# The Cost Consequences of Treatment-Resistant Depression

James M. Russell, M.D.; Kevin Hawkins, Ph.D.; Ronald J. Ozminkowski, Ph.D.; Lucinda Orsini, M.P.H.; William H. Crown, Ph.D.; Sean Kennedy, B.A.; Stan Finkelstein, M.D.; Ernst Berndt, Ph.D.; and A. John Rush, M.D.

*Context:* Treatment-resistant depression is a significant public health problem with profound effects on general medical and mental health–related health care costs.

*Objective:* To describe health care costs of patients with treatment-resistant depression as their illness progresses, in terms of pharmaceutical and medical expenditures, and to identify factors associated with increasing degrees of treatment resistance.

*Data Sources:* The MEDSTAT MarketScan Private Pay Fee for Service (FFS) Database, a medical and prescription claims database covering over 3.5 million enrollees, from 1995–2000.

**Design and Study Subjects:** 7737 patients with depression (ICD-9) who had 2 or more unsuccessful trials of antidepressant medication at an adequate dose for at least 4 weeks from 1995–2000 were defined as treatment-resistant in this study. Demographic and clinical characteristics were assessed for these patients with treatment-resistant depression. The number of changes in depression medication treatment regimens was used as a proxy for increasing degrees of treatment resistance and its severity.

*Major Outcome Measure:* Differences in health care expenditures associated with increasing degrees of treatment-resistant depression.

**Results:** Total depression-related and general medical health care expenditures increased significantly as treatment-resistant depression increased in severity. Multivariate analyses of patient demographic characteristics were not associated with ongoing treatment resistance. Disease severity, type of antidepressant at index, comorbid mental health disorders, and membership in a managed health care plan were associated with increasing degrees of treatment resistance.

*Conclusions:* Depression and general medical health care expenditures increase with the degree of treatment-resistant depression. Disease management interventions for treatment-resistant depression that result in sustained remission early in the course of illness are most likely to be cost effective.

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Corresponding author and reprints: James M. Russell, M.D., Lilly Corporate Center, MS 6112, Indianapolis, IN 46285 (e-mail: russelljm@lilly.com).

D epression affects up to 20% of the U.S. population within each generation.<sup>1</sup> Insured patients with depression in the United States incur up to 70% more medical expenditures than nondepressed patients.<sup>2</sup> Treatmentresistant depression commonly occurs in 10% to 50% of patients with depression.<sup>3–5</sup> Crown et al.<sup>6</sup> and Corey-Lisle et al.<sup>7</sup> have estimated the mean total annual health care costs for patients with treatment-resistant depression to be approximately \$11,000. Petersen and colleagues<sup>8(p1223)</sup> note that "treatment-resistant depression continues to present a formidable challenge to clinicians, accounting for over half the annual costs associated with treatment for depression and causing great frustration to patients."

The definition of treatment-resistant depression is highly variable.9 Treatment-resistant depression is often defined in terms of unsuccessful treatment attempts, by focusing on either a change in symptoms or the number of ongoing antidepressant medication regimen changes.<sup>10-15</sup> These depression medication regimen changes are generally associated with patient nonresponse to treatment rather than medication intolerance. Some studies identify patients as treatment-resistant if only 1 medication regimen change has occurred, provided the initial antidepressant prescribed was of adequate dose and duration.16-18 Others have required 2 or 3 medication regimen changes of adequate dose and duration before classifying patients as treatment resistant.<sup>19–25</sup> There are no widely accepted treatment guidelines for treatment-resistant depression, and few controlled trials to suggest which antidepressant treatments are the most effective in this patient population.

| Table 1. Diagnosis-Bas | sed Exclusion Criteria |
|------------------------|------------------------|
| ICD 0 Codes            | Diagnosis              |

| ICD-9 Codes   | Diagnosis                                                                                    |
|---------------|----------------------------------------------------------------------------------------------|
| 290.xx-295.xx | Senile/presenile psychosis, alcoholic psychoses,<br>drug psychoses, transient organic mental |
|               | disorder, other organic psychotic condition,                                                 |
|               | schizophrenic disorders                                                                      |
| 297.xx        | Paranoid states                                                                              |
| 298.xx        | Other nonorganic psychoses                                                                   |
| 299.xx        | Psychoses of childhood                                                                       |
| 331.0         | Alzheimer's disease                                                                          |
| 332.xx        | Parkinson's disease                                                                          |
| 317.xx-319.xx | Mental retardation                                                                           |
| 797.xx        | Senility without psychosis                                                                   |
|               |                                                                                              |

