clinician a broad variety of choices. Switches might be within a class (one selective serotonin reuptake inhibitor [SSRI] to another) or between classes (an SSRI to a tricyclic antidepressant). If a patient fails to achieve an adequate response, subsequent strategies often include simultaneous use of multiple drugs. Combination strategies generally refer to concomitant administration of 2 antidepressants at one time to obtain a synergistic pharmacologic effect.[15] Augmentation strategies involve the addition of a non-antidepressant agent to potentiate effects of the antidepressant. Common augmentation agents include mood stabilizers and atypical antipsychotic agents.[15] ECT and older, more toxic antidepressants such as MAOIs and are usually reserved as treatments of last resort for individuals who have failed all other courses of treatment.

For this study, identification of individuals with TRD was based on diagnoses and treatment patterns that could be identified within an administrative claims database. This claims data "signature," or treatment pattern, allowed us to develop an algorithm using ICD-9 codes and prescribed medications using NDC to classify patients with MDD into 2 groups: those who were TRD-likely and those who were TRD-unlikely.

All patients in the MDD sample receiving ECT or MAOIs (N = 32) at any time between 1996 and 1998 were automatically classified as TRD-likely. Patients within the MDD sample not receiving these treatments were classified as TRD-likely only if they met both TRD-scale criteria and TRD-matrix criteria identified in the treatment pattern algorithm. These criteria were based on treatment strategies outlined in published treatment guidelines[5,11] and included 3 dimensions of care: specific treatments, upward titration (or optimization of dosing), and switching strategies. Specific treatments included augmentation of antidepressants with mood stabilizers or atypical antipsychotic agents.

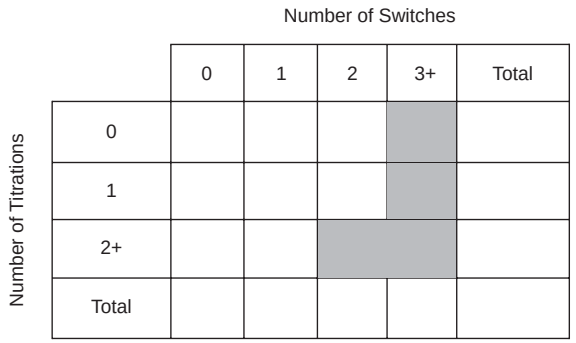
The scale classification (Table 1) assigned patients a score on the basis of specific treatments (receiving an antidepressant as well as an atypical antipsychotic or a mood stabilizer at any time during the 3-year study period). A score of 1 could be received for each specific treatment, for a maximum score of 2 on this dimension. The second dimension was scored between 0 and 3 on the basis of the number of switches among antidepressants, relative to the switching patterns of all patients. The third dimension was scored between 0 and 3 on the basis of the number of upward titrations of an antidepressant agent

Table 1. TRD-Scale Criteria[a]

Dimension	Measure	Scoring
I. Specific treatment	Treatment with an antidepressant and mood stabilizer (lithium, valproic acid, carbamazepine) Treatment with an antidepressant and an atypical antipsychotic	History of use of both an antidepressant and a mood stabilizer or an antidepressant and an atypical antipsychotic agent gives a patient a score of 1 for each specific treatment (maximum score = 2)
II. Switching	Score depends on number of switches relative to other individuals within the dataset	Score between 0 and 3, dependent on quartile of switches (maximum score = 3)
III. Titration	Score depends on number of titrations relative to other individuals within the dataset	Score between 0 and 3, dependent on quartile of titrations (maximum score = 3)

[a]Abbreviation: TRD = treatment-resistant depression. Scale criteria for inclusion in the TRD-likely sample are based on 3 dimensions: specific treatments, switches, and titrations. Each dimension is described, including specific measures, scoring, and maximum scores. To be classified as TRD-likely according to the scale criteria, a patient must receive a score of 5 or greater. Range of possible values is from 0 to 8.

