# The Impact of Treatment-Resistant Depression on Health Care Utilization and Costs

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**Background:** Approximately 50% of patients diagnosed with major depressive disorder will experience a recurrent or chronic course of illness for which long-term treatment is recommended. Moreover, at least 20% of patients diagnosed with depression do not respond satisfactorily to several traditional antidepressant medication treatment trials. Very little is known about the health care costs of patients with treatment-resistant depression.

Method: Based on medical claims data (MarketScan Research Database, The MEDSTAT Group, Cambridge, Mass.) from January 1, 1995, to June 30, 2000, a naturalistic, retrospective analysis was conducted to study the characteristics and health care utilization of patients with treatment-resistant depression. All patients having an International Classification of Diseases, Ninth Revision (ICD-9), diagnosis code for unipolar or bipolar depression with specified antidepressant dosing and treatment durations were initially selected. Patients were then classified as "treatment resistant" if either they switched from or augmented initial antidepressant medication with other antidepressants at least twice (outpatient treatmentresistant group) or they switched from or augmented their initial antidepressant medication and also had a claim for either a depression-related hospitalization or suicide attempt (hospitalized treatment-resistant group). Those meeting the initial medication and diagnosis selection criteria but not meeting the treatment-resistance criteria constituted the comparison group. Members of the comparison group had comparatively stable antidepressant medication use patterns, consistent with an acceptable response to treatment. Patients were followed for a minimum of 9 months. Resource utilization was calculated from index date to last available claims data point and then annualized.

**Results:** Treatment-resistant patients were more likely to be diagnosed with bipolar disorder or concurrent substance abuse or anxiety disorders than the comparison group (p < .001). Treatment-resistant patients were at least twice as likely to be hospitalized (general medical and depression related) and had at least 12% more outpatient visits (p < .02). Treatment resistance was also associated with use of 1.4 to 3 times more psychotropic medications (including antidepressants) (p < .001). Patients in the hospitalized treatment-resistant group had over 6 times the mean total medical costs of nontreatment-resistant depressed patients (\$42,344 vs. \$6512) (p < .001) and their total depression-related costs were 19 times greater than those of patients in the comparison group (\$28,001 vs. \$1455) (p < .001). *Conclusion:* Treatment-resistant depression is costly and associated with extensive use of depression-related and general medical services. These findings underscore the need for early identification and effective long-term maintenance treatment for treatment-resistant depression. (*J Clin Psychiatry 2002;63:963–971*)

Received Sept. 10, 2001; accepted April 4, 2002. From the MEDSTAT Group, Cambridge, Mass. (Drs. Crown and Ling and Ms. Poret); MIT Sloan School of Management, Cambridge, Mass. (Drs. Finkelstein and Berndt); the University of Texas Southwestern Medical Center at Dallas, Dallas, Tex. (Dr. Rush); and the University of Texas Medical Branch at Galveston, Galveston, Tex. (Dr. Russell).

Supported by funding from Cyberonics, Inc., Houston, Tex.

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wide and expanding portfolio of therapies exists to treat depression, but many patients do not achieve durable, long-term benefit.<sup>1-3</sup> Approximately 50% of patients in their first major depressive episode will experience at least a second episode of major depression. Additionally, 80% to 90% of those having experienced 2 or more episodes will have further recurrences.<sup>2-9</sup> A recent review<sup>6</sup> reports that only 25% to 35% of patients recovered fully from a depressive episode with traditional antidepressant monotherapy. Moreover, relapse or recurrence rates are as high as 20% to 37% during continuation or maintenance phase pharmacotherapy.<sup>10–16</sup> Thus, the current literature reflects a growing recognition that depression is often not an episodic or self-limiting illness, but rather a chronic and recurrent illness that can be resistant to current treatments. Hence, there is a need for more effective long-term treatment.7,14

Although often effective in short-term and maintenance treatment, traditional antidepressant strategies appear to have limited effectiveness for long-term chronic and recurrent treatment-resistant depression.<sup>4,5,8,17–19</sup> Evidence suggests that augmenting initial antidepressant medication with additional medications or psychotherapy benefits a number of patients. One study examining the treatment combination of antidepressants and psychotherapy found a 73% response rate during the initial treatment phase, which was significantly higher than either treatment as a monotherapy.<sup>20</sup> The longer-term maintenance of response to combination therapy has not yet been reported.<sup>4</sup> In another study,<sup>21</sup> the addition of an atypical antipsychotic to a selective serotonin reuptake inhibitor (SSRI) produced superior improvements over either agent alone in those with treatment-resistant depression. Again, however, data regarding long-term response are not yet available.

Although many open case studies provide some evidence for augmenting or switching strategies, few studies have utilized a randomized methodology to compare alternative therapies for treatment-resistant depression.<sup>22</sup> Despite all of those recent advances in treatment, many patients with depression do not respond adequately to any of them.