Given the high percentage of patients with an inadequate response to their initial antidepressant (30% - 46%), a change in the type of antidepressant or the use of an augmentation agent is often indicated.<sup>26,27</sup> Augmentation is defined as the addition of a second agent to an existing antidepressant, with the aim of achieving improved clinical response. Typical augmentation agents include lithium, buspirone, carbamazepine, valproate sodium, methylphenidate, amphetamine, or thyroid.<sup>28</sup> No particular strategy has shown a clear advantage over the other, although few randomized controlled trials have compared these different augmentation options.<sup>4,18,29</sup> In addition to pharmacotherapy, psychotherapy is often utilized to augment antidepressant medication. Other forms of treatment include sleep deprivation,<sup>16</sup> transcranial magnetic stimulation,<sup>30</sup> bright light augmentation,<sup>31</sup> vagus nerve stimulation,<sup>12</sup> psychosurgery,<sup>19</sup> and electroconvulsive therapy (ECT).<sup>17</sup>

There is limited research on the economic implications associated with the progression of treatment-resistant depression. On the basis of retrospective medical and pharmacy claims data, the aim of this study is to describe the health care cost burden of ongoing treatment-resistant depression, as patients with treatment-resistant depression progress through multiple unsuccessful treatment regimens. We hypothesize that as treatment-resistant depression progresses, monthly total depression-related and general medical health care expenditures will increase.

#### **METHOD**

### **Study Population**

The MEDSTAT Group's MarketScan Private Pay FFS Database, a medical and prescription claims database covering over 3.5 million enrollees from 1995–2000, was utilized. Patients with a depression diagnosis (ICD-9 diagnosis codes: 296.2, 296.3, 296.5, 296.6, 296.89, 300.4, 309.0, 309.1, or 311.0) were identified, and then additional criteria were employed to identify individuals with treatment-resistant depression. Since patients with treatment-resistant depression are often treated with atypical antipsychotics,<sup>32,33</sup> those with evidence of a major psychotic disorder between 1995 and 2000 were excluded (Table 1).

| Table 2. Antidepressant | Minimum Dosage Selection Criteria <sup>a</sup> |
|-------------------------|------------------------------------------------|
| Generic Antidepressant  | Dosage Requirement (mg/day)                    |

| Generic Antidepressant                                                                            | Dosage Requirement (mg/day)             |  |
|---------------------------------------------------------------------------------------------------|-----------------------------------------|--|
| TCAs                                                                                              |                                         |  |
| Amitriptyline <sup>b</sup>                                                                        | 75                                      |  |
| Clomipramine                                                                                      | 75                                      |  |
| Doxepin                                                                                           | 75                                      |  |
| Trimipramine                                                                                      | 75                                      |  |
| Desipramine                                                                                       | 75                                      |  |
| Imipramine                                                                                        | 75                                      |  |
| Amoxapine                                                                                         | 100                                     |  |
| Maprotiline                                                                                       | 100                                     |  |
| Nortriptyline                                                                                     | 40                                      |  |
| Protriptyline                                                                                     | 20                                      |  |
| SSRIs                                                                                             |                                         |  |
| Citalopram                                                                                        | 20                                      |  |
| Fluoxetine                                                                                        | 20                                      |  |
| Paroxetine                                                                                        | 20                                      |  |
| Fluvoxamine                                                                                       | 100                                     |  |
| Sertraline                                                                                        | 50                                      |  |
| MAOIs                                                                                             |                                         |  |
| Phenelzine                                                                                        | 45                                      |  |
| Isocarboxazid                                                                                     | 30                                      |  |
| Mirtazapine                                                                                       | 15                                      |  |
| Tranylcypromine                                                                                   | 20                                      |  |
| Other antidepressants                                                                             |                                         |  |
| Venlafaxine                                                                                       | 150                                     |  |
| Nefazodone                                                                                        | 300                                     |  |
| Trazodone                                                                                         | 150                                     |  |
| Bupropion                                                                                         | 225                                     |  |
| <sup>1</sup> Augmentation agents were thyroid supplements, buspirone,<br>stimulants, and lithium. |                                         |  |
| combined with other compo                                                                         | ounds.                                  |  |
|                                                                                                   | • • • • • • • • • • • • • • • • • • • • |  |

Abbreviations: MAOIs = monoamine oxidase inhibitors, SSRIs = selective serotonin reuptake inhibitors, TCAs = tricyclic antidepressants.