Figure 1. TRD-Matrix Criteria[a]



[a]Abbreviation: TRD = treatment-resistant depression. The shaded area represents the treatment pattern required for inclusion in the TRD-likely sample based on matrix criteria. Patients were classified as TRD-likely if they had an "inverted L" pattern, indicating a history of 3 or more switches, or at least 2 antidepressant switches and 2 upward titrations of antidepressant.

relative to all patients who used antidepressants. A total score of 5 was required for a patient to be considered TRD-likely (N = 493).

A preliminary sensitivity analysis was conducted to look at the effects of using different cutoff points to define the TRD sample. For example, a cutoff score of 6 (N = 294, or 7% of the MDD sample) resulted in a TRD sample that was even more specific in identifying TRD-likely patients than obtained using 5 as a cutoff. However, this approach resulted in a sample size that fell below the conservative estimates of TRD at 10% to 20% of the MDD population.[12,18] Therefore, the selection of 5 as a cutoff score for a patient to be considered TRD-likely (N = 493, or 12% of the MDD sample) represented the most rigorous standard possible within acceptable guidelines.

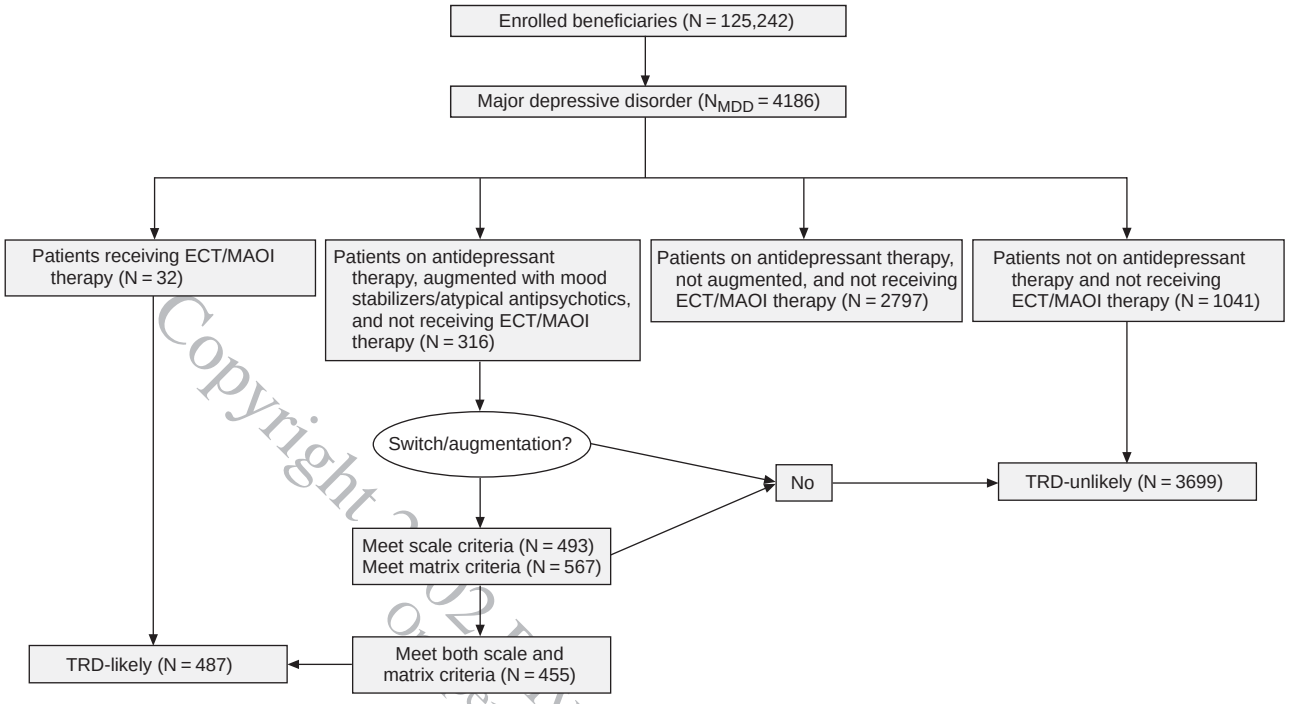
The matrix criteria (Figure 1) were based on a pattern of treatment that included a combination of switching and titration that was common for patients persisting in treatment and using a number of strategies associated with treatment resistance. Patients falling into an "inverted L" pattern, indicating that they had received 3 or more switches or at least 2 switches and 2 titrations were classified as TRD-likely (N = 567). This method corresponds to a widely accepted definition of TRD as "failure to adequately respond to trials of 2 antidepressants of different classes at adequate dose and duration."[12,14,18] Patients meeting both scale criteria and matrix criteria were considered TRD-likely ($N_{overlap}$ = 455), in addition to the ECT or MAOI patients (N = 32). Of the 4186 patients meeting criteria for depressive disorder in the dataset, 12% were identified as TRD-likely (N_{TRD} = 487) and 3699 were classified as TRD-unlikely (Figure 2).