Observed resistance to antidepressant treatment may be as likely to result from patients inability to tolerate certain adverse effects of therapy<sup>1,8,23</sup> or unwillingness/ inability to adhere to the treatment regimen,<sup>8,9</sup> as from limitations in the long-term efficacy of the treatment.<sup>24</sup> One third to one half of recurrences occur within 1 year of the initial depressive episode.<sup>1,2</sup> Subsequent episodes are often of longer duration, more severe, and less responsive to treatment than initial episodes.<sup>25</sup> Risk factors for treatment resistance include inadequate dosing or duration of pharmacologic treatment, noncompliance with therapy, and presence of comorbid psychiatric conditions.<sup>3</sup> These factors are also likely associated with significantly greater costs, but no published studies have examined the costs of treatment-resistant depression.

The present study helps to fill this gap in the literature by examining the clinical characteristics, health care utilization, and direct medical costs of patients with treatmentresistant depression through the use of retrospective claims data. Patients with treatment-resistant depression are hypothesized to be higher utilizers of both depressionrelated and general medical services. As a result, total health care costs are expected to be higher in patients with treatment-resistant depression when compared with apparent treatment responders.

### **METHOD**

The MEDSTAT Group's MarketScan Research Database (Cambridge, Mass.), a publicly available fee-forservice medical and prescription claims database of more than 2 million lives per year, was used to describe patterns of health care utilization and medical costs for patients who met criteria for treatment-resistant depression from January 1, 1995, to June 30, 2000. In addition to having an *International Classification of Diseases*, Ninth Revision (ICD-9), diagnosis code for bipolar or unipolar depression and evidence of antidepressant treatment, patients were required to meet criteria for adequate antidepressant dosing and treatment duration.<sup>26,27</sup> Upon meeting the inclusion criteria, patients were categorized into 3 groups: comparison (A), outpatient treatment resistant (B), and hospitalized treatment resistant (C).

The hospitalized treatment-resistant group (C) included patients who switched from or augmented their initial antidepressant medication at least once and had a depressionrelated hospitalization and/or an ICD-9–coded suicide attempt (300.90 or E950.x–E959.x) (N = 483). The outpatient treatment-resistant cohort (B) consisted of patients who switched from or augmented their initial antidepressant medication at least twice with other antidepressants but were not initially hospitalized (N = 2887). A randomly selected group (A) of patients diagnosed with depression who met initial antidepressant medication dosage selection criteria but did not meet criteria for treatment resistance were used for comparison (N = 7335).

The study period comprised 2 parts: the selection period and the observation period. The selection period was defined as the time from the date of the first antidepressant medication prescription until the date of discharge and/or suicide attempt for hospitalized patients, or the date the third different antidepressant medication prescription was dispensed for the outpatient treatment-resistant group. Costs during the selection period were not incorporated into the analyses. The observation period began at the index date (i.e., the day following hospital discharge and/or suicide attempt in the hospitalized group or the day following the dispensing of the third antidepressant medication in the outpatient group) and continued through the last available medical claims data point.

In addition to treatment-resistant criteria, patients had to meet the following criteria: aged 18 years or older upon enrollment; diagnosed with at least one ICD-9 code of unipolar or bipolar depression (ICD-9 code of 296.2, 296.3, 296.5, 296.6, 296.89, 300.4, 309.0, 309.1, or 311) from January 1, 1995, to June 30, 2000; the initial prescription of antidepressant medication at a minimum dosage for at least 8 weeks<sup>26</sup>; and no diagnosis of a major comorbid psychotic disorder (ICD-9 code of 290.xx, 295.xx, 297.xx, 298.xx, 299.xx, 317.xx–3119.xx, 331.0x, 332.xx, or 797.xx) from January 1, 1995, to June 30, 2000.

Patient characteristics, resource utilization for each group, and associated general medical, depression-related, and total health care costs were gathered and examined for the observation period. Data reported include information regarding initial antidepressant medication, diagnoses, mean number of antidepressant medications and other psychotropic and nonpsychotropic medications, frequency of outpatient visits, and hospitalization rates (Table 1).

Patients were followed for at least 9 months (longer if data were available). Comparison group patients were

# Table 1. Study Definitions

Table 1. Study Demittions	
Terms	Definition
Costs	
Pharmaceutical	Total receipts to pharmacy (insurer payment plus patient co-pay, coinsurance, and deductibles)
Outpatient visit	Total payment to providers for outpatient services, including insurer payment, deductibles, coinsurance, and co-pay
Hospitalization	Total payment to hospitals and providers for inpatient services, including issuer payment, deductibles, coinsurance, and co-pay
Total depression-related health care	Outpatient, inpatient, and laboratory costs associated with a depression diagnosis, including antidepressant and other psychotropic medication costs
Total general medical health care	Outpatient, inpatient, and laboratory costs associated with any diagnosis other than depression, including non-antidepressant medication costs
Total health care	Sum of depression-related and general medical costs, including outpatient, inpatient, medication, and laboratory costs, irrespective of diagnosis
Other terms	
Initial prescription	First prescription of an antidepressant medication meeting antidepressant dosing and duration criteria
Index date	Date patients met criteria for treatment resistance
Selection period	Date of initial antidepressant medication prescription to index date
Observation period	Index date to last available claims data point
Switching	Change to another antidepressant medication within selection period
Augmentation	Receipt of another antidepressant medication in addition to the initial antidepressant medication within selection period
Study groups	
Comparison group (A)	Depression-diagnosed patients who did not meet treatment-resistant criteria
Outpatient treatment-resistant group (B)	Patients who switched/augmented initial antidepressant medication with other antidepressant medications at least twice
Hospitalized treatment-resistant group (C)	Patients who switched/augmented initial antidepressant medication and had a depression-related hospitalization and/or suicide attempt (ICD-9 code 300.90 or E950.x-E959.x)
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required to be continuously enrolled and followed for a time period equal to the mean length of time for the observation period in the treatment-resistant cohorts. Annuabized expenditures were converted to year 2000 U.S. dollars using the medical and drug consumer price indexes of the U.S. Bureau of Labor Statistics.<sup>28</sup>