Patients had to be  $\geq 18$  years of age at the time of the depression diagnosis and to have had at least 4 weeks of treatment with an antidepressant medication (measured as 2 consecutive prescriptions) at a specified minimum dosage (Table 2). In order to derive a sample of patients with treatment-resistant depression, patients were required to have changed their antidepressant treatment regimen (switching/augmentation) at least twice or to have had 1 treatment regimen change and a depression-related hospitalization (ICD-9 diagnosis codes 296.2, 296.3, 296.5, 296.6, 296.89, 300.4, 309.0, 309.1, or 311.0 as primary or secondary diagnosis), electroconvulsive therapy (ECT) (Current Procedural Terminology codes 90870 or 90871), or a suicide attempt (ICD-9 diagnosis codes 300.90 or E950.x-E959.x). Therefore, a depression-related hospitalization, ECT, or suicide attempt was assumed to be equivalent to a change in antidepressant regimen for the purposes of identifying a cohort of patients with treatment-resistant depression. The date on which a patient met all study criteria for treatment-resistant depression was defined as the *index date*.

Consistent with the literature, the number of depression medication regimen changes during the entire study period was utilized as a measure of severity of treatment-resistant depression.<sup>12,13,15,34</sup> By definition, each patient in

the sample had a minimum of 2 and a maximum of 8 depression medication regimen changes. Patients were divided into 2 groups, those with only 2 depression medication regimen changes and those with 3 or more. For the latter group, the data reported represent information for the sequential time periods between each depression medication regimen change. For example, a patient with 8 depression medication regimen changes has data reported for each time period between the third, fourth, fifth, sixth, seventh, and eighth depression medication regimen changes. The last observation for each patient in the study was December 31, 2000, or the last day of eligibility for health care insurance. Observations beyond 8 medication regimen changes were not included in the study, because the sample size was insufficient to provide stable cost estimates.

#### **Demographic and Clinical Measures**

Demographic and clinical characteristics were measured at index. Demographics included age, gender, occupation, type of health care plan, and geographic location. Clinical characteristics consisted of comorbidity and disease severity measures and type of pharmacotherapy at index. The comorbidity and severity measures were designed to estimate the existence of any comorbidity or disease severity that might complicate treatment.<sup>8,26,35–38</sup>

Comorbid conditions included a diagnosis of a personality, anxiety, somatoform, substance abuse, or other mental disorder. The Charlson Comorbidity Index (CCI)<sup>39</sup> was also calculated for each patient. Higher CCI values indicate a greater probability of death or major disability due to a concurrent general medical condition.<sup>39</sup> Severity measures consisted of the type of depression diagnosis, number of hospitalizations, ECT,<sup>17,22,40</sup> presence of suicide attempt(s),<sup>41</sup> and whether depression treatment was provided by a psychiatrist.

## **Cost Analysis**

Total health care expenditures per month (year 2000 U.S. dollars) were calculated and compared for time periods between the index date and the time of each subsequent depression medication regimen change. Costs were categorized into total outpatient, inpatient, and pharmaceutical health care cost. Total depression-related and total general medical health care costs were also calculated. The number of months between each depression medication regimen change was also assessed.

## **Statistical Analyses**

Univariate and multivariate methods were used to study the treatment-resistant depression patients in this sample. Univariate methods were used to test for differences in health care expenditures as the treatmentresistant depression illness progressed in severity through multiple changes in antidepressant medication regimens and for the duration of time spent on each regimen. The univariate method utilized confidence intervals that were constructed using a Bootstrapping technique to test for statistically significant differences in health care expenditures and the duration of time on each antidepressant medication regimen.<sup>42</sup> To estimate the effect of demographic and clinical characteristics on the number of depression medication regimen changes, a negative binomial multivariate count regression model was utilized. SAS (SAS Institute, Inc., Cary, N.C.) was utilized for univariate analyses and Stata (StataCorp LP, College Station, Tex.), for multivariate analyses. Statistical significance was based on p values less than or equal to .05.