Cost Analysis

To follow individual treatment patterns over time, data from 1996 through 1998 were used to classify individuals as TRD-likely or TRD-unlikely. Cost estimates were calculated for 1998, the most current year of data. Direct costs included all health care payments by the employer for medical care and prescription claims. Comparisons were made between depressed patients who were classified as TRD-likely and TRD-unlikely and a 10% random sample of average beneficiaries. Direct and indirect costs were calculated on the basis of the actual cash outlays made by the employer.

Indirect costs were estimated for employee beneficiaries by a "data warehouse" approach similar to methods used by Burton and Conti[19] in their correlative research linking a range of illnesses to on-the-job productivity. The economic burden of lost productivity consists of lost time at work and diminished on-the-job productivity or "presenteeism." While on-the-job productivity measures are not available, data do include measures of periods of disability and actual daily payments received by the employee. Sporadic sick leave for shorter illnesses was imputed on the basis of days when medical care was provided. If there was a medical care occurrence on a regular workday for an employee and the employee was not on disability, the occurrence was counted as an absence. Hospital care was counted as a full-day absence, and office visits were counted as half-day absences. Since disability claims cover missed work time due to illness greater than 6 or more consecutive days, patients with disability claims were also assigned 5 work absence days. For this study, work loss is considered the sum of actual employer disability payments and imputed payments for illness absence time based on daily wage data. See Barnett et al.[20] for a more complete description of these methods using the same database.

Figure 2. Distribution of Patients[a]



[a]Abbreviations: ECT = electroconvulsive therapy, MAOI = monoamine oxidase inhibitor, MDD = major depressive disorder, TRD = treatment-resistant depression. The chart shows how TRD-likely and TRD-unlikely samples were derived from the total population. Out of greater than 100,000 total enrolled beneficiaries, 4186 met criteria for inclusion in the MDD sample. On the basis of the treatment pattern algorithm, 487 patients were classified as TRD-likely (N = 32 receiving ECT/MAOI therapy and N = 455 meeting both scale and matrix criteria) and 3699 were classified as TRD-unlikely.

Data analyses examined the 1-year differences in cost and health care utilization for patients with MDD classified as either TRD-likely or TRD-unlikely by the treatment pattern algorithm. Furthermore, the patients were compared with an employer population consisting of a 10% random sample of all beneficiaries. The comparisons included both the overall depressive patient sample and a subset sample of beneficiaries consisting of the primary, employed beneficiaries. The major analyses included the mean number of medical claims per patient by place of service (e.g., office visits, outpatient services, inpatient services), the mean cost of care per patient, and the mean annual cost per patient for medical and psychiatric care. Claims with a depression diagnosis (ICD-9 code) or for an antidepressant (based on NDC code) were defined as "depression-related."