# **Statistical Analyses**

Statistical tests were conducted to contrast the 2 treatment-resistant cohorts to the comparison group. Chisquare statistics were employed to assess statistical significance of categorical variables; 2-tailed t tests and median rank tests were used for continuous variables. Treatment groups were compared by demographic variables, plan type, index antidepressant, depression diagnosis, percentage of patients hospitalized (depression and non–depression related), mean number of hospitalizations, mean and median hospital days, outpatient visits (depression and non–depression related), mean number of distinct medications, and mean number of prescriptions. Additionally, total, depression-related, and general medical health care costs were compared.

## RESULTS

# **Sample Characteristics**

A total of 3370 patients diagnosed with depression met inclusion criteria for treatment resistance with 483 patients in the hospitalized treatment-resistant cohort (C) and 2887 in the outpatient treatment-resistant cohort (B). Patient groups were similar with respect to demographic characteristics and form of health insurance coverage. The patient population was predominately female (71.6%) with a mean age of 44 years. Employee beneficiaries constituted the majority of the sample, followed by spouse and dependents. Approximately half of the study sample members were in traditional indemnity plans (Table 2).

The most common initial antidepressant medication for all groups was an SSRI. However, more patients received an SSRI in the comparison group (84.6%) than in either the outpatient treatment-resistant group (65.6%) or the inpatient treatment-resistant group (67.5%). Tricyclic antidepressants (TCAs) were more likely to be prescribed to patients in either treatment-resistant group than the comparison group (Table 3).

Bipolar disorders were more prevalent in each treatment-resistant group than in the comparison group: 6:1 for the hospitalized treatment-resistant group and 2:1 in the outpatient treatment-resistant group (Table 3). Substance abuse-related anxiety and/or personality disorders were also more prevalent in each treatment-resistant group than in the comparison group.

# **Outpatient and Pharmaceutical Utilization**

Those in the treatment-resistant cohorts had a significantly greater number of total outpatient visits than the comparison group (hospitalized: p = .018, outpatient, p < .001). Greater than a third (37.9%) of the hospitalized treatment-resistant patients received electroconvulsive therapy (ECT) (Figure 1).

#### Table 2. Demographic Characteristics at Index Data<sup>a</sup>

	Comparison Group (A)	Outpatient Treatment-Resistant Group (B)	Hospitalized Treatment-Resistant Group (C)		p Value <sup>b</sup>	
Characteristic	(N = 7335)	(N = 2887)	(N = 483)	A vs B	A vs C	B vs C
Mean age, y	43.8	44.4	44.3	.006	.381	.757
Female, %	71.6	71.6	71.6	.979	.982	.974
Employee relationship, %				<.001	.107	.157
Employee	60.3	62.4	57.1			
Spouse	32.5	32.8	37.1			
Dependent	7.2	4.5	5.6			
Unknown	0.1	0.3	0.2			
Plan type, % (C)						
Indemnity plans	59.1	56.6	57.3	.025	.459	.769
Networked providers	40.1	42.6	41.8	.019	.457	.737
Other FFS plans	0.8	0.7	0.8	.595	.994	.811

<sup>a</sup>Data from MarketScan Research Database, The MEDSTAT Group, Cambridge, Mass., from January 1, 1995, to June 30, 2000. <sup>b</sup>Chi-square tests and t tests were used for categorical and continuous variables, respectively. <sup>c</sup>FFS = fee for service.



Table 3. Clinical Characteristics	<sup>a</sup> C					
	Comparison Group (A)	Outpatient Treatment-Resistant Group (B)	Hospitalized Treatment-Resistant Group (C)		p Value <sup>b</sup>	
Characteristic	(N = 7335)	(N = 2887)	(N = 483)	A vs B	A vs C	B vs C
Initial antidepressant treatment, %	10	~				
TCAs	2.0	6.8	7.0	<.001	<.001	.818
SSRIs	84.6	65.6	67.5	<.001	<.001	.426
MAOIs	0.1	1.0	1.0	.409	<.001	< .001
Atypical/heterocyclic	13.3	27,5	24.4	<.001	<.001	.164
ECT treatment, %	0.0	2.0	37.9	<.001	<.001	<.001
Depression type, %						
Unipolar	96.2	92.4	78.9	<.001	<.001	< .001
Bipolar	3.8	7.6	21.1	<.001	<.001	< .001
Comorbid disorders, %		L.				
Unique ICD-9 codes	6.8	7.7	10.9	<.001	<.001	<.001
Substance-abuse disorder(s)	2.4	4.4	13.9	<.001	<.001	<.001
Anxiety disorder(s)	9.7	15.4	26.1	<.001	< .001	<.001
Personality disorder(s)	1.2	2.4	-C 14.)	<.001	<.001	< .001