#### RESULTS

### Sample Characteristics at Index

A total of 7737 patients from 1995–2000 met study criteria for treatment-resistant depression. The sample was predominantly female (74%) with a mean age of 43 years (Table 3). Employee beneficiaries constituted the majority of the sample (59%), followed by spouses (34%) and dependents (7%). Fifty-three percent of the sample resided in the North Central region, 22% in the South, 15% in the Northeast, with the remainder in the West (8%). Fourteen percent of the sample was enrolled in a managed care plan.

The rate of comorbid substance abuse was 4.7%; anxiety disorder, 4.5%; and personality disorder, 2.0%. The mean score for the CCI was 0.47, indicating that general medical comorbidity was uncommon. The number of suicide attempts or ECT sessions at index was negligible, although some patients had ECT or hospitalizations for suicide attempts during the study.

Seventy-one percent of patients were prescribed SSRIs at index, while 14.5% received TCAs, 0.1% received MAOIs, and 14.7% received other antidepressants. Five percent of patients were prescribed mood stabilizers and 1.0% were prescribed atypical antipsychotics. A primary care physician treated most patients (88.1%) at index.

#### Health Care Costs

Mean total health care expenditures increased by 104% from \$571 per month (\$6852 per annum) to \$1165 per month (\$13,980 per annum) from the second to the eighth depression medication regimen (Figure 1). Detailed total monthly health care cost data by degree of increasing treatment-resistant depression are shown in Table 4. From the second to eighth regimen change, total pharmaceutical and outpatient expenditures had statistically significant increases of 133% (\$126 to \$294) and 111% (\$268 to \$566), respectively. Total inpatient expenditures increased by 74% (\$176 to \$306). Total depression-related health care costs increased by 176% from the second (\$139 per/month or \$1668 annually) to

| Table 3. Demographic and Clinical Characteristics at | Index | of |
|------------------------------------------------------|-------|----|
| 7737 Patients With Treatment-Resistant Depression    |       |    |

| Variable                                     | Mean    | %     |
|----------------------------------------------|---------|-------|
| Demographics                                 |         |       |
| Age, y                                       | 43.39   |       |
| Female                                       |         | 74.26 |
| Employee                                     |         | 58.92 |
| Spouse of insured                            |         | 33.95 |
| Child of insured                             |         | 6.74  |
| Other dependent of insured                   |         | 0.37  |
| Region of residence                          |         |       |
| Northeast                                    |         | 15.31 |
| North Central                                |         | 53.18 |
| Southern                                     |         | 21.71 |
| Western                                      |         | 8.16  |
| Plan type                                    |         |       |
| Managed care insurance                       |         | 13.86 |
| Switched health plans                        |         | 35.25 |
| Severity of illness and comorbidity measures |         |       |
| Bipolar diagnosis <sup>a</sup>               |         | 3.43  |
| Major depression diagnosis <sup>a</sup>      |         | 45.12 |
| Number of ECT sessions                       | 0.03    |       |
| Charlson Comorbidity Index                   | 0.47    |       |
| Personality disorder                         |         | 1.96  |
| Anxiety disorder                             |         | 4.53  |
| Somatoform disorder                          |         | 0.11  |
| Other mental health comorbidities            |         | 15.35 |
| Substance abuse                              |         | 4.65  |
| Prescribing physician is psychiatrist        |         | 11.92 |
| Type of pharmacotherapy                      |         |       |
| Antidepressant                               |         |       |
| SSRI                                         |         | 70.68 |
| TCA                                          |         | 14.45 |
| MAOI                                         |         | 0.14  |
| Other                                        |         | 14.72 |
| Atypical antipsychotics                      |         | 1.03  |
| Mood stabilizers                             |         | 5.28  |
| 851 450/ C                                   | ICD 0 1 | •     |

<sup>a</sup>51.45% of patients were initially diagnosed with ICD-9 depression diagnoses of 300.4, 309.0, or 311.0, which are more commonly used in primary care.

Abbreviations: ECT = electroconvulsive therapy, MAOI = monoamine oxidase inhibitor, SSRI = selective serotonin reuptake inhibitor, TCA = tricyclic antidepressant.