RESULTS

Demographic Characteristics

Demographic characteristics of the overall MDD sample, as well as the subset sample of employees with depressive disorders, are presented in Table 2. The overall sample consisted of 4186 patients treated for MDD in 1996, of which 487 (12%) were classified as TRD-likely. The percentage of female patients in these groups broke out as follows: 61% in the overall sample, 67% in the TRD-likely sample, 60% in the TRD-unlikely sample (different statistically from the TRD-likely sample: $\chi^2 = 7.82$, df = 1, p = .0052), and 49% among the random sample of average beneficiaries. The mean ± SD age of the MDD sample was 45.7 ± 10.2 years, and the majority of patients (68%) fell between the ages of 36 and 55 years. In addition, the difference in mean ages of TRD-likely compared with TRD-unlikely patients was 1.4 years (statistically significant: t = 3.01, df = 665, p = .0027).

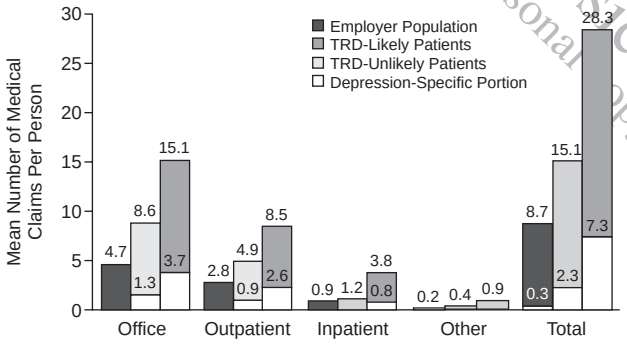
The subset of employees included 1692 who were treated for MDD in 1996, 180 (11%) of whom were classified as TRD-likely. The percentage of female workers broke out as follows: 32% in the overall sample, 41% in the TRD-likely sample, 31% in the TRD-unlikely sample (statistically different than the TRD-likely sample: $\chi^2 = 7.13$, df = 1, p =. 0076), and 15% among the random sample of average employees. These findings highlight the fact that there exists a predominantly male workforce in this particular company. The mean ± SD age of the employed MDD sample was 45.0 ± 8.9 years, and the majority (74%) of workers fell between the ages of 36 and 55 years. In addition, the difference in mean ages of TRD-likely compared with TRD-unlikely employees was 0.5

Table 2. Demographic Characteristics of Overall Sample and Employee Subset, 1998[a]

	Overall Depression Sample				Employee Subset			
Characteristic	All Patients With MDD (N = 4186)	TRD-Likely (N = 487)	TRD-Unlikely (N = 3699)	Average Beneficiary[b]	All Employees With MDD (N = 1692)	TRD-Likely (N = 180)	TRD-Unlikely (N = 1512)	Average Employee[c]
Female, %	61	67	60	49	32	41	31	15
Status, %								
Employee	46	42	47	45	100	100	100	100
Retired	7	7	7	8	0	0	0	0
Spouse or dependent	47	51	47	46	0	0	0	0
Age, y								
Mean	45.7	46.9	45.5	47.4	45.0	45.4	44.9	47.4
SD	10.2	9.0	10.3	11.3	8.9	8.7	8.9	9.5
Median	47	47	47	49	46	46	46	49
Mode	46	46	46	52	46	44	45	52
Range, %								
18–35	15	9	16	16	15	12	16	13
36–45	29	32	29	21	34	36	33	23
46–55	39	42	39	37	40	40	40	44
56–64	17	18	17	26	12	13	11	20

[a]Abbreviations: MDD = major depressive disorder, TRD = treatment-resistant depression.
[b]Average member (in terms of demographic characteristics, health care utilization, and costs) from the 10% random sample of beneficiaries (including employees and dependents).
[c]Average member from the employed subset of the 10% random sample of beneficiaries.

Figure 3. Mean Number of Medical Claims Per Patient for 1998[a]



[a]Abbreviation: TRD = treatment-resistant depression. This chart depicts the mean number of claims for TRD-likely patients, TRD-unlikely patients, and a random sample of average beneficiaries (employer population). The differences in the number of medical claims are significant at the 95% confidence level among the 3 groups, except for "other" services. Other services include home care, nursing/extended care facility care, psychiatric day care, substance abuse treatment facilities, and clinical laboratory charges. Depression-specific medical use is limited to services directly associated with depression diagnosis.

years (not statistically significant: t = 0.63, df = 1690, p = .5302).