<sup>a</sup>Data from MarketScan Research Database, The MEDSTAT Group, Cambridge, Mass., from January 1, 1995, to June 30, 2000. Abbreviations: ECT = electroconvulsive therapy; ICD-9 = *International Classification of Diseases*, Ninth Revision: MAOIs = monoamine oxidase inhibitors; SSRIs = selective serotonin reuptake inhibitors; TCAs = tricyclic antidepressants. Chi-square tests and t tests were used for categorical and continuous variables, respectively.



Figure 1. Electroconvulsive Therapy (ECT) Service

The mean number of distinct currently prescribed antidepressant medications was highest for outpatient treatment-resistant patients (2.2), followed by hospitalized treatment-resistant patients (1.9), and patients in the comparison group (1.4). Nonpsychotropic medications followed the same pattern-mean distinct medications per patient were 7.7, 6.7, and 5.9 for the outpatient treatment-resistant, hospitalized treatment-resistant, and comparison groups, respectively. All of these comparisons were statistically significant (p < .05). In addition, hospitalized treatment-resistant patients had a significantly higher mean number of distinct nonantidepressant psychotropic medications (2.2), followed by the outpatient treatment-resistant (1.4) and comparison groups (0.7) (p < .001) (Table 4).

The mean number of antidepressant medication prescriptions per year was substantially higher in the hospi-

Table 4. Outpatient Visits a	nd Pharmaceutical	Utilization <sup>a</sup>
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	Comparis (A (N =	on Group A) 7335)	Outpatient Treatment-Resistant Group (B) (N = 2887)		Hospitalized Treatment-Resistant Group (C) (N = 483)		p Value <sup>b</sup>		
Utilization	Mean	SD	Mean	SD	Mean	SD	A vs B	A vs C	B vs C
Outpatient visits <sup>c</sup>									
Total visits	5.6	6.8	6.3	7.2	6.6	8.8	<.001	.018	.526
Depression related	0.2	0.8	0.2	1.0	0.5	2.6	.761	.060	.070
General medical	5.4	6.8	6.1	7.1	6.1	8.1	<.001	.048	.899
Distinct medications <sup>c</sup>									
Total medications	8.0	9.1	11.3	7.8	10.8	9.1	<.001	<.001	.215
Antidepressants	1.4	0.7	2.2	1.0	1.9	1.3	<.001	<.001	<.001
Other psychotropics	0.7	1.0	1.4	1.4	2.2	1.9	<.001	<.001	<.001
Nonpsychotropics	5.9	5.7	7.7	6.9	6.7	7.4	<.001	.022	.004
Prescriptions <sup>c</sup>									
Total prescriptions	29.5	28.3	51.7	41.2	52.0	45.4	<.001	<.001	.877
Antidepressants	7.3	5.4	15.7	9.8	13.5	13.0	<.001	<.001	<.001
Other psychotropic drugs	• 3.9	6.9	8.4	11.2	14.5	15.7	<.001	<.001	<.001
Nonpsychotropic drugs	18.4	22.8	27.6	30.8	24.0	29.0	<.001	<.001	.018

<sup>a</sup>Data from MarketScan Research Database, The MEDSTAT Group, Cambridge, Mass., from January 1, 1995, to June 30, 2000. <sup>b</sup>Chi-square tests and t tests were used for categorical and continuous variables, respectively.

<sup>c</sup>Annualized per patient.



talized (13.5) and outpatient (15.7) treatment-resistant groups than in the comparison group (7.3) (p < .001). Relative to the comparison group, treatment-resistant patients were also prescribed more nonantidepressant psychotropic (8.4–14.5 vs. 3.9) (p < .001) and nonpsychotropic medications per year (27.6–24.0 vs. 18.4) (p < .02) (Table 4).

# **Hospitalization Rates**

A greater proportion of patients in the hospitalized treatment-resistant cohort had depression-related and general medical hospitalizations (36.9% and 13.7%) during the observation period than those in the outpatient treatment-resistant (7.0% and 10.3%) or comparison groups (2.0% and 6.6%) (Figure 2, Table 5). Of those hospitalized, the hospitalized treatment-resistant patients had significantly more depression-related hospitalizations

during the observation period compared with the outpatient treatment-resistant group and the comparison group, respectively (2.5 vs. 1.7 and 1.3; p < .001) (Table 5).

# **Health Care Costs**

**Total depression-related costs.** During the observation period, annualized total depression-related costs were significantly higher for the hospitalized treatment-resistant group (\$28,001) followed by the outpatient treatment-resistant group (\$3699) and the comparison group (\$1455) (p < .001) (Figure 3, Table 6). The significantly higher total depression-related costs were generally the result of higher depression-related hospitalization costs due to increased hospitalization rates in this cohort (Figure 2).