Figure 1. Monthly Health Care Expenditures by Number of Depression Medication Regimen Changes in 7737 Patients From 1995–2000<sup>a</sup>



†Significantly different from second medication change cohort.

| Table 4. Mean Medical Ex                                                                                    | penditures for Increa                                                   | asing Degree of Treatr                                                           | nent Resistance and l                                                    | Mean Time at Each Le          | vel <sup>a</sup>     |                                 |                     |
|-------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------|----------------------------------------------------------------------------------|--------------------------------------------------------------------------|-------------------------------|----------------------|---------------------------------|---------------------|
|                                                                                                             |                                                                         |                                                                                  | Number of I                                                              | Depression Medication Re      | egimen Changes       |                                 |                     |
|                                                                                                             | 2                                                                       | 3                                                                                | 4                                                                        | 5                             | 9                    | 7                               | 8                   |
|                                                                                                             | (N = 342)                                                               | (N = 7395)                                                                       | (N = 5535)                                                               | (N = 3170)                    | (N = 1498)           | (N = 561)                       | (N = 133)           |
| Variable                                                                                                    | Mean (95% CI)                                                           | Mean (95% CI)                                                                    | Mean (95% CI)                                                            | Mean (95% CI)                 | Mean (95% CI)        | Mean (95% CI)                   | Mean (95% CI)       |
| Health care costs (\$/mo)                                                                                   |                                                                         |                                                                                  |                                                                          |                               |                      |                                 |                     |
| Total                                                                                                       | 571 (482 to 659)                                                        | 824 (790 to 857)*†                                                               | 817 (779 to 854)†                                                        | 941 (886 to 995)*†            | 1024 (937  to  1110) | 1089 (955 to 1222) <sup>†</sup> | 1165 (929 to 1400)† |
| Inpatient                                                                                                   | 176 (112 to 240)                                                        | 272 (246 to 298)*†                                                               | 206 (181 to 232)                                                         | 266 (225 to 307)              | 264 (203 to 325)     | 265 (185 to 345)                | 306 (152 to 460)    |
| Outpatient                                                                                                  | 268 (237 to 299)                                                        | 385 (372 to 399)*†                                                               | 399 (382 to 416)†                                                        | 433 (411 to 455)†             | 480 (442 to 518)†    | 513 (454 to 572)†               | 566 (449 to 683)†   |
| Pharmaceutical                                                                                              | 126 (109 to 143)                                                        | 167 (161 to 173)*†                                                               | 212 (204 to 220)*†                                                       | 243 (233 to 253)*†            | 280 (262 to 298)*†   | 312 (275 to 349)                | 294 (243 to 345)†   |
| General medical costs                                                                                       | 432 (344 to 520)                                                        | 629 (596 to 662)*†                                                               | 594 (564 to 624) <sup>†</sup>                                            | 665 (618 to 712) <sup>†</sup> | 712 (637 to 787)†    | 815 (696 to 934)                | 772 (590 to 954)†   |
| Depression-related costs                                                                                    | 139 (116 to 162)                                                        | $202 (190 \text{ to } 214)^{*}$                                                  | 224 (208 to 240)†                                                        | 278 (255 to 301)*†            | 308 (273 to 343)†    | 278 (232 to 324)†               | 384 (247 to 521)†   |
| Time at each level of                                                                                       | 39.7 (5.30 to 74.0)                                                     | 8.5 (-8.3 to 25.3)                                                               | 7.2 (–7.2 to 21.6)                                                       | 6.5 (-6.0 to 19.0)            | 6.2 (-5.4 to 17.7)   | 6.0 (-4.7 to 16.5)              | 5.5 (-3.4 to 14.3)  |
| treatment resistance, mo                                                                                    |                                                                         |                                                                                  |                                                                          |                               |                      |                                 |                     |
| <sup>a</sup> Level or degree of treatment<br>*Significantly different from<br>†Significantly different from | resistance defined by the mean in previous level mean with 2 depression | he number of depression<br>of treatment-resistant de<br>n medication regimen cha | medication regimen chapression ( $p \le .05$ ).<br>mges ( $p \le .05$ ). | nges during study period.     |                      |                                 |                     |
| •                                                                                                           | ×                                                                       | ,                                                                                | с ч                                                                      |                               |                      |                                 |                     |