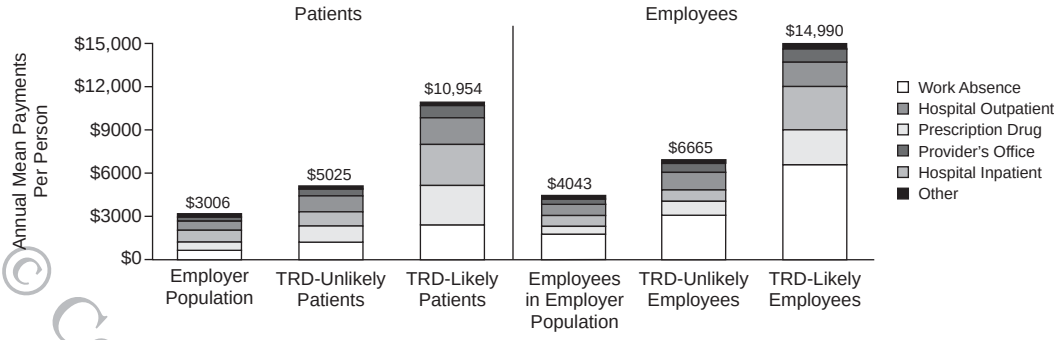
Health Care Utilization

Utilization of health care services (inpatient, outpatient, office visits) was examined for 1998 to characterize patterns of health care use by MDD patients classified as either TRD-likely or TRD-unlikely. Utilization measures included the overall number of claims and claims by specific site of service. A substantial percentage of all individuals with MDD had at least 1 medical claim, including 94% of all TRD-likely patients and 87% of all TRD-unlikely patients. As illustrated in Figure 3, both groups used significantly more medical services than the average beneficiary. This was true when comparing TRD-likely patients with the average beneficiary (t = 13.07, df = 494, p < .0001) and when comparing the TRD-unlikely patient with the average beneficiary (t = 18.16, df = 5121, p < .0001). Additionally, patients classified as TRD-likely used 1.9 times more services than patients who were classified as TRD-unlikely (a mean of 28.3 visits as compared with 15.1 visits; t = 8.65, df = 532, p < .0001). These patterns were consistent for both visits to a provider's office and use of outpatient services.

TRD-likely patients utilized significantly more inpatient services than either TRD-unlikely patients (t = 3.04, df = 506, p = .0025) or the average beneficiary (t = 3.43, df = 490, p = .0007). However, this difference between TRD-unlikely patients and the average beneficiary was not significant (t = 2.32, df = 5,482; p = .0204); analysis found that this pattern of insignificance continues even excluding all depression patients from the 10% sample. Use of "other" services (home care, extended care facilities, substance abuse treatment, and clinical laboratory) was not meaningfully different between any of the groups.

Depression-related services accounted for 26% of overall health service use for TRD-likely patients, but only 15% for TRD-unlikely patients. Moreover, 94% of all TRD-likely patients had at least 1 medical claim in 1998, in comparison with 87% of TRD-unlikely patients and 72% of average beneficiaries. We also considered whether use-of-care distributions had an impact on the

Figure 4. Mean Cost Per Patient and Per Employee for Medical Care, Prescription Drug, and Work Absence[a]



[a]Abbreviation: TRD = treatment-resistant depression. Individual cost categories are shown as proportions of the total cost for each group. This figure is broken down into 2 groups: (1) the patient population (all TRD-likely and TRD-unlikely patients) plus the average beneficiary (a 10% random sample of the employer population) and (2) a subset of this group labeled "employees." The employee group consists of only the primary employed beneficiaries. The differences in various types of costs are statistically significant at the 95% confidence level among the 3 groups for both the entire patient sample and for the employee subsample except for costs classified as "other." Other services include home care, nursing/extended care facility care, psychiatric day care, substance abuse treatment facilities, and clinical laboratory charges.

t tests. To confirm the results of the t tests for the differences in use of care, we used nonparametric 2-sample tests for the differences in median scores between the groups. All of the pairwise differences in the number of claims by place of service among the TRD-likely, TRD-unlikely, and the average beneficiary were statistically significant after the Bonferroni adjustment.