Depression-related outpatient costs were also highest for patients in the hospitalized treatment-resistant group (\$3939), followed by the outpatient treatment-resistant group (\$974) and the comparison group (\$494) (p < .001). Antidepressant and other psychotropic medication acquisition costs were greater in each treatment-resistant group than in the comparison group (p < .001) (Table 6).

*General medical costs.* General medical outpatient costs were highest for the hospitalized treatment-resistant group (\$4987), followed by the outpatient treatment-resistant group (\$3297) and the comparison group (\$2695). Hospitalization costs followed the same pattern—\$8073, \$1708, and \$1480 for the hospitalized treatment-resistant, outpatient treatment-resistant, and comparison groups, respectively. Pharmaceutical costs were higher in each treatment-resistant group than in the comparison group. Total general medical costs were \$14,343 for the hospitalized treatment-resistant group, \$6542 for the outpatient treatment-resistant group, and \$5057 for the comparison group (p < .001) (Table 6).

Fable 5. Subsequent Depression-Related and General Medical Hospitalizations <sup>a</sup>								
	Comparison Group (A)	Outpatient Treatment- Resistant Group (B)	Hospitalized Treatment- Resistant Group (C)		p Value <sup>b</sup>			
Hospitalizations	(N = 7335)	(N = 2887)	(N = 483)	A vs B	A vs C	B vs C		
Depression related <sup>c,d</sup>	(N = 148)	(N = 201)	(N = 178)					
No. of hospitalizations among users, mean (SD)	1.3 (0.8)	1.7 (1.4)	2.5 (2.8)	.002	<.001	.001		
Annualized total hospital days, mean (SD)	12.8 (13.5)	13.5 (27.3)	32.2 (65.1)	.791	.001	.004		
Annualized total hospital days, median	8.7	5.7	12.7	.007	.026	<.001		
General medical <sup>c</sup>	(N = 485)	(N = 298)	(N = 66)					
No. of hospitalizations among users, mean (SD)	1.3 (0.9)	1.5 (1.3)	1.6 (1.0)	.134	.096	.598		
Annualized total hospital days, mean (SD)	8.6 (13.3)	5.9 (7.9)	13.0 (18.4)	.005	.122	.014		
Annualized total hospital days, median	5.3	3.1	6.7	<.001	.309	.008		

<sup>a</sup>Data from MarketScan Research Database, The MEDSTAT Group, Cambridge, Mass., from January 1, 1995, to June 30, 2000. <sup>b</sup>Chi-square tests and trests were used for categorical and continuous variables, respectively.

Conditional on being hospitalized during observational period.

<sup>d</sup>Excluding selection event.



*Total health care costs.* Both outpatient and hospitalization total health care costs (general plus depressionrelated) were significantly higher in the hospitalized treatment-resistant cohort than in the outpatient treatmentresistant or comparison groups (p < .001). Mean total costs for outpatient visits were \$8926, \$4271, and \$3188 for the hospitalized treatment-resistant, outpatient treatmentresistant, and comparison cohorts, respectively (p < .001). Those in the hospitalized treatment-resistant cohort had the highest mean hospitalization costs (\$30,166), followed by the outpatient treatment-resistant group (\$2456) and comparison group (\$1611).

Total pharmaceutical costs were similar in the treatmentresistant groups. Total pharmaceutical payments were \$3251 for the hospitalized treatment-resistant group (with antidepressants accounting for \$1097), \$3513 for the outpatient treatment-resistant group (with antidepressant medication costs being \$1508), and \$1713 for the comparison group (with \$678 for antidepressant medications).

Total annualized health care costs were highest in the hospitalized treatment-resistant cohort (\$42,344), followed by the outpatient treatment-resistant group (\$10,241) and the comparison group (\$6512). The significantly greater total costs in the hospitalized treatment-resistant group were the result of both higher general medical and depression-related outpatient and hospitalization costs (Table 6) (Figure 3).

Table 7 reports the results of an ordinary least squares regression in which the dependent variable is the logarithm of total health care expenditures. A number of variables were significantly related to higher expenditures including age, female gender, indemnity plan type, receipt of electroconvulsive therapy, substance abuse comorbidity, anxiety disorder comorbidity, and personality disorder comorbidity. Moreover, unipolar patients had lower expected total costs than bipolar patients. After controlling for all these other factors, health care expenditures for patients in both the outpatient and hospitalized treatmentresistant cohorts were significantly higher than those for patients in the comparison group.

# Sensitivity Analyses

We examined whether the results were sensitive to the inclusion of bipolar patients by also conducting all of the analyses on the sample with bipolar patients omitted. Omitting bipolar patients had the effect of reducing total expenditure levels slightly in all of the study groups, but had no effect on the statistical significance of differences among the groups. After omitting bipolar patients, mean total annualized health care costs were \$40,463 for the hospitalized treatment-resistant cohort, followed by \$9889 for the outpatient group and \$6393 for the comparison group (p < .001 for all comparisons).

We also estimated separate multivariate models for the unipolar and bipolar samples. In each case, the hospitalized and outpatient treatment-resistant groups had higher health care expenditures than the comparison group.