Table 5. Influence of Predictive Variables on Increasing Levels of Treatment Resistance (negative binomial regression model)<sup>a</sup>

| 17<br>93<br>14<br>69<br>53<br>52<br>55 |
|----------------------------------------|
| 17<br>93<br>14<br>69<br>53<br>52<br>55 |
| 93<br>14<br>69<br>53<br>52<br>55       |
| 14<br>69<br>53<br>52<br>55             |
| 69<br>53<br>52<br>55                   |
| 53<br>52<br>55                         |
| 52<br>55                               |
| 55                                     |
| 06                                     |
| 06                                     |
| 90                                     |
| 51                                     |
| 98                                     |
|                                        |
| 63                                     |
| 68                                     |
| 29                                     |
| 87                                     |
| 05                                     |
| 01                                     |
| 31                                     |
| 01                                     |
| 14                                     |
| 01                                     |
|                                        |
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|                                        |
| 01                                     |
| 01                                     |
| 01                                     |
| 17                                     |
| 01                                     |
| 83                                     |
| 06                                     |
|                                        |
| 01                                     |
| 01                                     |
| 01                                     |
|                                        |

<sup>a</sup>A negative coefficient indicates a variable that is *not* associated with increasing levels of treatment resistance.

Abbreviations: CCI = Charlson Comorbidity Index,

MAOI = monoamine oxidase inhibitor, MDD = major depressive disorder, SSRI = selective serotonin reuptake inhibitor, TCA = tricyclic antidepressant.

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the eighth medication regimen change (\$384 per/month or \$4608 annually). These costs were significantly higher for the fifth to the eighth medication regimen change when compared with the third ( $p \le .05$ ), indicating a potential disease-management intervention timepoint.

Total general medical health care costs showed a trend in increased costs as the number of medication regimen changes increased, although most sequential medication regimen change intervals were not significantly different from each other. Costs related to general medical care accounted for 66% to 76% of total costs, while 24% to 33% were attributed to depression.

#### **Multivariate Analyses**

A negative binomial count multivariate regression model was utilized to identify characteristics that correlate with increasing degrees of treatment-resistant depres-

| Table 6. Marginal Eff | fects of Associated Variables of | n |
|-----------------------|----------------------------------|---|
| Increasing Degrees of | of Treatment Resistance          |   |

| Variable                                                             | Change in Expected<br>Number of Medication<br>Regimen Changes | p Value |
|----------------------------------------------------------------------|---------------------------------------------------------------|---------|
| Demographics                                                         |                                                               |         |
| Managed care insurance                                               | 0.10                                                          | .014    |
| Severity of illness and comorbidity                                  |                                                               |         |
| measures                                                             |                                                               |         |
| Personality disorder                                                 | 0.22                                                          | .007    |
| Anxiety disorder                                                     | 0.19                                                          | .002    |
| Somatoform disorder                                                  | 0.60                                                          | .055    |
| Other mental health                                                  | 0.25                                                          | .001    |
| comorbidities                                                        |                                                               |         |
| Diagnosis of MDD                                                     | 0.17                                                          | .001    |
| Type of pharmacotherapy at index                                     |                                                               |         |
| TCA                                                                  | 0.36                                                          | .001    |
| MAOI                                                                 | 1.67                                                          | .004    |
| Other                                                                | 0.45                                                          | .001    |
| Multiple antidepressants                                             | -0.81                                                         | .001    |
| Abbreviations: MAOI = monoamine<br>depressive disorder, TCA = tricyc | e oxidase inhibitor, MDD<br>lic antidepressant.               | = major |

sion as defined by the number of depression medication regimen changes (Table 5). Variables at index associated with increasing degrees of treatment resistance were comorbid personality, anxiety, somatoform, or other mental health disorder, diagnosis of major depressive disorder (severity measure), treatment with TCAs, MAOIs, or non-SSRIs at index (relative to SSRI), and enrollment in a managed health care insurance plan. Patients prescribed multiple antidepressants at index were less likely to have ongoing treatment resistance.

To evaluate the magnitude of each variable's influence on the number of depression medication regimen changes, the marginal effect of each variable was calculated (Table 6). Marginal effects are defined as the difference in the expected number of depression medication regimen changes for patients with or without a characteristic of interest. Most of the marginal effects were small; however, in the absence of multicollinearity, they are additive. For example, a patient with managed health care, a TCA at index, and a comorbid somatoform disorder diagnosis is expected to have 1.06 more depression medication regimen changes than a patient without these characteristics.

### **COMMENTS**

To better comprehend the economic impact of the progression of treatment-resistant depression, we examined records of 7737 patients with treatment-resistant depression from 1995–2000 in a large retrospective medical claims database. Consistent with the literature, depression medication regimen changes were used to define the degree of treatment resistance. Demographics, clinical characteristics, and health care expenditures were examined. Total medical health care expenditures increased significantly with increasing levels of treatment resistance. Mean annual health care expenditures increased from \$6852 for patients with 2 depression medication regimen changes to \$13,980 for those with 8 medication regimen changes.