Analysis of Cost

Figure 4 and Tables 3A and 3B show that mean ± SD 1998 employer costs for medical services, pharmaceuticals, and expenditures associated with work loss for TRD-likely patients (including spouses and dependents) totaled $10,954 ± $18,052. These costs were approximately twice those of the MDD patients classified as TRD-unlikely (mean ± SD = $5025 ± $9045), which in turn were substantially greater than the costs of the average beneficiary (mean ± SD = $3006 ± $7466). The cost differences between TRD-likely and TRD-unlikely patients and average beneficiaries were statistically significant across all types of service and groups ($t \geq 3.07$, $df \geq 490$, $p \leq .0023$ in all cases), except for the difference between TRD-unlikely patients and the average beneficiary in hospital inpatient costs ($t = 2.66$, $df = 5264$, $p = .0079$). A similar pattern can be observed in comparing costs among TRD-likely and TRD-unlikely employees and the average employee beneficiary. Inpatient services represented 26% of total costs for TRD-likely patients and 19% of total costs for TRD-unlikely patients. The mean ± SD cost of inpatient services for a TRD-likely patient was $2838 ± $13,427 compared with $954 ± $5151) for TRD-unlikely patients. For inpatient hospitalizations, TRD-unlikely patients more closely approximated the utilization patterns and costs of the average beneficiary (1.2 claims, $954 and 0.9 claims, $707, respectively). In addition, TRD-likely patients incurred almost 10 times the inpatient costs for depression as did TRD-unlikely patients.

In the TRD-likely sample, although the utilization of depression-specific services was high, depression accounted for only 23% of total costs (mean ± SD = $2486 ± $4328), whereas 77% of costs (mean ± SD = $8468 ± $17,068) were attributed to other diagnoses. Considering only the TRD-likely employees, costs associated with depression are somewhat higher, averaging $3801 ± $6327 (25% of total costs). Non–depression-related services for these patients constituted 75% of all service use, with a mean ± SD annual cost of $11,189 ± $11,655.

When comparing indirect costs (disability and absenteeism), TRD-likely patients had significantly greater costs associated with work loss than either TRD-unlikely patients ($t = 4.90$, $df = 551$, $p < .0001$) or the random sample of average beneficiaries ($t = 7.66$, $df = 495$, $p < .0001$). However, because the diagnostic information on the disability claims is incomplete, the split between depression and nondepression disability costs underestimates the depression component. TRD-likely patients had less disability due to depression but far more disability for all other reasons than TRD-unlikely patients.

DISCUSSION

Validity of the Treatment Pattern Algorithm

Pivotal to the validity of an algorithm is the degree to which it accurately classifies depressed patients as either TRD-likely or TRD-unlikely. Accuracy, or the degree to which an instrument can differentiate between an obtained result and assumed truth,[21] is based on the concepts of sensitivity and specificity. Sensitivity refers to the ability of an instrument to identify all individuals with a given

Table 3A. Differences in Mean Costs Among TRD-Likely Patients, TRD-Unlikely Patients, and Average Beneficiaries in 1998[a]

Variable	TRD-Likely Patients		TRD-Unlikely Patients		Average Beneficiaries[b] (all claims)
	Depression Costs	All Other Claims	Depression Costs	All Other Claims	
Health care costs per patient, $					
Office	265 (501)	640 (1153)	92 (275)	393 (838)	269 (868)
Inpatient	644 (3247)	2194 (12,862)	66 (671)	888 (5098)	707 (4294)
Outpatient	223 (651)	1644 (3645)	62 (279)	1029 (2812)	696 (2670)
Other	51 (328)	142 (684)	14 (214)	78 (468)	48 (374)
Pharmacy	955 (992)	1748 (2284)	331 (578)	808 (1616)	638 (1209)
Subtotal	2138 (3781)	6368 (16,275)	565 (1109)	3196 (7503)	2358 (6442)
Work absence costs per patient, $					
Absenteeism	273 (991)	379 (1166)	91 (571)	293 (1191)	245 (891)
Disability	75 (1167)	1721 (4588)	101 (1327)	779 (3120)	403 (2255)
Subtotal	348 (1517)	2100 (4832)	192 (1439)	1072 (3364)	648 (2524)
Total costs, $	2486 (4328)	8468 (17,068)	757 (1887)	4268 (8793)	3006 (7466)