A sensitivity analysis of the economic results was also conducted to investigate the influence of expenditure

$\begin{tabular}{ c c c c c c c c c c c c c c c c c c c$	Table 6. Annualized I	Depression-Related, Gene	eral Medical, and Total	Health Care Costs <sup>a</sup>			
$\begin{tabular}{ c c c c c c c c c c c c c c c c c c c$		Heal	th Care Costs (U.S. \$, yea	ar 2000)			
$ \begin{array}{c c c c c c c c c c c c c c c c c c c $		Comparison	Outpatient Treatment-	Hospitalized Treatment-		h	
Health Care Costs $(N = 7335)$ $(N = 2887)$ $(N = 483)$ A vs BA vs CB vs CDepression related <sup>c</sup> Mean (SD) costPharmaceutical <sup>d</sup> 831 (766)1976 (1796)1969 (1892)<.001<.001.931Outpatient494 (1072)974 (2449)3939 (6120)<.001<.001<.001<.001Hospitalization <sup>e</sup> 130 (1323)748 (6729)22,093 (45,266).001<.001<.001<.001Total1455 (2141)3699 (8252)28,001 (47,323)<.001<.001<.001<.001Median cost Pharmaceutical66316041593<.001<.001.001<.001		Group (A)	Resistant Group (B)	Resistant Group (C)		p Value <sup>0</sup>	
$ \begin{array}{c ccccccccccccccccccccccccccccccccccc$	Health Care Costs	(N = 7335)	(N = 2887)	(N = 483)	A vs B	A vs C	B vs C
$ \begin{array}{c ccccccccccccccccccccccccccccccccccc$	Depression related <sup>c</sup>						
$\begin{array}{c ccccccccccccccccccccccccccccccccccc$	Mean (SD) cost						
Outpatient $494 (1072)$ $974 (2449)$ $3939 (6120)$ $< .001 < .001 < .001$ $< .001$ Hospitalizatione $130 (1323)$ $748 (6729)$ $22,093 (45,266)$ $.001 < .001 < .001$ Total $1455 (2141)$ $3699 (8252)$ $28,001 (47,323)$ $< .001 < .001 < .001$ Median costPharmaceutical $663$ $1604$ $1593$ $< .001 < .001 < .001$ Outpatient $(69)$ $226$ $1742$ $< .001 < .001 < .001$	Pharmaceutica1 <sup>d</sup>	831 (766)	1976 (1796)	1969 (1892)	<.001	<.001	.931
Hospitalizatione130 (1323)748 (6729) $22,093 (45,266)$ .001<.001<.001Total1455 (2141)3699 (8252)28,001 (47,323)<.001	Outpatient	494 (1072)	974 (2449)	3939 (6120)	< .001	<.001	<.001
Total      1455 (2141)      3699 (8252)      28,001 (47,323)      <.001      <.001      <.001        Median cost      Pharmaceutical      663      1604      1593      <.001	Hospitalization <sup>e</sup>	130 (1323)	748 (6729)	22,093 (45,266)	.001	<.001	<.001
Median cost      Pharmaceutical      663      1604      1593      < .001      .050        Output      .001      .022      .1742      .001      .00	Total	1455 (2141)	3699 (8252)	28,001 (47,323)	<.001	<.001	<.001
Pharmaceutical      663      1604      1593      <.001      .050        Output	Median cost						
$0.001 \pm 0.01 \pm 0.01 \pm 0.01$	Pharmaceutical	663	1604	1593	< .001	<.001	.050
Outpatient $\sim$ 08 230 1/45 <.001 <.001	Outpatient	68	236	1743	< .001	<.001	<.001
Hospitalization 0 0 8131 <.001 <.001 <.001	Hospitalization	0	0	8131	< .001	<.001	<.001
Total 893 2189 13,418 <.001 <.001 <.001	Total	893	2189	13,418	< .001	<.001	<.001
General medical	General medical	ろ					
Mean (SD) cost	Mean (SD) cost						
Pharmaceutical 882 (1687) 1537 (2534) 1283 (2139) <.001 <.001 .019	Pharmaceutical	882 (1687)	1537 (2534)	1283 (2139)	<.001	<.001	.019
Outpatient      2695 (5788)      3297 (6288)      4987 (10,394)      <.001      .001	Outpatient	2695 (5788)	3297 (6288)	4987 (10,394)	< .001	<.001	.001
Hospitalization 480 (9794) 1708 (9662) 8073 (34,637) .288 <.001 <.001	Hospitalization	1480 (9794)	1708 (9662)	8073 (34,637)	.288	<.001	<.001
Total 5057 (13,604) 6542 (13,510) 14,343 (38,583) <.001 <.001 <.001	Total	5057 (13,604)	6542 (13,510)	14,343 (38,583)	< .001	<.001	<.001
Median cost	Median cost						
Pharmaceutical 354 767 564 <.001 <.001 <.001	Pharmaceutical	354	767	564	< .001	<.001	< .001
Outpatient 978 1389 2096 <.001 <.001 <.001	Outpatient	978	1389	2096	< .001	<.001	<.001
Hospitalization 0 0 0 0 <.001 <.001 <.001	Hospitalization	0	0	0	< .001	<.001	<.001
Total 1691 2750 4211 <.001 <.001 <.001	Total	1691	2750	4211	< .001	<.001	<.001
Total health care	Total health care						
Mean (SD) cost	Mean (SD) cost	10					
Pharmaceutical 1713 (2010) 3513 (3,457) 3251 (3,270) < .001 < .001 .120	Pharmaceutical	1713 (2010)	3513 (3,457)	3251 (3,270)	< .001	<.001	.120
Outpatient 3188 (5929) 4271 (6,880) 8926 (12,198) <.001 <.001 <.001	Outpatient	3188 (5929)	4271 (6,880)	8926 (12,198)	<.001	<.001	<.001
Hospitalization 1611 (9913) 2456 (11,909) 30,166 (61,720) .001 < .001 < .001	Hospitalization	1611 (9913)	2456 (11,909)	30,166 (61,720)	.001	<.001	<.001
Total 6512 (13,915) 10,241 (16,334) 42,344 (66,582) < .001 < .001 < .001	Total	6512 (13,915)	10,241 (16,334)	42,344 (66,582)	< .001	<.001	<.001
Median cost	Median cost		2/ 6/				
Pharmaceutical 1179 2684 2362 <.001 <.001 .002	Pharmaceutical	1179	2684	2362	< .001	<.001	.002
Outpatient      1465      2164      5636      <.001      <.001	Outpatient	1465	2164	5636	< .001	<.001	<.001
Hospitalization 0 0 0 11,038 <.001 <.001 <.001	Hospitalization	0	0	11,038	<.001	<.001	<.001
Total 3194 5833 22,730 <.001 <.001 <.001	Total	3194	5833	22,730	<.001	<.001	<.001