General medical expenditures accounted for 66% to 76% of health care expenditures, whereas depression-related costs accounted for the minority of costs (24%–33%). In addition, at index, primary care physicians treated 88% of patients. These data support the importance for collaboration between general medical, pharmacy benefit, and mental health carve-out insurance carriers to develop and fund depression disease management programs.

A negative binomial multivariate count regression model identified clinical characteristics that were predictive of ongoing treatment-resistant depression. Patient demographics were poor predictors of ongoing treatmentresistant depression, with the exception of being in a managed health care plan. It has been argued that management of these patients has been particularly challenging for managed care organizations.<sup>43</sup>

Clinical characteristics such as personality, anxiety, and somatoform disorders or other mental health comorbidities were associated with greater degrees of treatment resistance in patients with treatment-resistant depression. The literature has reported that adequate control of comorbidities must be maintained for depression to remit, <sup>8,26,35–38</sup> which implies that these clinical characteristics should be closely monitored when patients first present. If these comorbid disorders are diagnosed early and treated adequately, their contribution to the progression of treatment-resistant depression might diminish.

The type of pharmacotherapy at index was also associated with ongoing treatment resistance. Seventy percent of patients were on SSRI therapy at index. Patients treated with SSRIs at index had fewer medication regimen changes compared with patients treated with TCAs, MAOIs, and other antidepressants. It is not known whether patients prescribed TCAs, MAOIs, or other antidepressants had previously received an SSRI before the study began. Future research could address this issue. Moreover, patients prescribed multiple antidepressants at index had fewer medication changes, a finding suggestive of potentially effective treatment strategies for treatmentresistant depression.

#### LIMITATIONS

This analysis is subject to the limitations associated with use of a large retrospective claims database. These data do not contain clinical information or other interactions with a patient. For purposes of this study, it is assumed that every depression medication regimen change was evidence of treatment failure and/or a poor response to pharmacotherapy. It is difficult to confirm ongoing treatment resistance without an examination of symptoms using a standardized rating of depression symptom severity.

Depression is a chronic/episodic disease that can extend over a long period of time, especially for those with treatment-resistant depression. A description of care before and after the study period (5 years) is not available. The first medication regimen change reported in this study may not have been the first medication change for patients in this study. Therefore, the cost consequences of each subsequent treatment change may be overstated. It is therefore recommended that the reader use these data as indicative of a trend whereby ongoing treatment resistance becomes more costly with each subsequent medication change.

Although we did require that each patient in this study had at least two 30-day prescriptions of antidepressants at minimum doses (defined in Table 2), it is possible that the data may also reflect costs of treatment for patients that had inadequate trials. A further limitation is that some patients may have received antidepressant treatment for comorbid illnesses other than the required ICD-9 diagnosis of depression (i.e., depression and chronic pain). The cost estimates may therefore be over- or understated for some patients. Individual medical claims most often have only 1 diagnosis even though patients may have multiple other comorbidities that were not recorded in billing documents submitted to insurance carriers. The level of comorbidity reported in this article may be understated as with most medical claims database studies.

#### CONCLUSIONS

Depression and general medical health care expenditures increase with the degree of treatment-resistant depression. Disease management interventions for treatment-resistant depression that result in sustained remission early in the course of illness are most likely to be the most cost effective.

*Drug names:* amitriptyline (Elavil and others), amphetamine (Adderall and others), bupropion (Wellbutrin and others), buspirone (BuSpar and others), carbamazepine (Carbatrol, Tegretol, and others), citalopram (Celexa), clomipramine (Anafranil and others), desipramine (Norpramin and others), doxepin (Sinequan and others), fluoxetine (Prozac and others), imipramine (Tofranil, Surmontil, and others), isocarboxazid (Marplan), lithium (Eskalith, Lithobid, and others), maprotiline (Ludiomil and others), methylphenidate (Focalin, Ritalin, and others), mirtazapine (Remeron), nefazodone (Serzone), nortriptyline (Aventyl, Pamelor, and others), paroxetine (Paxil and others), phenelzine (Nardil), protriptyline (Vivactil), sertraline (Zoloft), tranylcypromine (Parnate), trazodone (Desyrel and others), trimipramine (Surmontil), valproate sodium (Depacon and others), venlafaxine (Effexor).

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