[a]Abbreviation: TRD = treatment-resistant depression. Standard deviations are given in parentheses.
[b]10% random sample of all beneficiaries.

Table 3B. Differences in Mean Costs Among TRD-Likely Employees, TRD-Unlikely Employees, and Average Employees in 1998[a]

Variable	TRD-Likely Employees		TRD-Unlikely Employees		Average Employees[b] (all claims)
	Depression Costs	All Other Claims	Depression Costs	All Other Claims	
Health care costs per employee, $					
Office	333 (624)	631 (710)	106 (303)	396 (842)	275 (562)
Inpatient	1232 (4924)	1682 (7181)	94 (860)	816 (4761)	735 (4153)
Outpatient	256 (678)	1507 (2137)	55 (248)	1063 (2556)	740 (2433)
Other	131 (529)	149 (549)	31 (328)	101 (579)	62 (420)
Pharmacy	908 (943)	1539 (1950)	253 (502)	656 (1257)	547 (988)
Subtotal	2860 (5469)	5508 (8638)	539 (1246)	3032 (6679)	2359 (5932)
Work absence costs per employee, $					
Absenteeism	738 (1523)	1026 (1739)	223 (877)	717 (1779)	637 (1348)
Disability	203 (1916)	4655 (6589)	248 (2068)	1906 (4656)	1047 (3542)
Subtotal	941 (2386)	5681 (6552)	470 (2222)	2624 (4860)	1684 (3850)
Total costs, $	3801 (6327)	11,189 (11,655)	1010 (2674)	5655 (9636)	4043 (8397)

[a]Abbreviation: TRD = treatment-resistant depression. Standard deviations are given in parentheses.
[b]Employed subset of 10% random sample of all beneficiaries.

condition (i.e., minimize false negatives), whereas specificity refers to the ability to exclude all individuals without the condition (i.e., minimize false positives). Generally, there is no perfect testing measure, and tests with higher specificity tend to have lower sensitivity. To assure that those classified as TRD-likely had true treatment resistance versus those who did not respond for other reasons (e.g., inadequate treatment), rigorous criteria were adopted. For purposes of this analysis, the algorithm was designed to have greater specificity than sensitivity; that is to say, the approach here was to choose a strict cutoff score to limit the possibility of introducing false positives into the TRD-likely "gray" area. To the extent that some patients with TRD were classified as TRD-unlikely using this approach, our ability to isolate meaningful differences in these groups could have been compromised. The fact that we identified significant differences in patterns of utilization, disability, and costs suggests that further refinements to improve the algorithm may widen these differences even further. Future research using a combination of clinical information meshed with claims data should investigate these issues further.

This study classified 12% of all patients with MDD as TRD-likely. The patients selected for inclusion by the algorithm followed treatment patterns associated with treatment resistance as identified in the literature[15,16] and produced results that were consistent with conservative estimates (e.g., between 10% and 20%) provided by the epidemiologic literature.[12,18] Findings consistent with conservative estimates verified that the algorithm identified individuals with symptoms severe enough to persist in treatment. Moreover, these patients participated in established treatment guidelines rather than remaining at inadequate doses or discontinuing therapy.