<sup>a</sup>Data from MarketScan Research Database, The MEDSTAT Group, Cambridge, Mass., January 1, 1995, to June 30, 2000. Health care expenditures were calculated during the observational period.

<sup>b</sup>p Values are obtained from t tests.

Depression-related payments sum claims with ICD-9 codes 230-319.00 and/or procedures 90801-90899.

<sup>d</sup>Includes antidepressant medications and other psychotropic medications.

<sup>e</sup>The mean is calculated among both users and nonusers of inpatient mental health services

#### Table 7. Multivariate Analysis of Total Payments<sup>a</sup>

	Parameter	Standard		
Variable	Estimate	Error	t Value	p Value <sup>b</sup>
Intercept	7.1406	0.0698	102.24	<.0001
Age	0.0179	0.0010	17.80	<.0001
Female	0.0833	0.0234	3.56	.0004
Indemnity plan type	0.1046	0.0211	4.96	<.0001
Employee	0.0048	0.0217	0.22	.8247
SSRI	0.0148	0.0261	0.57	.5706
ECT	0.8730	0.1113	7.84	<.0001
Unipolar disorder	-0.3647	0.0460	-7.93	<.0001
Substance abuse	0.5914	0.0574	10.31	<.0001
Anxiety disorder	0.3302	0.0324	10.19	<.0001
Personality disorder	0.5160	0.0735	7.02	<.0001
Treatment-resistant depression	n			
Hospitalized cohort	1.3691	0.0538	25.45	<.0001
Outpatient cohort	0.4918	0.0244	20.19	<.0001
ICD-9 comorbidities	0.0271	0.0006	42.80	<.0001

<sup>a</sup>Adjusted  $R^2 = 0.32$ . Abbreviations: ECT = electroconvulsive therapy; ICD-9 = International Classification of Diseases, Ninth Revision; SSRI = selective serotonin reuptake inhibitor.

<sup>b</sup>p Values are obtained from t tests.

outliers on the substance of the findings. Patients with costs above 99% of the data were excluded to determine if the findings were unduly influenced by these values. Both means and medians were recalculated and compared; the significant findings remained consistent.

# DISCUSSION

In this study, we used a large retrospective medical claims database to characterize 2 groups of patients with treatment-resistant depression. One treatment-resistant group was identified as having failed 2 courses of antidepressant therapy and having an inpatient hospitalization expressly due to depressive illness or other intervention following a diagnosed suicide attempt. The second treatment-resistant group included patients with evidence of a failure of the initial course of antidepressant therapy, requiring at least 2 changes in the antidepressant medication treatment regimen, but experiencing no depressionrelated hospitalization initially. The characteristics and experience of these 2 groups were compared to a sample of other patients with depression that apparently responded to initial treatment (as indicated by a stable medication use pattern). We believe that this is the first naturalistic, retrospective analysis to have successfully identified and contrasted the experience of patients with treatment-resistant depression to treatment responders.

A major finding of this study is that total annualized health care costs were highest for the hospitalized treatment-resistant patients and were generally the result of significantly greater general medical and depressionrelated hospitalization costs. Total health care costs for the hospitalized treatment-resistant cohort were 4 times greater than for the outpatient treatment-resistant cohort and 6.5 times greater relative to the comparison group. Furthermore, total depression-related costs in the hospitalized treatment-resistant cohort were 8 times greater than those in the outpatient treatment-resistant cohort and 19 times greater than those in the comparison group.