Health Care Utilization and Costs

Although there are many studies describing the burden of illness in depression, none examined the differential consequences for patients with resistance to current therapies. This study demonstrated that a subset of patients receiving treatments generally associated with TRD had significantly greater direct and indirect costs. Current research is demonstrating an association between recovery from depression and corresponding decreases in direct costs and indirect costs.[10] Therefore, it would follow that costs associated with effectively treated TRD patients should more closely resemble those of depressed patients without treatment resistance. Note that our definition of TRD-likely/unlikely "tilts" in favor of minimizing false positives, which tends to raise the average costs of the TRD-likely group as well as the costs of the TRD-unlikely group. Since we are testing the difference between TRD-likely and TRD-unlikely patients in the presence of these directional changes, we have no prior hypothesis on whether our algorithm has resulted in a discrepancy that is higher for the TRD-likely than the TRD-unlikely group.

Direct costs for patients with depressive illnesses are not limited to the cost of treating depression or even psychiatric comorbidities, but also include increased medical utilization for nonpsychiatric complaints.[22] Since this study demonstrated a statistically significant difference in utilization between TRD-likely and TRD-unlikely patients, timely and effective treatment of resistant patients could have a dramatic impact on utilization of medical services for nonpsychiatric conditions including primary care physicians, outpatient services, and laboratory services.

One area that has tremendous cost savings potential is the use of inpatient hospitalizations. With adequate treatment of depression resulting in a significant reduction in hospitalization costs[23] and acute inpatient hospitalizations representing the most costly health care expenditure, benefits of improved TRD outcomes are obvious. As demonstrated in this study, TRD-likely patients had statistically significantly greater inpatient hospital stays and associated costs than the employer population, whereas TRD-unlikely patients more closely resembled average beneficiaries in terms of acute hospitalizations. From a statistical perspective, although this initial exploration of TRD and its economic consequences is limited to descriptive measures, future research should consider development of multivariate models that involve more extensive testing.

Considering that depression is responsible for almost 11% of total years lived with a disability by any cause worldwide,[1] it is not surprising that depressive illness accounts for a significant amount of employers' costs due to work loss and reduced productivity. Given the differences in costs between TRD-likely and TRD-unlikely patients reported in this study, significant cost savings potentially could be realized by the development of more effective therapies for treatment-resistant patients.

Although the data and treatment pattern algorithm used within this study provide a unique opportunity to study the costs of depression for TRD-likely patients, a number of limitations must be acknowledged. Because this study relied on insurance claims data, the findings are subject to the usual limitations of administrative datasets. These limitations include the possibilities of inadequate treatment, inaccurate diagnoses, coding inaccuracies, and missing data (such as out-of-plan use). Furthermore, there are potential selection biases associated with the possibility that mental illness may be underreported in claims data due to social stigma, practice differences between primary care physicians and specialists, and other factors.

Although the claims data allow patients to be identified by patterns of treatment, the lack of clinical measures does not allow for an assessment of medication response. Even if patients follow patterns associated with treatment resistance, confirmation of diagnosis requires clinical information indicating treatment efficacy. Estimates of titration and switching may not reveal adequacy or quality of treatment or adherence to prescribed therapies. These issues cannot be resolved definitively without prospective clinical data.

This research is the first to document the extent to which patterns associated with TRD can be found in a claims data setting and provides an economic comparison of the associated costs for TRD-likely patients as compared with TRD-unlikely patients and average beneficiaries. Patients identified by the algorithm exhibiting treatment patterns generally associated with TRD used 1.9 times more health care services per year than TRD-unlikely patients. The increased health care utilization and costs associated with work loss represented an almost 4-fold increase in annual costs as compared with the average beneficiary. Most of this additional cost is for non–depression-related services and suggests an opportunity for medical offsets.

The validity of the treatment algorithm should be tested by replication studies in additional datasets including application in special populations (e.g., Medicaid systems). Sensitivity and specificity analysis may determine that minor modifications to the algorithm will increase accuracy. While the analysis performed here suggests that the selection algorithm seems reasonable, given the limitations of claims data, further validation of the algorithm should be accomplished by comparison with available clinical records. Finally, prospective observational studies are recommended to establish the association between clinical nonresponse or partial response and associated patterns of antidepressant use.

Drug names: carbamazepine (Tegretol and others), valproic acid (Depakene and others).

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