The demographic characteristics of those with treatmentresistant depression were similar to the comparison group in this predominantly employee-based population. As expected, the vast majority of those in our sample were female. Patients with evidence of treatment resistance were more likely to be treated by psychiatrists for their depression and were more likely to be prescribed antidepressants that were not SSRIs during the observation period.

We identified differences between patients with and without treatment resistance in terms of their health status and concomitant diagnoses. Treatment-resistant patients were more likely to have had bipolar disorder, substance abuse-related anxiety and personality disorders, and greater numbers of general medical comorbidities than patients in the comparison group.

Patients in each treatment-resistant group had higher mean hospitalizations for depression-related causes than the comparison group. Among patients who were admitted, those in the hospitalized treatment-resistant group had much longer mean lengths of stay than patients in either the comparison group or the outpatient treatment-resistant group. A significantly higher incidence of treatment with ECT occurred in hospitalized treatment-resistant patients and may have contributed to the higher depression-related health care costs in this cohort.<sup>29,30</sup> The treatment-resistant groups were also prescribed a wider range of antidepressant medications than those without treatment resistance and made more intensive use of other psychotropic medications.

Relative to the comparison and outpatient groups, the treatment-resistant hospitalized group had significantly higher depression-related and general medical health care costs, reflecting the higher health care utilization and hospitalization rates in this cohort.<sup>4,20</sup> The annualized difference in total health care expenditures between the hospital-

ized treatment-resistant cohort and the comparison group (\$35,832) suggests that the costs of unsuccessful antidepressant therapies are very high. However, this is only a first approximation of the cost difference. For example, it would be very valuable to understand more about how long patients have been ill, as well as the relationship between health care expenditures and medication changes over time.

Our analysis is subject to many of the welldocumented limitations associated with the use of large, retrospective administrative claims databases to gain insights into the patterns and costs of care. These data do not permit an examination of symptoms using standard symptom-based assessments (e.g., Hamilton Rating Scale for Depression<sup>31</sup> or Clinical Global Impressions scale<sup>32</sup>). Another potential limitation is the lack of a clean preperiod (i.e., time preceding study entry during which no depression diagnosis and treatment occurs, thereby indicating that the study period is a new episode). Establishing a clean period for patients with treatment-resistant depression is difficult due to the chronicity of the condition. Furthermore, we only examine patients seeking care from traditional physicians; treatment-resistant depressed patients who seek alternative therapies not covered by their health insurer are not captured in these data. Finally, this study measures only direct costs. Measures of lost work productivity and the cost of care provided by family members are not included in the current analysis; therefore, the current findings are likely to be an underestimate of the true cost of treatment-resistant depression. It would be useful to examine further the total and depression-related health care costs for treatment-resistant depression using a naturalistic, prospective design to determine if these findings can be replicated. Other factors not examined in this study may contribute to the high costs associated with treatment-resistant depression. These issues (e.g., illness history and initial causes of treatment resistance) require further investigation and are best addressed in prospective study designs. Finally, almost nothing is known about the effects of mental illness on the health care utilization of family members-related to mental illness or otherwise.

In addition, the costs and benefits associated with early intervention and more effective therapies could be explored using decision analytic models. This type of research would enable costs and benefits to be estimated under alternative assumptions about the timing and efficacy of interventions. Such research might be particularly informative if estimates of clinical efficacy of alternative therapies for treatment-resistant depression were available from clinical trials.

# CONCLUSION

It is clear that patients with treatment-resistant depression had discernibly different patterns of illness and treatment, compared with those whose depression apparently responded to initial antidepressant treatment. Those with treatment resistance made more extensive and costly use of medical services, both depression-related and general medical. Total costs in the hospitalized treatment-resistant group were significantly higher at \$42,344 compared with \$10,241 and \$6512 in the outpatient treatment-resistant and comparison groups, respectively. This study underscores the importance of early identification and effective long-term treatment for patients with treatment-resistant depression. To prevent future episodes of depressive illness and associated functional impairment and to reduce health care utilization, it is crucial that early identification and effective treatment of treatment-resistant patients be provided.

*Disclosure of off-label usage:* The authors have determined that, to the best of their knowledge, no investigational information about pharmaceutical agents has been presented in this article that is outside U.S. Food and Drug Administration–approved labeling.

In the spirit of full disclosure and in compliance with all ACCME Essential Areas and Policies, the faculty for this CME activity were asked to complete a full disclosure statement. The information received is as follows: Dr. Crown has received grant/research support from Cyberonics and The MEDSTAT Group. Dr. Finkelstein is a consultant for The MEDSTAT Group and has received grant/research support from Merck, Pfizer, and Wyeth. Dr. Berndt is a consultant for Cyberonics, Dr. Ling is an employee of The MEDSTAT Group. Dr. Rush is a consultant for Bristol-Myers, Cyberonics, Lilly, Forest, GlaxoSmithKline, fanssen, Merck, and Stanley Foundation; has received grant/research support from Cyberonics, Robert Wood Johnson, National Institute of Mental Health, and Stanley Foundation; and is a member of the speakers advisory board for Bristol-Myers, Cyberonics, Forest, GlaxoSmithKline, and Wyeth. Ms. Poret and Dr. Russell have no significant commercial relationships to disclose relative to the presentation.

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